
SONOVue®
Sulphur Hexafluoride

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SonoVue® is:

Patient-friendly

· Well tolerated

· No human plasma-derived components

User-friendly

· Storage at room temperature

· Two years' shelf life

· Six hours' stability after reconstitution

Technology-friendly

· Real-time imaging (low MI)

· Intermittent imaging (high MI)

SonoVue®: an ultrasound contrast agent enabling real-time imaging

SonoVue® is a flexible shell ultrasound contrast agent designed and optimized with regard to the resistance to pressure. This has led to the selection of SF_6, a gas with a low solubility in blood for the gaseous phase of the microbubbles, and to a phospholipidic monolayer[1,2,3] for the shell.

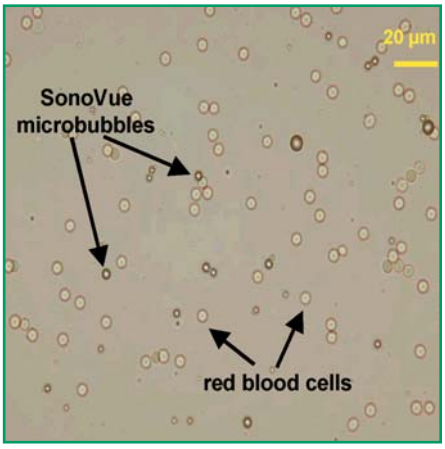
The development of equipment technology yielded some new contrast-specific imaging techniques, dedicated to a better differentiation between the signal from microbubbles and the signal from tissues.

Contrast-specific imaging adds a high clinical value to ultrasound by allowing the differentiation of normal from pathologic tissues through the dynamic study of the macro and microvasculature[4,5,6].

SonoVue® microbubbles are very flexible and resistant to pressure. They exhibit significant harmonic response even at very low MI

SonoVue® microbubbles, thanks to the high flexibility and resistance to pressure of their shell, are strongly echogenic in a wide range of frequencies and acoustic pressure. They exhibit significant harmonic response even at very low MI. Therefore SonoVue® can be used with both destructive and conservative contrast-specific imaging methods[1].

SonoVue® can be used with both high-and low MI contrast-specific imaging methods



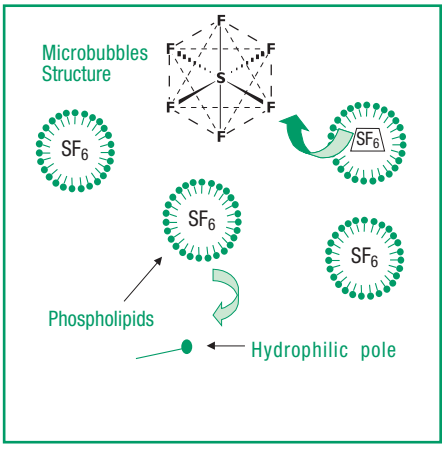


Fig.1. SonoVue® microbubbles microscopic image.

Fig.2. Schematic representation of SonoVue® microbubbles structure.

Improved assessment of focal liver lesions with contrast-enhanced ultrasound

Accurate detection and characterization of liver lesions with acoustic properties similar to those of the surrounding normal liver parenchyma has always been a significant limitation of conventional grey scale imaging. Bidimensional ultrasonography is highly sensitive and specific in characterizing cysts and calcifications, leading to a definitive diagnosis, but showed several limitations in patients with primary and secondary liver tumors. The addition of color, power, and spectral Doppler provides additional vascular information which may limit or expand the diagnostic possibilities. Unfortunately, the ability of conventional Doppler to provide this vascular information is often limited in the evaluation of liver masses, which may be located deep in the abdomen, small in size, and prone to motion artifacts from either respiratory or cardiac movement.[7,8,9]

To improve the detection and characterization of focal liver lesions, ultrasonography must better exploit the differences in blood flow between normal and pathological tissue through the use of a microbubble-based ultrasound contrast agent. SonoVue® has been shown to improve the accuracy of ultrasonography for the evaluation of focal liver lesions.[10,11,12,13,14]

SonoVue® was originally developed and used to overcome the limits on performance of ultrasonography in the assessment of the vascularity of liver lesions by increasing the linear backscattering from the microvascular blood pool. SonoVue® has been shown to be highly effective in enhancing Doppler signals within the liver vasculature for several minutes following an intravenous slow bolus administration. SonoVue® improves the diagnostic confidence and accuracy in the characterization of focal liver disease.

SonoVue® improves the diagnostic confidence and accuracy in the characterization of focal liver disease.

Figure 3 underlines a significant reduction of inconclusive examinations after SonoVue® injection compared with unenhanced ultrasound[15] in a population of patients with benign lesions proven by biopsy or combined CT/MRI.

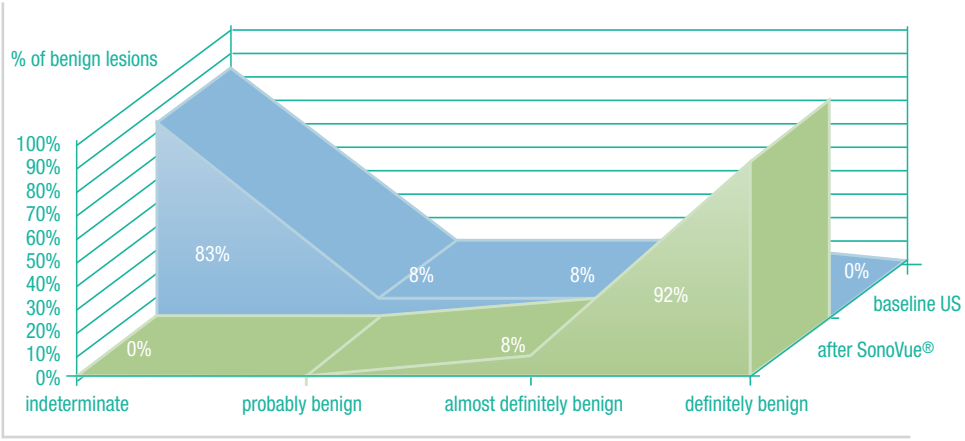


Fig.3. SonoVue® administration markedly decreased the number of inconclusive ultrasound examinations.

New ultrasound imaging techniques have been developed to improve the detection of SonoVue® in the microvascular blood pool by using the non-linear resonance of microbubbles within the ultrasound beam. Such non-linear response of SonoVue® to the incident ultrasound field may be segmented from that of tissue by transmitting at the fundamental transducer frequency but receiving at the second harmonics (second harmonic imaging) or via subtraction techniques using multiple, consecutive pulses of inverted phase (pulse inversion/phase inversion imaging). Unlike radiographic or MR contrast agents, SonoVue® is not extravasated from the vessel lumen. Any echo received from a SonoVue® microbubble may be inferred to demonstrate the presence of a vessel[16].

Pulse/phase inversion harmonic imaging and the use of lower output power (mechanical index < 0.3) limit contrast destruction and permit adequate contrast differentiation between normal and pathologic tissues lying deep in the liver. To further improve the characterization of focal liver lesions, imaging with these newer broadband US techniques must be based on exploitation of differences in blood flow between the normal and pathological tissues. The concept is not novel and it is derived from bolus dynamic CT and MR imaging. The novelty is that microbubbles are pure intravascular agents and they can be observed as they sequentially fill the hepatic arteries, the portal veins and the liver parenchyma microcirculation, and that dynamic bolus imaging with SonoVue® may be repeated several times during the same exam due to the limited persistence of microbubbles in the body[16]. Several recent studies have reported the improvement of diagnostic performance for characterization of focal liver lesions after the use of SonoVue® compared with conventional ultrasound. Von Herbay et al. investigated the ability of enhanced ultrasound with SonoVue® to reveal differences between benign and malignant focal liver lesions[8].

The study has demonstrated that SonoVue®-enhanced assessment improved sensitivity from 78% to 100% and specificity from 23% to 92% compared with baseline ultrasound (Fig. 4). Receiver operating characteristic analysis revealed a significant improvement in this discrimination (area under the receiver operating characteristic curve, 0.510 +/- 0.054 [SD] at baseline sonography, 0.998 +/- 0.003 with SonoVue-enhanced sonography; P < .001).

Compared to unenhanced ultrasound, SonoVue®-enhanced assessment improved sensitivity from 78% to 100% and specificity from 23% to 92%

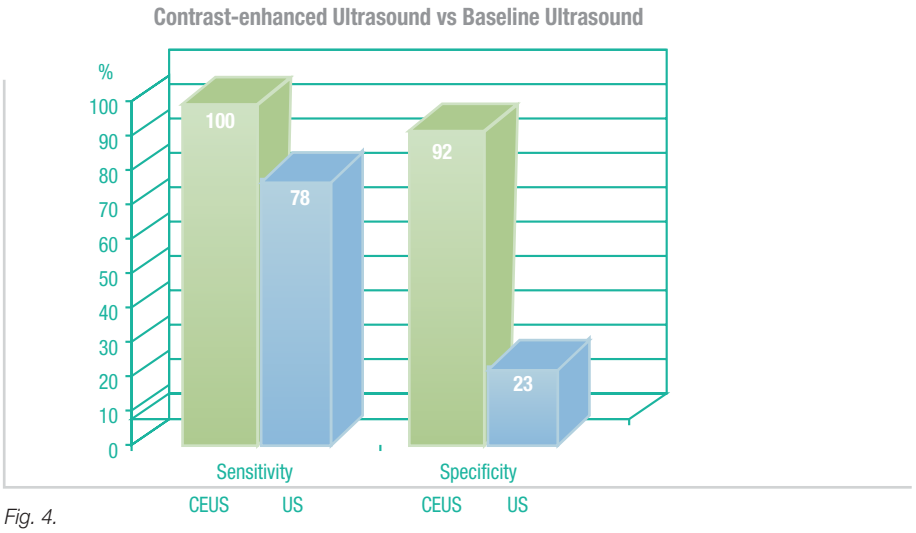


Fig. 4.

Another multi-center study published by Quaia et al. including 452 solid focal liver lesions[11] confirms the high level of accuracy of contrast enhanced ultrasound performed with SonoVue® by revealing a concordance level with reference standards of 88% and 85%. The diagnostic confidence was significantly higher after contrast ultrasound (0.831 to 0.978) (Fig. 5). Respectively for reader 1 and reader 2 the sensitivity improved from 52% to 81% and 54% to 85% and the specificity from 40% to 95% and 43% to 95%. The interreader agreement increased (k: 0.61 at baseline ultrasound versus 0.71 at contrast-enhanced US).

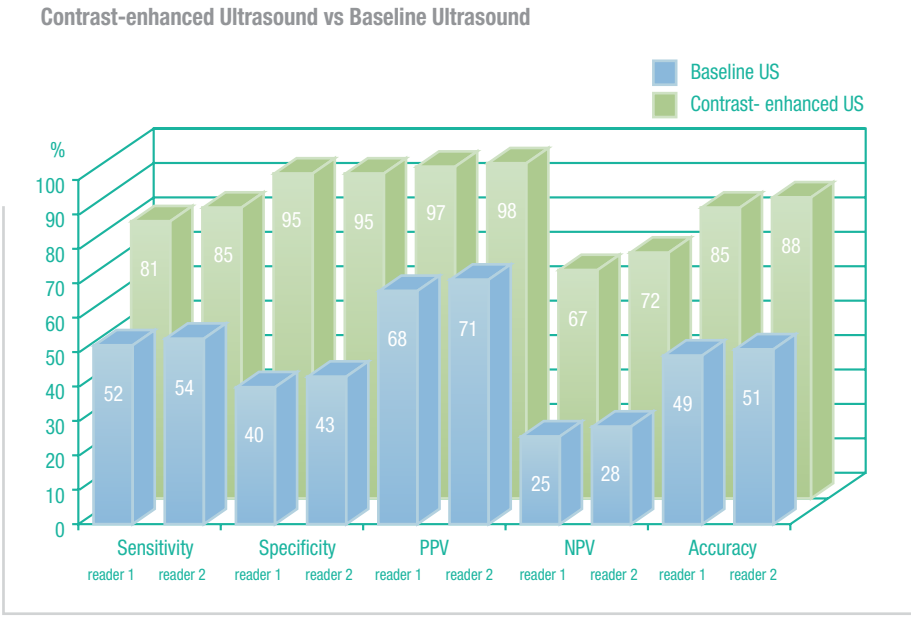


Fig. 5. Diagnostic performance of baseline and contrast-enhanced ultrasound at off-site retrospective analysis[11].

Konopke et al[17] have published the first results on sensitivity of contrast-enhanced ultrasound in screening for liver lesions in comparison with native ultrasound, CT and intra-operative finding as reference standard. The results give a sensitivity value of liver metastases detection for native ultrasound, enhanced CT and ultrasound of 53%, 76% and 86%.

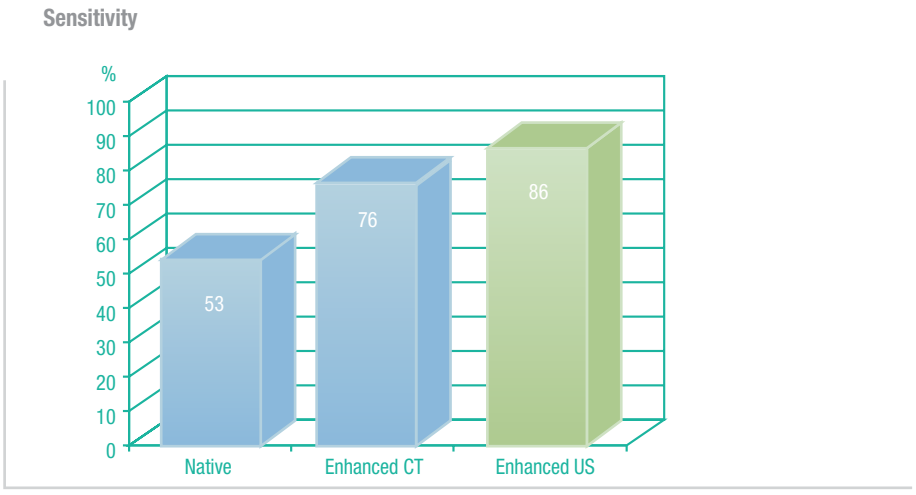


Fig. 6. Sensitivity of liver metastases detection[17].

The EFSUMB* Guidelines for the Use of Contrast Agents in Ultrasound

The EFSUMB has established guidelines on the use of contrast agents in ultrasound based on comprehensive literature surveys including results from prospective clinical trials. On issues where no significant study data were available, evidence was obtained from expert committee reports or was based on the actual consensus of experts in the field of US and contrast-enhanced ultrasound (CEUS) during the consensus conference. These guidelines are intended to give general advice for the use of ultrasound contrast agents. The chart below is generated from the enhancement pattern table present in the EFSUMB guidelines.

Enhancement (E)patterns of benign focal liver lesions

Tumor Entity	Arterial Phase	PV Phase	Delayed Phase
Haemangioma			
Typical Features	peripheral-nodular E,no central E Rim E	partial/complete centripetal filling	complete E.
Additional Features	small lesion:complete, rapid centripetalE		non-enhancing central areas (partial thrombosis,fibrosis)
FNH			
Typical Features	hyper-enhancing,complete,early	hyper-enhancing	iso-,hyper-enhancing
Additional Features feeding artery	spoke wheel arteries, centrifugal filling	hypo-enhancing central scar	hypo-enhancing central scar
Focal fatty sparing			
Typical Features	iso-enhancing	iso-enhancing	iso-enhancing
Focal fatty change			
Typical Features	iso-enhancing	iso-enhancing	iso-enhancing
Regenerative nodule			
Typical Features	iso-enhancing	iso-enhancing	iso-enhancing
Additional Features	hypo-or hyper-enhancing		
Cyst			
Typical Features	non-enhancing	non-enhancing	non-enhancing
Adenoma			
Typical Features	hyper-enhancing,complete	iso-enhancing	iso-enhancing
Additional Features	non-enhancing areas (haemorrhage)	hyper-enhancing non-enhancing areas (haemorrhage)	non-enhancing areas (haemorrhage)
Abscess			
Typical Features	rim E,no central E	hyper-/iso-enhancing rim, no central E	hypo-enhancing rim, no central E
Additional Features	enhanced septa hyper-enhanced liver segment	hypo-enhancing rim enhanced septa	

Enhancement (E)patterns of malignant focal liver lesions

Tumor Entity	Arterial Phase	PV Phase	Delayed Phase
HCC			
Typical Features	hyper-enhancing,complete non-enhancing areas (necrosis)	iso-,hypo-enhancing non-enhancing areas (necrosis)	hypo-enhancing
Additional Features	"chaotic" vessels enhancing tumor thrombus in PV +HCC/ portal vein		
Hypovascular Mets			
Typical Features	rim E	hypo-enhancing	hypo-,non-enhancing
Additional Features	complete E non-enhancing areas (necrosis)	non-enhancing areas (necrosis)	
Hypervascular Mets			
Typical Features	hyper-enhancing,complete	hypo-enhancing	hypo-,non-enhancing
Additional Features	"chaotic" vessels		
Cholangio carcinoma			
Typical Features	rim E	hypo-,non-enhancing	hypo-,non-enhancing
Additional Features	non-enhancing		

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** European Federation of Societies for Ultrasound in Medicine and Biology*

SonoVue® coupled with real-time low-MI technologies allows dynamic examinations and characterization of lesions according to their vascular pattern

SonoVue® vascular pattern in focal liver lesions is very similar to that observed with CT and MRI contrast agents.

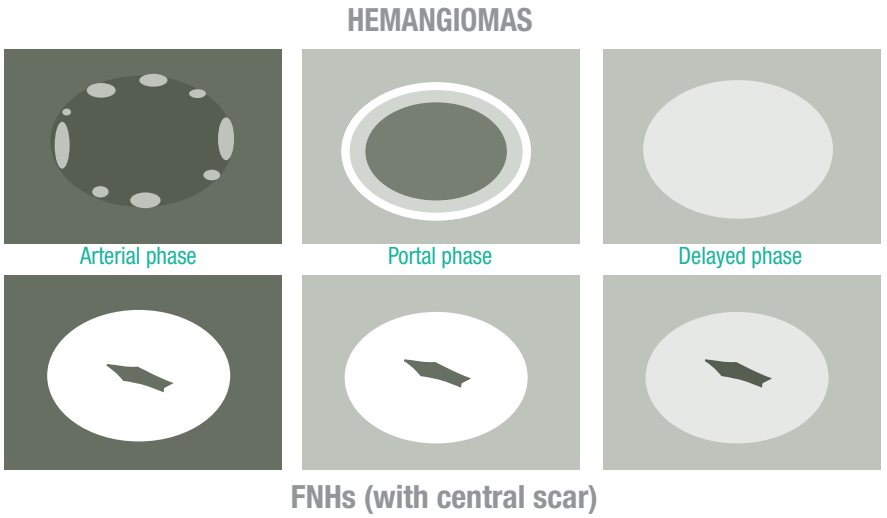


*Fig.5. Schematic contrast ultrasound uptake of the most frequent **benign** focal liver lesions.*

A study[18] shows that HCCs are hypervascular in arterial in 95% of the cases and hypoechoic in late phase in 70%.

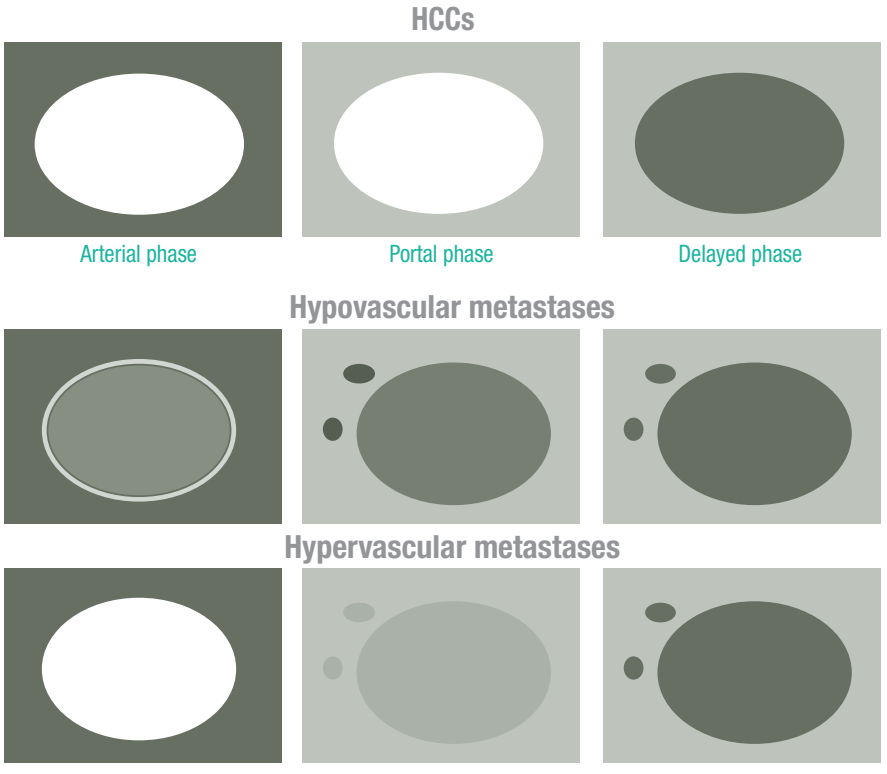


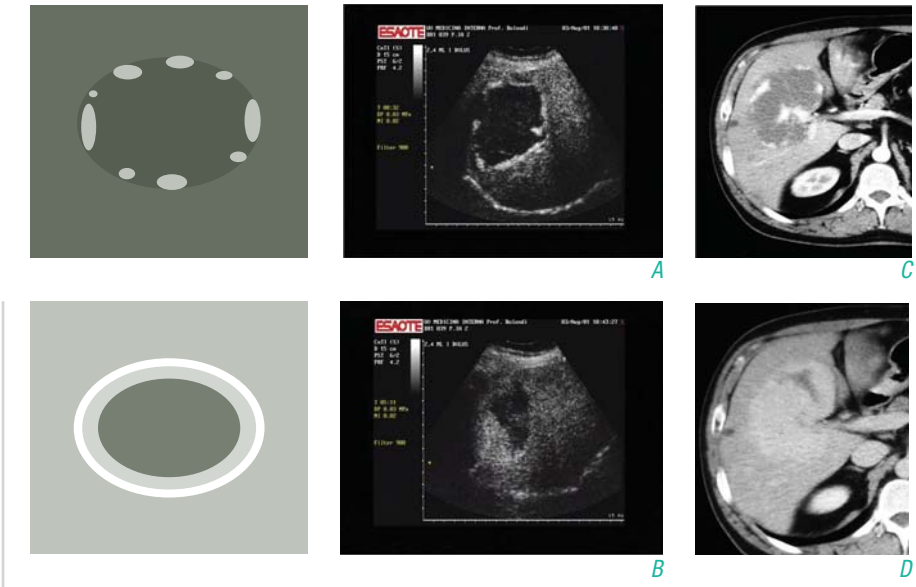
*Fig.6. Schematic contrast ultrasound uptake of the most frequent **malignant** focal liver lesions.*

Schematic models generated from: "The EFSUMB Guidelines for the Use of Contrast Agents in Ultrasound"

1) Hemangioma

Hemangiomas are the most common benign tumors in the liver and usually present a homogeneous hyperechogenicity; however, it is not rare to observe hemangiomas with the heterogeneous aspects that might mimic other focal liver lesions.

The vascular pattern of hemangiomas is described as a slow globular peripheral enhancement that tends toward progressive centripetal filling[18,19,20]. In the late sinusoidal phase the echogenicity of the hemangioma is iso- or hyperechoic to the surrounding liver parenchyma.

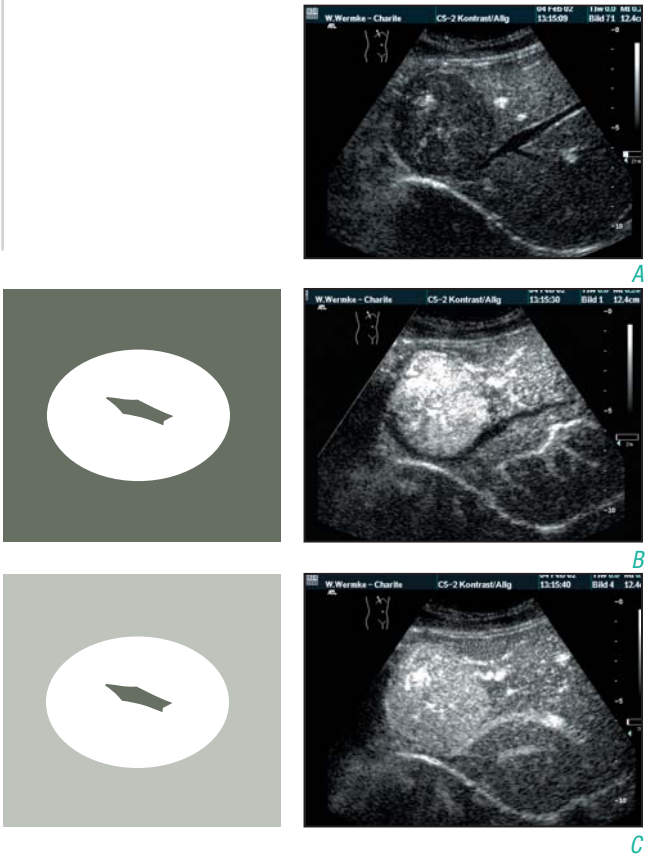


CASE 1:
Courtesy of Prof. Bolondi, Bologna, Italy (Esaote, Megas with CnTI)
Typical slow globular centripetal filling of a hemangioma. Successive contrast-enhanced ultrasound images in comparison with contrast-enhanced helical CT.

Hemangioma: the vascular pattern after SonoVue® is similar to that observed with extracellular contrast-enhanced CT or MRI[9,19,20]

2) Focal nodular hyperplasia

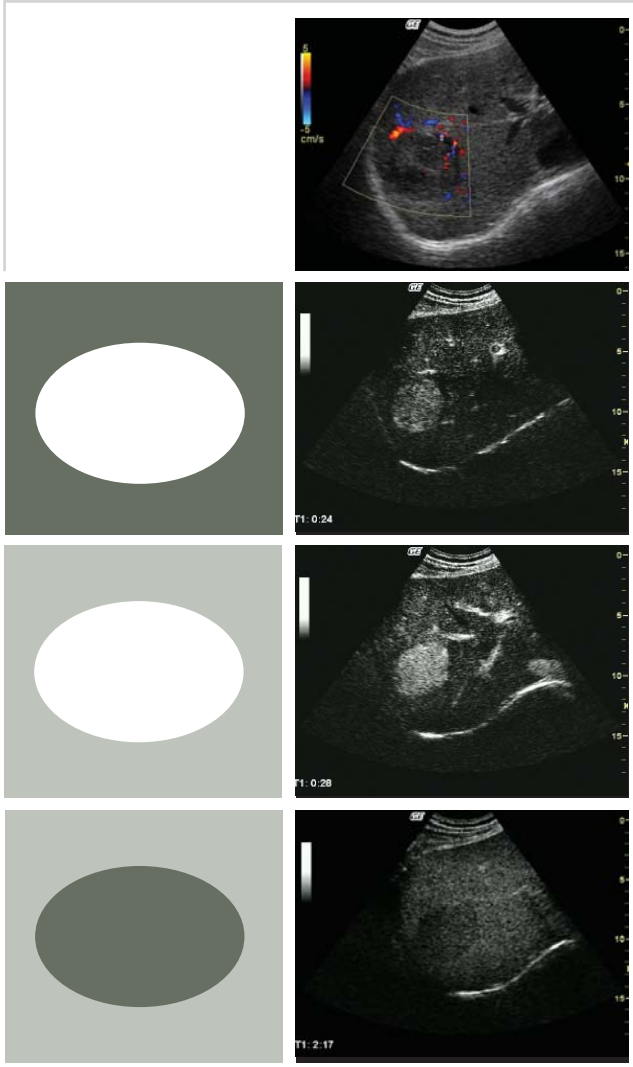
In conventional ultrasound, focal nodular hyperplasias (FNHs) normally appear hyper- or hypoechoic compared to the normal liver parenchyma. FNHs are most often asymptomatic and are discovered as an incidental finding; however, various echographic signatures could lead to more costly and invasive examinations. FNH is a hypervascular lesion, demonstrating a typical strong enhancement in the very early arterial phase with a typical stellate pattern. A central scar is often present. In the portal phase the lesion tends to be as echogenic as or more intense than the surrounding liver[11-14].



CASE 2:
Courtesy of Prof. Wermke, Charité Hospital, Berlin, Germany
(Philips, HDI 5000)
A) Nine seconds after injection, SonoVue® appears in the arterial circulation.
B) In the arterial phase, the lesion enhances strongly compared with normal parenchyma. Typical rapid centrifugal stellate pattern of a FNH.
C) In the portal phase, 40s after injection, liver parenchyma enhances, the lesion is still hyperechoic.

3) Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver worldwide. Although unenhanced ultrasound is the frontline examination, this modality suffers from a poor detection rate of 58% in patients at risk[14] and can not compete with the sensitivity level of CT and MRI. The appearance of HCC in ultrasound is variable and non specific. In contrast ultrasound the HCC demonstrates a peculiar dynamic vascular pattern similar to the one seen in CT or MRI. The typical vascular pattern is described as a strong and fast enhancement in arterial phase followed by a rapid washout in portal phase. A recent study[18] shows that more than 95% of the HCC will enhance in arterial. In absence of fibrosis or necrosis the enhancement is homogenous. In portal phase almost all HCC appear isoechoic to the liver parenchyma. In late phase, according to the same study 70% of HCC are hypoechoic and 30% isoechoic.

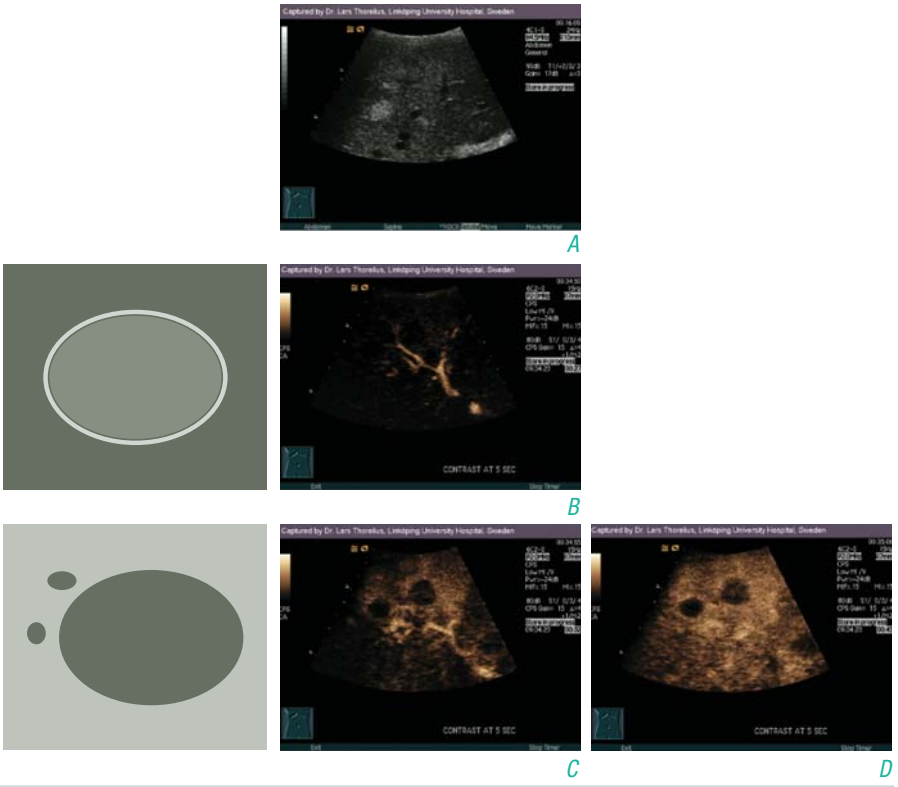


CASE 3:
Courtesy of Dr. H.P. Weskott, Hannover, Germany
(GE, Logic 9)
A) Baseline image.
B) In the arterial phase, the HCC is markedly enhanced compared with the normal liver parenchyma.
C) In the portal phase, the liver tissue starts enhancing. The lesion is still hyperechoic.
D) In late phase, the lesion appears hypodense with respect to the enhanced hepatic tissue.

4) Metastases

The high variability of lesion echostructure and relatively poor contrast between liver metastases and the surrounding liver parenchyma explain the low detection and sensitivity rates of non-enhanced sonography, ranging from 57% to 92%[21] or 63% to 85%[11] as reported in different articles in the literature.

The tumoral vascular morphology varies with respect to hyper- and hypovascular metastases. Hypovascular metastases enhance in the arterial phase and demonstrate a hypoechoic signal in the portal and late sinusoidal phases signifying no contrast uptake. In the arterial phase, hypervascular metastases yield a marked enhancement followed by a fast washout. They appear hypo- or slightly hypoechoic in the portal phase compared with the enhanced normal liver parenchyma[9].



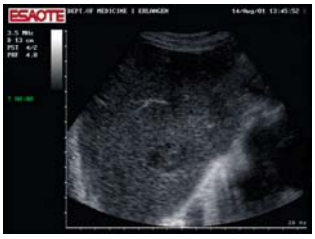
CASE 4:

Courtesy of Dr. Lars Thorelius, Linköping, Sweden. (Siemens Sequoia)

A) Metastasis from colorectal cancer.

B) In the arterial phase, no enhancement of the lesion.

C, D) In the portal and late phases, lesions appear as marked hypoechoic areas with respect to the normal liver parenchyma.



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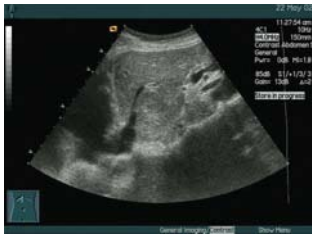

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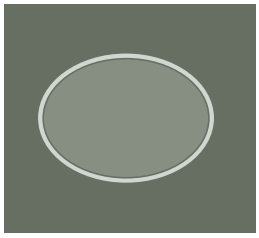

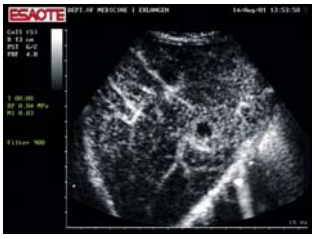

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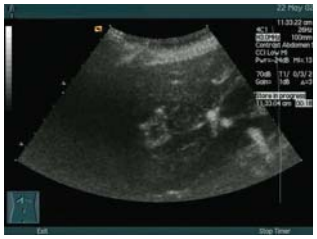

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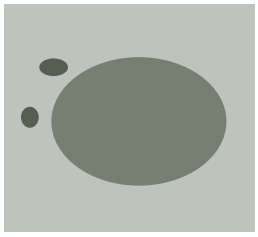

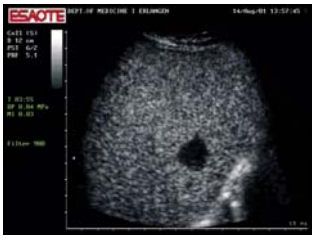

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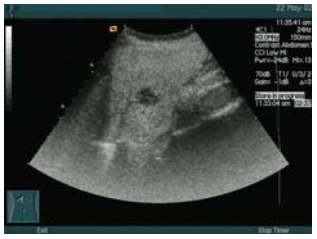


6C

CASE 5:

Courtesy of Dr. Becker, Erlangen,Germany (Technos, Esaote)

Metastasis with rim enhancement.

A) Unenhanced ultrasound showing a hypoechoic lesion.

B) Eight seconds after injection in the arterial phase, strong rim enhancement of the lesion.

C) In the very late phase, the lesion is markedly hypoechoic compared with the entire liver.

CASE 6:

Courtesy of Dr. Siosteens, Stockholm, Sweden (Sequoia, Siemens)

Metastasis in a 61-year-old female patient with primary breast and ovarian cancer.

A) At baseline the lesion is poorly discriminated.

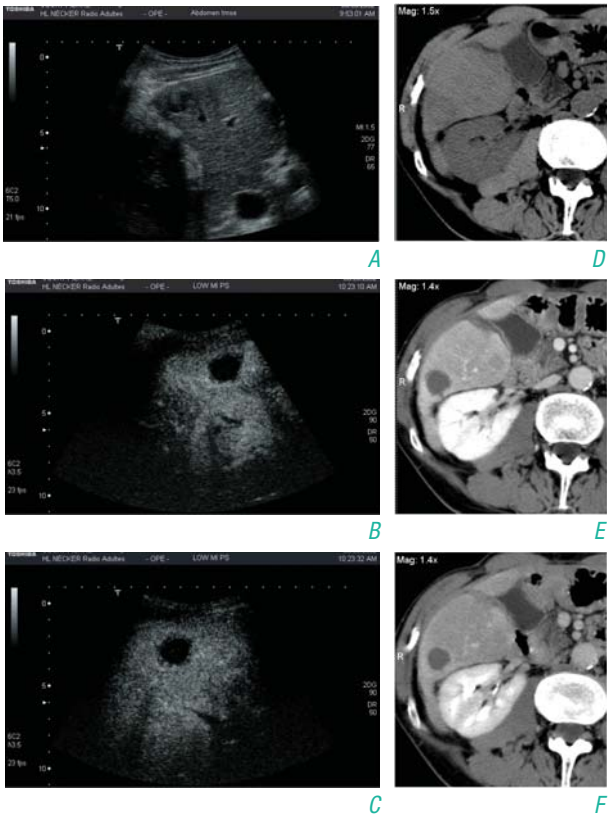
B) In arterial phase a peripheral enhancement is clearly shown.

C) In the late portal phase there is a clear difference between the hypoechoic lesion and the normal liver.

Guidance, monitoring and control of percutaneous treatment of liver tumors

Percutaneous ablation therapies play a key role in the management of patients with liver malignancies, both HCC and metastases. Diagnostic imaging in patients undergoing local ablative treatment includes US, contrast-enhanced CT and/or enhanced MRI during pretreatment diagnostic work-up and at distinct time points within the follow-up of the patient. Unenhanced US, even when combined with color/power Doppler, does not provide any reliable information about the outcome of ablation treatments. In fact, the assessment of vascularization and tissue perfusion is crucial to differentiate necrosis from residual viable tumor. Biphasic helical CT or dynamic gadolinium-enhanced MRI can predict the extent of the coagulation area to within 2–3 mm. When US is used as the imaging modality for guiding ablations the addition of ultrasound contrast agent can provide important information in each of the following procedural steps[9,22,23]:

- Pre-treatment assessment of lesion vascularity in order to compare pre- and post-ablation patterns at the end of ablation and for better delineation of lesions poorly visualized on baseline US scans
- Guidance of the ablation needle/probe into lesions not visualized or not well delineated with unenhanced US
- Immediate assessment of the therapeutic result to detect residual viable tumor areas
- Post-ablation assessment of the treated area vascularity



CASE 7:

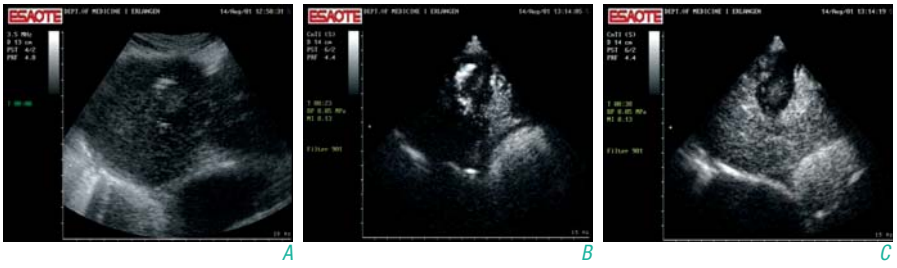
Courtesy of Dr. Correas, Paris, France (Toshiba Aplio)

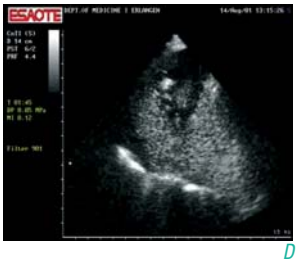
A 55-year-old patient with chronic hepatitis C,HIV infection and cirrhosis.

A) Heterogeneous subcapsular mass, diameter of 1.5 cm, biopsy-proven HCC.

B,C) Real-time low-MI examination after injection of SonoVue® (2.4 ml) performed immediately after radiofrequency ablation. During the different vascular phases, the lesion is strictly avascular, without any sign of incomplete treatment.

D,E,F) Multidetector multiphase CT: absence of any enhancement during arterial phase, matching contrast-enhanced ultrasound with SonoVue®. Treatment is considered successful with no sign of local recurrence; CT did not offer any additional information compared to contrast ultrasound.





CASE 8:

Courtesy of Dr. Becker, Erlangen, Germany (Esaote Technos with CnTI)

Recurrence of an ablated HCC.

B) In arterial phase (23s after injection), the still viable part of the lesion is quickly enhanced by SonoVue®, the proximal necrotic area appears markedly hypoechoic demonstrating very precisely the region to be retreated.

C) In portal phase, 38s after injection, the surrounding normal parenchyma enhances.

D) Sixty-four seconds after injection, the residual tumor appears hypoechoic compared with the surrounding tissue.

SonoVue® safety

In 51 completed clinical studies including 3,212 subjects, SonoVue® has been shown to be well-tolerated in all investigated patient groups, including patients with cardiovascular disease. The overall incidence of adverse events considered to be of possible, probable or unknown relationship to SonoVue® is low (7.7%) and the majority were of mild intensity and resolved without sequelae. Only one serious adverse event was considered of potential, in this case unknown, causal relationship. It described a patient with a sensory motor paresis of the right arm, which occurred approximately 20 hours after SonoVue® administration.

During post marketing surveillance hypersensitivity reactions were reported in rare instances (approximately 1:10,000) following the administration of SonoVue®, which could include skin reactions, bradycardia, hypotension or anaphylactoid shock. In patients with preexisting severe cardiovascular disease, bradycardia and hypotension were accompanied by myocardial ischemia and/or myocardial infarctions in single cases.

In very rare cases (0.0015%), fatal outcomes have been reported in temporal association with SonoVue®. In all these patients there was a high underlying risk for (spontaneous) major cardiac complications, which could have led to the fatal outcome. The contraindications for SonoVue® include patients with recent acute coronary syndrome or clinically unstable ischemic cardiac disease, including evolving or ongoing myocardial infarction, typical angina at rest within the last 7 days, significant worsening of cardiac symptoms within the last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders. When SonoVue® is administered, patients should be under medical supervision and emergency equipment and personnel trained in its use must be readily available.

For additional product and safety information and complete information on indications and contraindications please refer to the updated SonoVue® SPC.

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Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

SonoVue®, 8 microlitres / ml, powder and solvent for dispersion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulphur hexafluoride microbubbles 8μl per ml

On reconstitution as directed, 1 ml of the resulting dispersion contains 8 μl sulphur hexafluoride in the microbubbles, equivalent to 45 μg.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for dispersion for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

SonoVue® is for use with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio.

SonoVue® should only be used in patients where study without contrast enhancement is inconclusive.

Echocardiography

SonoVue® is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation.

Doppler of macrovasculature

SonoVue® increases the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal to noise ratio.

SonoVue® increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment.

Doppler of microvasculature

SonoVue® improves display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.

4.2 Posology and method of administration

This product should only be used by physicians experienced in diagnostic ultrasound imaging.

The microbubble dispersion is prepared before use by injecting through the septum 5 ml of sodium chloride 0.9%w/v solution for injection to the contents of the vial. The vial is then shaken vigorously for a few seconds until the lyophilisate is completely dissolved. The desired volume of the dispersion can be drawn into a syringe any time up to six hours after reconstitution. Just before drawing into the syringe, the vial should be agitated to re-suspend the microbubbles. SonoVue® should be administered immediately after drawing into the syringe by injection into a peripheral vein. Every injection should be followed by a flush with 5 ml of sodium chloride 0.9%w/v solution for injection.

The recommended doses of SonoVue® are:

B-mode imaging of cardiac chambers, at rest or with stress: 2 ml.

Vascular Doppler imaging: 2.4 ml.

During a single examination, a second injection of the recommended dose can be made when deemed necessary by the physician.

Elderly Patients

The dosage recommendations also apply to elderly patients.

Paediatric Patients

The safety and effectiveness of SonoVue® in patients under 18 years old has not been established and the product should not be used in these patients.

4.3 Contraindications

SonoVue® should not be administered to patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue®.

SonoVue® is contraindicated for use in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders.

SonoVue® is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome.

The safety and efficacy of SonoVue® have not been established in pregnant and lactating women therefore, SonoVue® should not be administered during pregnancy and lactation (see Section 4.6).

4.4 Special warnings and special precautions for use

It should be emphasised that stress echocardiography, which can mimic an ischaemic episode, could potentially increase the risk of SonoVue® utilisation. Therefore, if SonoVue® is to be used in conjunction with stress echocardiography patients must have a stable condition verified by absence of chest pain or ECG modification during the two preceding days.

Moreover, ECG and blood pressure monitoring should be performed during SonoVue® enhanced echocardiography with a pharmacological stress (e.g.

with dobutamine). ECG monitoring should be performed in high-risk patients as clinically indicated.
Care should be taken in patients with ischaemic cardiac disease because in these patients allergy-like and/or vasodilatory reactions may lead to life-threatening conditions.
Emergency equipment and personnel trained in its use should be readily available. Caution is advised when SonoVue® is administered to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease.
It is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue®.
Numbers of patients with the following conditions who were exposed to SonoVue® in the clinical trials were limited, and therefore, caution is advisable when administering the product to patients with: acute endocarditis, prostetic valves, acute systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent thromboembolism, and end-stage renal or hepatic disease.
SonoVue® is not suitable for use in ventilated patients, and those with unstable neurological diseases.
In animal studies, the application of echo-contrast agents revealed biological side effects (e.g. endothelial cell injury, capillary rupture) by interaction with the ultrasound beam. Although the biological side effects have not been reported in humans, the use of a low mechanical index is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed. There was no apparent relationship with respect to occurrence of adverse events in the clinical studies for patients receiving various categories of the most common concomitant medications.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 Preclinical safety data). Caution should be exercised when prescribing to pregnant women. It is not known if sulphur hexafluoride is excreted in human milk. Therefore, caution should be exercised when SonoVue® is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacokinetic and pharmacodynamic profiles, no or negligibile influence is expected with the use of SonoVue® on the ability to drive or use machines.

4.8 Undesirable effects

The undesirable effects reported with SonoVue® were, in general, non-serious, transient and resolved spontaneously without residual effects. In clinical trials, the most commonly reported adverse reactions are headache (2.3%), injection site pain (1.4%), and injection site reaction including bruising, burning and paraesthesia at the injection site (1.7%).
There were changes in ECG, blood pressure and in some laboratory parameters measured, but these were not deemed to be of clinical significance.
The adverse reactions reported among 1788 adult patients in clinical studies are:

Body system	Common (>1/100, <1/10)	Uncommon (>1/1,000 - <1/100)
Metabolism and nutrition disorders		Hyperglycaemia
Nervous system disorders	Headache	Paraesthesia, dizziness, insomnia, taste perversion
Eye disorders		Vision blurred
Vascular disorder		Vasodilatation
Respiratory, thoracic and mediastinal disorders		Pharyngitis, sinus pain
Gastrointestinal disorders	Nausea	Abdominal pain
Skin and subcutaneous tissue disorders		Pruritus, rash erythematous
Musculoskeletal, connective tissue and bone disorders		Back pain
General disorders and administration site conditions	Injection site pain, injection site reaction, including bruising, burning and paraesthesia at the injection site	Chest pain, pain n.o.s., asthenia

One case of sensory-motor paresis was reported.

Post marketing

Rare cases suggestive of hypersensitivity, which could include: skin erythema, bradycardia, hypotension or anaphylactic shock have been reported following the injection of SonoVue®. In some of these cases, in patients with underlying coronary artery disease, bradycardia and hypotension were accompanied by myocardial ischemia and/or myocardial infarctions.
In very rare cases, fatal outcomes have been reported in temporal association with the use of SonoVue®. In all these patients there was a high underlying risk for major cardiac complications, which could have led to the fatal outcome.

4.9 Overdose

Since there have been no cases of overdose reported to date, neither signs nor symptoms of overdosage have been identified. In a Phase I study doses up to 56 ml of SonoVue® were administered to normal volunteers without serious adverse events being reported. In the event of overdosage occurring, the patient should be observed and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOTHERAPEUTIC GROUP: ULTRASOUND CONTRAST MEDIA

ATC CODE V08DA.

The addition of sodium chloride 0.9%w/v solution for injection to the lyophilised powder followed by vigorous shaking results in the production of the microbubbles of sulphur hexafluoride. The microbubbles have a mean diameter of about 2.5μm, with 90% having a diameter less than 6μm and 99% having a diameter less than 11μm. Each millilitre of SonoVue® contains 8μl of the microbubbles. The interface between the sulphur hexafluoride bubble and the aqueous medium acts as a reflector of the ultrasound beam thus enhancing blood echogenicity and increasing contrast between the blood and the surrounding tissues.

The intensity of the reflected signal is dependent on concentration of the microbubbles and frequency of the ultrasound beam. At the proposed clinical doses, SonoVue® has been shown to provide marked increase in signal intensity of more than 2 minutes for B-mode imaging in echocardiography and of 3 to 8 minutes for Doppler imaging of the macrovasculature and microvasculature.

Sulphur hexafluoride is an inert, innocuous gas, poorly soluble in aqueous solutions. There are literature reports of the use of the gas in the study of respiratory physiology and in pneumatic retinopexy.

5.2 Pharmacokinetic properties

The total amount of sulphur hexafluoride administered in a clinical dose is extremely small, (in a 2 ml dose the microbubbles contain 16 μl of gas). The sulphur hexafluoride dissolves in the blood and is subsequently exhaled.

After a single intravenous injection of 0.03 or 0.3 ml of SonoVue/kg (approximately 1 and 10 times the maximum clinical dose) to human volunteers, the sulphur hexafluoride was cleared rapidly. The mean terminal half-life was 12 minutes (range 2 to 33 minutes). More than 80% of the administered sulphur hexafluoride was recovered in exhaled air within 2 minutes after injection and almost 100% after 15 minutes.

In patients with diffuse interstitial pulmonary fibrosis, the percent of dose recovered in expired air averaged 100% and the terminal half-life was similar to that measured in healthy volunteers.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and toxicity to reproduction. Caecal lesions observed in some repeat- dose studies with rats, but not in monkeys, are not relevant for humans under normal conditions of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Macrogol 4000

Distearoylphosphatidylcholine

Dipalmitoylphosphatidylglycerol Sodium

Palmitic acid

Solvent:

Sodium chloride 0.9% w/v solution for injection

6.2 Incompatibilities

SonoVue should not be admixed with any other medicinal product except the solvent provided.

6.3 Shelf life

2 years.

Once reconstituted, chemical and physical stability has been demonstrated for 6 hours. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Presentation 01(with integral Bio-Set transfer system) -

25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride in a colourless Type I glass vial, with elastomeric closure and integral transfer system.

Type I glass pre-filled syringe containing 5 ml sodium chloride 0.9%w/v solution for injection.

Presentation 02 (with separate MiniSpike transfer system):-

25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride in a colourless

Type I glass vial, with elastomeric closure.

Separate transfer system.

Type I glass pre-filled syringe containing 5 ml sodium chloride 0.9%w/v solution for injection.

6.6 Instructions for use/handling

Before use examine the product to ensure that the container and closure have not been damaged.

SonoVue® must be prepared before use by injecting through the septum 5 ml of sodium chloride 0.9%w/v solution for injection to the contents of the vial. The vial is then shaken vigorously for twenty seconds after which the desired volume of the dispersion can be drawn into a syringe as follows, depending on the presentation :

Presentation 01 (with integral Bio-Set transfer system)

1. Remove vial cap and syringe tip-cap.
2. Connect the syringe (without plunger rod) to the Bio-Set transfer system by screwing it in clockwise.
3. While holding the vial vertically on a table, push firmly down on the syringe until the red line disappears into the white tube of the transfer system with a click.
4. Connect the plunger rod by screwing it in clockwise into the syringe.
5. Empty the contents of the syringe into the vial by pushing on the plunger rod.
6. Shake vigorously for 20 seconds to mix all the contents in the vial (white milky liquid).
7. Invert the system and carefully withdraw SonoVue® into the syringe.
8. Unscrew the syringe from the transfer system.

Presentation 02 (with separate MiniSpike transfer system)

1. Connect the plunger rod by screwing it clockwise into the syringe.
2. Open the MiniSpike transfer system blister and remove syringe tip cap.
3. Open the transfer system cap and connect the syringe to the transfer system by screwing it in clockwise.
4. Remove Flipcap glass protective disk from the vial. Slide the vial into the transparent sleeve of the transfer system and press firmly to lock the vial in place.
5. Empty the contents of the syringe into the vial by pushing on the plunger rod.
6. Shake vigorously for 20 seconds to mix all the contents in the vial (white milky liquid).
7. Invert the system and carefully withdraw SonoVue® into the syringe.
8. Unscrew the syringe from the transfer system.

SonoVue® should be administered immediately by injection into a peripheral vein.

If SonoVue® is not used immediately after reconstitution the microbubble dispersion should be shaken again before being drawn up into a syringe. Chemical and physical stability of the microbubble dispersion has been demonstrated for 6 hours.

The vial is for a single examination only. Any unused dispersion remaining at the end of an examination must be discarded.

7. MARKETING AUTHORISATION HOLDER

Bracco International B.V.
Strawinskylaan 3051
1077ZX Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/01/177/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 March 2001

10. DATE OF REVISION OF THE TEXT

27 September 2004