SonoVue® Product Monograph
Dynamic Contrast Enhancement in Real Time
Welcome to Bracco Imaging

Bracco Imaging S.p.A., part of the Bracco Group, is one of the world’s leading companies in the diagnostic imaging business. Headquartered in Milan, Italy, Bracco Imaging develops, manufactures and markets diagnostic imaging agents and solutions that meet medical needs.

Bracco Imaging offers a product and solution portfolio for all key diagnostic imaging modalities: X-Ray Imaging (including Computed Tomography-CT, Interventional Radiology, and Cardiac Catheterization), Magnetic Resonance Imaging (MRI), Contrast Enhanced Ultrasound (CEUS), Nuclear Medicine through radioactive tracers, and Gastrointestinal Endoscopy. The diagnostic imaging offer is completed by several medical devices and advanced administration systems for contrast imaging products in the fields of radiology and cardiology. These include the Empower line of contrast injection systems for CT and MRI procedures, the syringe-less contrast administration system CT Exprés and VueJect, our ultrasound contrast agents’ infusion pump.

The Company operates in over 90 markets worldwide, either directly or indirectly, through subsidiaries, joint ventures, licenses and distribution partnership agreements. With an on-going research covering all key modalities, Bracco Imaging has a strong presence in key geographies: North America; Europe and Japan operating through the Joint Venture Bracco-Eisai Co., Ltd. The Company also operates in Brazil, South Korea, and China through the Joint Venture Bracco Sine Pharmaceutical Corp. Ltd. Operational investments have been made in order to achieve top quality and compliance with a sustainable eco-friendly production. Manufacturing activities are located in Italy, Switzerland, Japan, China and Germany.

Our Commitment to R&D and Innovation

Bracco Imaging is an innovative Research and Development (R&D) player with an efficient process oriented approach and a track record of innovation in the diagnostic imaging industry. R&D activities are managed in the three Research Centres located in Colleretto Giacosa (Ivrea, Italy), Plan les Ouates (Geneva, Switzerland) and Princeton (New Jersey, USA).

Our Group currently owns approximately 1500 patents registered throughout the world. Our history of developing proprietary products includes: iopamidol, the first ready-to-use, non-ionic/low osmolar contrast agent for X-Ray, launched in 1981 and still the leading product in many markets under different brand names; lomeron®, launched in 1994, the ready-to-use, non-ionic/low osmolar contrast agent for X-Ray, with the highest iodine concentration on the market; MultiHance®, the MRI contrast agent with high relaxivity and dual route of excretion, launched in 1998; SonoVue®, the ultrasound contrast agent with the broadest range of applications, launched in 2001 and CardioGen, the first and only agent approved for cardiac positron emitting tomography (PET).

The Group is currently engaged in the development of new imaging agents and solutions, specifically designed to improve patient management through increased accuracy in diagnoses.
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SONOVUE® PRODUCT CHARACTERISTICS

SonoVue® is a second generation ultrasound contrast agent which has been developed to obtain an optimal backscattered signal over a broad frequency range, with good pressure stability, and persistence in the blood stream.

It consists of microscopically small microbubbles (diameter always < 20 µm, 99% < 10 µm) surrounded and stabilized by a highly elastic membrane of phospholipids. The microbubbles are filled with an inert gas of poor aqueous solubility (sulphur hexafluoride SF₆) resulting in a long persistence in the microbubbles. The gas is eliminated by the lungs in the exhaled air. (Fig.1).

This results in prolonged stability of the microbubbles in the blood stream, along with rapid pulmonary elimination.

Physicochemical characteristics

SonoVue®-microbubbles are suspended in physiological saline solution (0.9 % saline solution). About 200 million microbubbles with a total gas content of 8 µl sulphur hexafluoride are contained in a 1 ml ready-to-use suspension. This small amount of gas is sufficient to enhance the entire blood vessel system for several minutes. After preparation, 1 vial contains 5 ml ready-to-use suspension.

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Acoustic characteristics

SonoVue®-microbubbles create a boundary layer to the surrounding blood with a high impedance mismatch. This results in a strong backscatter of the ultrasound signal, i.e. a high echogenicity of the microbubbles. Using conventional ultrasound technology, an amplification of the ultrasound signal of about 30 dB is obtained [1] (corresponding to a 1000-fold amplification).

In the ultrasound beam SonoVue®-microbubbles start oscillating during insonation; this oscillation is particularly strong if the insonation frequency corresponds to the resonance frequency of the microbubbles [2]. Resonance oscillations over a wide frequency range are obtained due to the size distribution of the SonoVue® microbubbles, so that SonoVue® gives a good signal over the entire range of frequencies used for medical imaging (1-40 MHz). With higher frequencies, however, the resonance effect decreases slightly, which generally results in a need for a somewhat higher dose of the contrast agent.

SonoVue® can be used in combination with conventional ultrasound technology for signal amplification, e.g. in (colour) Doppler sonography. In this case, the examination is performed with the usual high insonation power (high-MI¹ imaging), which may be reduced somewhat to avoid blooming artefacts, if required. Using the usual high insonation power in conventional ultrasound, the resulting oscillation of the microbubbles is so strong that the microbubble membranes break down within a short time, resulting in microbubble disruption and escape of the encapsulated gas.

This destruction of microbubbles in the ultrasound beam results in a loss of echogenicity of the contrast agent (CA) within a few seconds. This is particularly apparent in the capillaries where, in contrast to larger vessels, replacement of destroyed microbubbles by new microbubbles occurs relatively slowly because of the slower capillary blood flow velocity.

Due to prominent microbubble destruction in conventional ultrasound, specific contrast modes have been developed by the machine manufacturers, typically involving markedly reduced insonation power (low-MI imaging) to minimize microbubble destruction. These contrast-specific modes allow continuous insonation of the microbubbles which keeps them oscillating thereby enabling real-time contrast imaging in parenchymal tissue. The oscillating microbubbles create a specific echo signal with non-linear characteristics and harmonic frequencies.

Ultrasound machines can detect this specific echo signal despite the substantially reduced signal intensity (compared to conventional ultrasound) and distinguish it from the linear tissue signal (Fig. 2). This allows an effective separation of contrast agent signals from tissue signals, which can be displayed as a pure contrast agent image or as overlay or side-by-side images in combination with the anatomical tissue image (Fig. 3).

¹ Mechanical Index
**Fig. 2:**
Principle of signal discrimination of tissue and microbubble response.

On most modern machines a pulse summation process is used. Two or more pulses are transmitted one after the other (green), differing in their form (e.g. inverted phase, modulated amplitude, etc.). The backscattered impulses from tissue (orange) follow exactly the pulse shape of the transmitted pulse (linear response). The microbubbles on the other hand start to oscillate in their particular resonance frequency and produce their own specific signal (blue), which does not follow exactly the pulse shape of the transmit pulse (non-linear response). Using a dedicated mathematical calculation of the received responses by the contrast-specific software of the ultrasound machine, the linear responses from tissue are cancelled, resulting in a suppression of tissue signals, while the non-linear signals from microbubbles are displayed selectively as contrast image (red).

**Fig. 3:**
Contrast sonography using the contrast mode (low-MI imaging).

In the dual mode (split screen) the contrast image (gold-coloured, right) is displayed side-by-side with the corresponding B-mode image (grey tone image, left). Both images are processed simultaneously in real time from the same data set.

With kind permission of Prof. Dr. Strobel, University Clinic Erlangen.
Pharmacodynamic characteristics

SonoVue® is an inert ultrasound contrast agent and has no pharmacological effect. The physical effect consists of the interaction between microbubbles and ultrasound waves, which lead to the creation of a specific echo signal (contrast enhancement).

The intensity of the contrast agent signal depends on the emitted insonation power, the insonation frequency, and the concentration of microbubbles, unless excessively high contrast agent concentrations are used (resulting in shadowing and signal oversaturation) [3]. Using defined insonation parameters (system settings), the received signal intensity is linearly dependent on the local contrast agent concentration. This enables quantification of the amount of contrast agent present and therefore quantitative assessment of the relative blood volume in the tissue (Fig. 4).

After intravenous bolus injection of SonoVue® the microbubbles quickly enter the blood circulation, resulting in a signal increase in the vascular system. Increasing the dose initially leads to a corresponding increase in signal intensity, but only until a certain maximum dose is reached (Fig. 5).

A further increase in dose prolongs the duration of contrast enhancement (because of venous pooling of the contrast agent), but runs the risk of oversaturation in well-perfused structures.

Therefore in clinical practice a dose of 2.0 ml (echocardiography) or 2.4 ml (peripheral macro- and microvessels) is recommended. During a single examination, a second injection of the recommended dose can be made when deemed necessary by the physician. This results in contrast enhancement of approx. 2 minutes (cardiac chambers) or 3–8 minutes (peripheral organs). The contrast intensity thereafter diminishes as the microbubbles are washed out.
Pharmacokinetic characteristics

SonoVue®-microbubbles are transported in the body by the blood stream. They move freely through capillaries and follow the distribution kinetics of red blood cells.

The size of the microbubbles prevents them from leaving the vascular system (except in the case of active bleeding).

Therefore SonoVue® is a pure “blood pool contrast agent”. This is an important difference compared to standard CT- and MRI-contrast agents, which distribute into the entire interstitial fluid (so-called “extracellular fluid contrast agents”) (Fig. 6).

Fig. 5:
Course and duration of contrast enhancement in arterial blood circulation (aorta) after i.v. injection of different SonoVue® doses (in rabbits).
Up to a dose of 0.05 ml (corresponding to about 2 ml in humans) an increasing dose leads to higher signal intensities. A further increase in dose prolongs the duration of contrast enhancement (venous pooling of the contrast agent).

Fig. 6:
Schematic representation of SonoVue® microbubbles in the vascular bed.
The microbubbles cannot leave the intact vascular bed because of their size and thus enhance exclusively the intravascular compartment (blood pool contrast agent).
Sulphur hexafluoride is a poorly soluble gas that dissolves slowly in the blood and is subsequently exhaled. It does not diffuse out from the microbubbles as long as these remain in the body’s circulating system.

In clinical studies in healthy volunteers the mean half-life of elimination of the injected SF$_6$ gas was 12 minutes (2-33 minutes) using terminal doses between 0.03 and 0.3 ml/kg body weight (corresponding to approx. 1- and 10-fold of the standard clinical dose).

After 15 minutes the entire gas volume applied was recovered in the exhaled breath [4] (Fig. 7). 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.

The phospholipids forming the membrane of the microbubbles are naturally occurring components of cell membranes (distearoylphosphatidylcholine and dipalmitoylphosphatidylglycerol-Na). They are degraded by the endogenous phospholipid metabolic pathway.
Preparation of SonoVue®

SonoVue® is supplied as a kit containing a vial with the phospholipids (lyophilisate) in a sulphur hexafluoride atmosphere, a prefilled syringe with physiological saline solution (0.9% saline solution) and a Mini-Spike transfer system.

The suspension must be reconstituted before application. Reconstitution of the microbubbles is not difficult, but it is important to follow the instructions carefully to achieve the optimum effect of the contrast agent.

1. Connect the plunger rod by screwing it clockwise into the syringe.

2. Open the transfer system cap and connect the syringe to the transfer system by screwing it in clockwise.

3. Empty the contents of the syringe into the vial by pushing on the plunger rod.

4. Open the Mini-Spike transfer system blister and remove the syringe tip-cap.

5. Remove the 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.

6. Shake vigorously for 20 seconds to mix all the contents in the vial (resulting in a milky white liquid).

7. Invert the system and carefully withdraw the required dose of SonoVue® into the syringe.

8. Unscrew the syringe from the transfer system.
1. Echocardiography

Reliable endocardial border delineation is essential for assessment and quantitative determination of ventricular volumes and the resultant ejection fraction (EF). In non-contrast echocardiography endocardial border delineation may be hindered by trabecular structures in the cavity and “drop outs” (i.e. areas of the cardiac wall with insufficient reflection of sound waves)[5].

In stress echocardiography endocardial border delineation is suboptimal in about one third of patients [6]. This can lead to erroneous assessment of left ventricular function, limited reproducibility and unnecessary further diagnostic tests as a result of non-interpretable images (recommendation for contrast echocardiography from the European Association of Echocardiography, EAE [7]).

SonoVue® improves endocardial border delineation.

The EAE recommends the use of an ultrasound contrast agent (USCA) in patients with suboptimal images at non-contrast echocardiography to improve endocardial border delineation when two or more adjacent segments cannot be clearly detected, or if accurate and reproducible measurements of left ventricular volumes and ejection fraction (EF) are required [7].

In a controlled multi-centre study using SonoVue®, detection of the endocardial border was scored by 2 blinded offsite readers for each of the 16 endocardial segments using a quality scale of 0–2 (0 = non-detectable, 1 = poorly detectable, 2 = well detectable), resulting in a maximum score value of 32 (i.e. all segments well detectable). A total summed score from 0–32 for all segments combined was then calculated. The mean total score increased significantly after the administration of SonoVue®, for reader 1 from 16.39 to 30.50 and for reader 2 from 16.07 to 29.54 [8] (Fig. 8, 9).

**Fig. 8:**
Detectability of the left ventricular endocardial border with and without SonoVue®.

Each of the 16 endocardial segments was scored by 2 blinded offsite readers (OR1 and OR2) on a scale from 0–2 (0 = non-detectable, 1 = poorly detectable, 2 = well detectable), resulting in a maximum score value of 32 (i.e. all segments well detectable). Shown is the mean score of 120 patients with the respective standard deviation. With SonoVue® the readers reported clearly better detectability of the endocardium with less variability.
Fig. 9: Echocardiography without and with SonoVue®.
Image of the apical four-chamber view at end diastole (left) and end systole (right) without (top row) and with contrast enhancement (bottom row) respectively. After administration of SonoVue®, the left ventricle fills homogeneously with microbubbles, including the spaces between intracavitary trabeculae and endocardium. Detectability of the endocardium is therefore significantly improved.
With kind permission of PD Dr. von Bardeleben, University Medicine of the Johannes-Gutenberg-University, Mainz.
Improved delineation of endocardial borders also facilitates the use of automatic cardiac wall detection techniques (Fig. 10).

It is important that the software for cardiac wall detection is set up in the reverse mode, i.e. light-shaded structures are interpreted as cavitary lumen and dark structures as cardiac wall. A good and homogeneous opacification of the ventricle enables the software to reliably identify the endocardial border (Fig.11).

**Fig. 10:**
Automatic contour detection (acoustic quantification, Philips) after opacification of the left ventricle with SonoVue®.
With kind permission of Prof. Dr. Agati, La Sapienza University, Rome.
Delineation of the left ventricular cavity - SonoVue® improves the delineation of the endocardial border

The assessment of the left ventricular cavity depends from a clear and unambiguous delineation of the endocardial border, which is often of high clinical importance, in particular in critically ill patients or patients with severe heart insufficiency.

The reproducibility of measured values is especially important for longitudinal follow-up studies.
Wall motion – SonoVue® improves the assessment of wall motion abnormalities in echocardiography at rest and during stress

Assessment of systolic LV function depends on the evaluation of endocardial inward and outward movement and myocardial wall thickening. [5] An optimal and reliable evaluation of myocardial contraction requires good depiction of the endocardial border and myocardial wall. Both are significantly improved with the use of the echo contrast agent SonoVue® (Fig. 12) [9, 10, 11].

Without a contrast agent, the endocardial border is often not clearly detectable in all segments, and myocardial thickening is difficult to assess [7].

With proper adjustment of the ultrasound machine, homogeneous opacification of the cardiac cavities and cardiac wall is obtained after administration of the contrast agent, resulting in possibly improved delineation of the cardiac wall and better assessment of its motion pattern (Fig.13,14) [10].
Fig. 13:
Image of a wall motion abnormality after contrast enhancement with SonoVue®.
Reduced contraction (hypokinesis) of the cardiac wall is clearly seen in the apical septal region.
With kind permission of PD Dr. von Bardeleben, University Medicine of the Johannes-Gutenberg-University, Mainz.

Fig. 14:
Comparative images of a patient’s non-contrast echocardiography, SonoVue®-enhanced echocardiography, cardio-MRI and cineventriculography.
Depicted are images from the respective end diastole (top row) and end systole (bottom row).
Detection of regional wall motion abnormalities is an essential element in the diagnosis of coronary heart disease (CHD) [5].

Segmental perfusion abnormalities usually result in a fixed or stress-induced disturbance of wall motion and wall thickening. Detection of such wall motion abnormalities requires a clear demonstration of all cardiac segments in the different standard sectional planes [12].

During stress echocardiography, rapid documentation of all image planes is mandatory, in particular at higher stress levels (Fig. 15) [5].

Fig. 15:
Stress echocardiography without contrast agent and after administration of SonoVue®.
The top row shows the images at rest, with end-systolic frames from apical 4-chamber and 2-chamber views. The bottom row shows the corresponding images during peak stress. The impaired contractile function under stress is clearly better visible with SonoVue® (right square) compared to the images without a contrast agent (left square).
With kind permission of Dr. Jung, Medical Polyclinic Innenstadt, Ludwig-Maximilians-University, Munich.
2. Macrovasculature (vascular imaging)

The standard method for imaging vessels in ultrasound is colour-coded duplex sonography. Based on a velocity-dependent identification of blood, the intravascular lumen is depicted as a colour-coded 2D-image, which presents an anatomical image of vascular structures.

Doppler enhancement

The physical limit of colour-coded duplex sonography is found at slow blood flow velocities and in small blood volumes [13]. In the first case blood-derived signals cannot be distinguished from tissue signals (which also show slight movements) and in the second case blood signals are obscured by background noise. SonoVue® enhances the echogenicity of the blood by approximately 30 dB [14], which means a 1000-fold increase in signal intensity.

The demonstration of weak Doppler signals can thus be improved considerably so that blood flow can still be identified or excluded in borderline situations. This leads to significantly better diagnostic accuracy for the detection of vascular abnormalities with Doppler sonography [15] (Fig. 16).

![Demonstration of blood flow in a lower leg artery with colour-coded duplex and spectral-Doppler sonography without (left) and with SonoVue® (right).](image)

After administration of SonoVue® the colour-coded image in the vascular lumen and the flow spectrum can be clearly depicted and assessed.
Transcranial sonography

Doppler signal enhancement has particular importance for transcranial sonography. Due to sound wave attenuation caused by passage through the cranial bone, an adequate Doppler signal cannot be obtained in about 20% of patients (insufficient bone window) [16] (Fig. 17).

Reliable diagnosis of a cerebrovascular occlusion (e.g. in the case of a stroke) based on a missing Doppler signal is not possible. Therefore use of an ultrasound contrast agent is recommended in all cases in which there is insufficient Doppler signal, especially if a vascular occlusion is suspected [17, 18].

The signal enhancement after administration of SonoVue® is usually so strong that over enhancement (colour blooming) often occurs immediately after administration. In such cases, reduction of the gain (colour amplification) and/or much slower injection of SonoVue® (fractionated administration) is recommended.

Fig. 17: Transcranial colour-coded duplex sonography (TCCS) for imaging cerebral arteries without (left) and with SonoVue® (right).
In this patient with a poor bone window, a Doppler signal is barely detectable without contrast enhancement. After administration of SonoVue® the segments of the intracranial arteries can be clearly depicted and assessed. While the distal middle cerebral artery (MCA) at the bottom of the picture is clearly visible, the signal for the proximal MCA is completely missing, demonstrating an occlusion of the MCA.
With kind permission of PD Dr. Allendörfer, Asklepius Clinic Bad Salzhausen.
CEUS angiography

Despite the improved demonstration of Doppler signals after administration of a contrast agent, the basic problem of colour-coded duplex sonography remains: the production of an anatomical image (vascular structure) from velocity-derived data [13].

The physical limitations of Doppler sonography (slow flow velocities, low flow volumes, inadequate angles, reduced spatial resolution) cannot be overcome by the contrast agent. However, a clearly more accurate representation of vascular structures can be obtained by direct (velocity independent) imaging of the contrast agent (CEUS angiography) [19] (Fig. 18).

Using this technique, even small vessels can be clearly delineated and depicted without any motion artefacts [20].

CEUS angiography is an excellent technique for the demonstration of local vascular pathologies and follow-up examinations during and after vascular interventions [21].

Studies using SonoVue® enhanced ultrasound angiography in comparison to CTA reveal a similar sensitivity and specificity for the diagnosis of aortic dissections [22] and detection of endoleaks following endovascular abdominal aortic aneurysm repair [23].

Fig. 18: Imaging of the carotid artery by means of power-Doppler sonography (left) and CEUS angiography with SonoVue® (right).

With colour-coded duplex sonography (CCDS) the vessel is clearly depicted and coded in colour, however the colour pixels somewhat exceed the vascular lumen and overwrite structures of the vascular wall (colour blooming and motion artefacts).

With CEUS angiography a substantially more accurate delineation of the vascular wall is obtained and a floating embolus can be depicted clearly in the carotid lumen.

With kind permission of Prof. Dr. Clevert, Clinic Großhadern of the Ludwig-Maximilians-University Munich.
Fig. 19: 
**Imaging of an abdominal aortic aneurysm after endovascular stent implantation (EVAR).**
Extravasation of contrast agent in the aneurysmatic sac is depicted with both CT angiography (top) and CEUS angiography using SonoVue®. With dynamic CEUS angiography extravasation of contrast agent can be depicted at the proximal as well as at the distal end of the stentgraft (longitudinal section mid).

With kind permission of Prof. Dr. Clevert, Clinic Großhadern of the Ludwig-Maximilians-University Munich.
3. Microvasculature – Imaging of tissue perfusion for assessment of the vascularization of focal lesions in liver and breast

SonoVue® is a purely intravascular contrast agent (blood pool contrast agent) which precisely follows distribution kinetics of red blood cells. The vascular supply of parenchymal tissue (vascularization) can therefore be assessed by monitoring the wash-in of the contrast agent (Fig. 20).

A high density of (intact) microvessels results in a strong intensity of contrast enhancement. The dynamic course of the contrast agent inflow and outflow (wash-in and wash-out) allows the assessment of microvascular blood flow within the parenchyma. Microvascular structure (vascular geometry) and density as well as the dynamic pattern of contrast enhancement are often altered in focal parenchymal lesions in a characteristic manner.

The assessment of these parameters is the basis for specific characterization of focal lesions in terms of viability, malignancy and type [24].

Assessment of perfusion – SonoVue® improves the demonstration of focal liver lesion vascularization and allows more specific characterization

Dynamic examination of the inflow and outflow of SonoVue® microbubbles in real time allows, in the early phase of contrast wash-in, the demonstration of small intraparenchymal vessels (vascularization), and thus an assessment of the vascular architecture of focal lesions. A short time later the contrasted blood fills also the parenchymal microvessels (capillary networks). These can no longer be discriminated as individual vessels against the enhanced background parenchyma.
An advantage of contrast enhanced sonography (CEUS) is the possibility for continuous examination during the entire enhancement period (dynamic real-time imaging). Conversely, in computer tomography (CT) and magnetic resonance imaging (MRI) generally only individual scans at a few pre-defined time points can be performed.

Liver

The liver has a dual blood supply from the hepatic artery and the portal vein. Due to the longer supply route, contrast agent coming through the portal vein arrives later than contrast agent coming through the hepatic artery; therefore enhancement of the parenchyma can be allocated to each of the two vascular systems (arterial and portal-venous phase). In healthy liver parenchyma most of the blood supply comes from the portal vein (Fig. 21).

The temporal and spatial course of parenchymal enhancement allows the characterization of focal liver lesions. Crucial assessment criteria are:

- degree of vascularization (hyper-, iso- or hypo-vascularized compared to normal liver)
- vascular architecture (e.g. spoke-and-wheel type, basket type, peripheral-nodular)
- temporal dynamics (fast / slow, early / late)

Focal liver lesions have characteristic enhancement patterns, which are the basis for the determination of malignancy. Although enhancement patterns sometimes overlap across different types of focal lesion, in most cases the enhancement pattern observed allows the definite diagnosis of the lesion type (Fig. 22, 23).

The enhancement patterns of different focal liver lesions following the injection of a contrast agent have been described in detail in the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [24]. These guidelines also contain recommendations for the examination procedure and the necessary instrumentation of the ultrasound machine.
Fig. 22:
Enhancement pattern of a focal nodular hyperplasia after injection of SonoVue®.
In the early arterial phase the stellate vessels originating from the central artery are clearly visible. A few seconds later the lesion is completely and intensely enhanced, indicating a strong arterial blood supply. In the late phase the lesion shows no early wash-out of the contrast agent, indicating a conserved portal-venous blood supply – a sign of the benign character of the lesion.

With kind permission of Dr. Stock, Clinic Rechts der Isar of the TU Munich.
Fig. 23:
Enhancement pattern of metastases from colon carcinoma after injection of SonoVue®.
Clear enhancement can be seen in the early arterial phase, especially in the rim area of the lesion. In the portal-venous phase and notably in the late phase the lesion shows increasing wash-out of the contrast agent. This is due to absent portal-venous blood – and is a sign of the malignant character of the lesion.
With kind permission of Prof. Dr. Wermke, Charité, Campus Mitte, Berlin.
In the scheme below typical criteria of the most important types of focal liver lesions are summarised (Fig. 24).

![Diagram of liver lesions enhancement patterns](image)

In a large multi-centre study of the German Society for Ultrasound in Medicine (DEGUM) involving 1349 patients the enhancement patterns of focal liver lesions were assessed after SonoVue® administration. Determinations were made of how often the individual characteristic criteria of different lesion types could actually be detected [26].

Fig. 24: Schematic illustration of the enhancement pattern of focal liver lesions in comparison to surrounding normal liver tissue. The architecture of the supplying vessels as well as the pattern and temporal course of the enhancement allows the assessment of malignancy and in many cases also a definite diagnosis of the lesion type [25].
In general, the enhancement patterns found at CEUS are similar to those found at contrast-enhanced CT and contrast-enhanced MRI (Fig. 25). Primary liver tumours are characterised by arterial hyperenhancement due to formation of tumour-specific vascularisation (neoangiogenesis) and liver metastases are characterised by portal-venous and late-phase contrast wash-out due to lacking portal-venous blood supply.

Nevertheless, some differences related to the different distribution profiles of the contrast agents used need to be considered for accurate image interpretation (the microbubbles of ultrasound contrast agents have a purely intravascular distribution, while the usual iodine-containing contrast agents used in CT and the gadolinium-containing contrast agents used in MRI distribute throughout the interstitial fluid).

The altered vascularization of focal liver lesions visible in CEUS allows for improved lesion characterisation, e.g. of liver metastases. Liver metastases can be characterised reliably in the late phase as contrast defects in a well-enhanced liver parenchyma. The duration of the late phase is sufficient (about 4–6 minutes) to examine the whole liver (Fig. 26).
The DEGUM multi-centre study also investigated the reliability of focal liver lesion characterization on CEUS in comparison to a reference standard (histology or CT and/or MRI).

After SonoVue® administration, 723 / 755 malignant lesions (sensitivity 95.8%) and 476 / 573 benign lesions (specificity 83.1%) were classified correctly [27]. The sensitivity and specificity of CEUS were significantly better than with non-contrast B-mode- and colour-duplex sonography and were comparable to findings from computed tomography (CT) [28] and magnetic resonance imaging (MRI) [29] (Fig. 27). The high accuracy of SonoVue® for the characterization of focal liver lesions has been confirmed by other large multi-centre studies [30-34].

### Total population:

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### Subset: patients with histological confirmation (n = 1006)

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### Subset: patients with CT and/or MRI and final histology as reference standard (n = 227)

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<td>SonoVue®</td>
<td>94.0 %</td>
<td>82.9 %</td>
<td>90.3 %</td>
<td>91.6 %</td>
<td>87.5 %</td>
</tr>
<tr>
<td>CT</td>
<td>90.7 %</td>
<td>81.6 %</td>
<td>87.2 %</td>
<td>91.5 %</td>
<td>80.0 %</td>
</tr>
<tr>
<td>MRI</td>
<td>83.0 %</td>
<td>71.4 %</td>
<td>79.0 %</td>
<td>84.6 %</td>
<td>69.0 %</td>
</tr>
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</table>

![Fig. 27: Results of the DEGUM multi-centre study on the characterization of focal liver lesions with SonoVue®.](image)

Graphical representation of the accuracy of CT, MRI and CEUS with SonoVue® from the subgroup of 227 patients out of the DEGUM study (see tables above) having CT and/or MRI as comparator as well as final histology as reference standard. SonoVue®-enhanced ultrasound resulted in the highest diagnostic accuracy of all 3 imaging modalities, if compared to histology as gold standard.
CEUS is also helpful for the characterization of non-neoplastic focal liver lesions. In patients with focal pain or blurred parenchymal texture, solid and liquid focal lesions (focal oedema, contusion or laceration) can be characterised and focal haemorrhagic lesions can be diagnosed with high sensitivity [35-37] (Fig. 28).

Fig. 28:  
Characterisation of a focal liver lesion with blurred parenchymal texture

In the B-mode image (left) a blurred shadow can be seen below the liver capsule. Free fluid cannot be clearly detected. With CEUS using SonoVue® (right) a clearly delineated hematoma can be characterised between the liver parenchyma and the liver capsule with a clearly visible laceration in the liver parenchyma. At the time of the examination no microbubbles come out of the tissue laceration, indicating the absence of blood flow (no active bleeding present).

With kind permission of Dr. Thorelius, Herlev Hospital Copenhagen, Denmark.
The vascularisation within focal liver lesions can be assessed quantitatively using a dedicated quantification software (e.g. VueBox™).

When contrast is used to enhance the diagnostic performance of ultrasoundography, modern image processing techniques allow the quantitative assessment of signal changes over time in selected regions of interest. Quantification of the microcirculation of the lesion is therefore possible, opening the way for more reliable and reproducible analysis [38, 39, 40] (Fig. 29).

![Fig. 29:](image)

**Quantitative evaluation of contrast enhancement in the GIST metastasis**

Reduced contrast uptake after the start of Imatinib therapy (blue) compared to the situation before therapy (red) is clearly visible, indicating decreased tumour perfusion. Before therapy, the peak enhancement inside the tumour was over 1,500 relative intensity units (a.u.) and the area-under-the-curve (AUC) amounted to 39,014. Seven weeks after the start of Imatinib therapy the tumour showed clearly reduced contrast uptake with a peak enhancement of only 550 relative intensity units and an AUC of 7,490.
Breast – SonoVue® allows the depiction of focal lesion vascularization in the breast

Breast ultrasound requires the use of high-frequency transducers. Historically the available transducers produced only low quality ultrasound contrast enhancement in the contrast mode.

Examination of focal breast lesions was possible only by using contrast-enhanced colour Doppler sonography (CCDS). Today high-frequency transducers are available that are able to detect small amounts of contrast agent in the contrast-specific mode (Fig. 30, 31).

Even though the characterization of focal breast lesions based on contrast enhancement is more difficult compared to focal liver lesions, the enhancement pattern can contribute valuable information for the assessment of breast tumour malignancy [41,42].
The wash-in of SonoVue® in breast tumours seems to correlate with the density of microvessels in the tumour [43]. Future studies need to verify if this correlation can be used for the assessment of neoadjuvant therapies with anti-angiogenic drugs [44].

Health economy and cost-effectiveness

Besides the diagnostic performance and clinical value, health economical and cost aspects of diagnostic examinations are becoming more and more important. In times of limited resources in health care systems all over the world the costs of a medical procedure have to be justified in relation to the (expected) clinical benefit. First pharmaco-economic assessments have already been performed for contrast-enhanced ultrasound with SonoVue® to demonstrate the cost effectiveness. Although the results of such pharmaco-economic assessments are strongly related to national (or even regional) healthcare systems, they can give an idea on the cost efficiency compared to alternative imaging examinations.

In several countries an independent assessment system for healthcare products and services is established, assessing the impact on healthcare budgets and patient benefit. Based on these assessments, recommendations are given for the implementation and reimbursement of these products and services. These assessments include calculations of incidence and prevalence of the disease intended to treat, impact on the health status and quality of life of the patients as well as costs for procedures, patient management and staff training.

One example of such a healthcare economy assessment organisation is the National Institute for Health and Clinical Excellence (NICE) in the UK. In 2012, the NICE issued a guideline on the use of SonoVue®-enhanced CEUS in liver imaging [45], giving recommendations for the implementation of CEUS in the routine diagnostic workflow for the assessment of focal liver lesions. In particular, this guideline provides the following recommendations.
• Contrast-enhanced ultrasound with SonoVue® is recommended for investigating potential liver metastases in adults:
  - if contrast-enhanced computed tomography (CT) is not clinically appropriate, is not accessible or is not acceptable to the person,
  - and in whom an unenhanced ultrasound scan is unsatisfactory and contrast is needed for further diagnosis.

• Contrast-enhanced ultrasound with SonoVue® is recommended for characterising focal liver lesions in adults whose cirrhosis is being monitored:
  - if contrast-enhanced magnetic resonance imaging (MRI) is not clinically appropriate, is not accessible or is not acceptable to the person,
  - and when unenhanced ultrasound scan is inconclusive.

For the detection of coronary artery disease (CAD) ECG usually is the first choice but often non-diagnostic. Echocardiography or Nuclear Medicine Imaging (SPECT) is recommended in case of non-diagnostic ECG [46]. Although non-invasive imaging of (inducible) ischemia is clearly recommended before myocardial revascularisation by recent guidelines [47], diagnostic coronary angiography is often the definitive examination to make the diagnosis of CAD and stratify patients for treatment.

Echocardiography at rest and under stress should be the preferred diagnostic examination in these patients, with good diagnostic accuracy, high patient safety and favourable costs. However, insufficient image quality resulting in non-diagnostic echocardiograms is one of the major limitations resulting in high numbers of SPECT and diagnostic cath lab examinations [48, 49].
SAFETY

SonoVue® is an ultrasound contrast agent which was first approved in 15 countries of the European Union (EU) in 2001. Since then it has been administered to over 2.7 million patients.

SonoVue has an established safety profile, with a low rate of adverse events. [50].

Most of the reported adverse events following the administration of SonoVue® are mild, transient, and resolve spontaneously without sequelae.

In rare cases hypersensitivity reactions may occur, which in extreme cases can be life-threatening or even fatal. Therefore adequate precautionary measures must be taken to treat such hypersensitivity reactions.

Toxicological characteristics

Standard pre-clinical studies on safety pharmacology, genotoxicity and reproductive toxicity have revealed no particular risks of SonoVue® for humans. SonoVue® is not nephrotoxic and does not impair thyroid function.

Experimental studies on animals revealed no harmful effects on pregnancy, embryonic/fetal development, parturition or postnatal development.

Data from clinical studies

To date 75 clinical studies on SonoVue® have been conducted in 6307 volunteer subjects and patients (status: September 2013).

In these studies 331 (5.2%) out of 6307 subjects (healthy volunteers and patients) experienced undesirable effects (UE) with a possible causal relationship to SonoVue®. Most of these UE were of mild intensity and resolved spontaneously.

Twenty-eight participants experienced at least one serious UE (0.4%). In 23 cases (incl. 9 deaths) the serious UE was not causally related to SonoVue®. In two participants the causal connection was unknown (chest pain with lowered blood pressure and elevated ST in ECG and sensomotoric paresis in right arm); however subsequent information received from the investigator in one case indicated that the UEs were clearly related to concomitant medication, and was thought to be due to underlying disease for the other respectively. One serious UE (facial flushing with vasovagal syncope) was reported for a third participant which was thought to be of probable relation to SonoVue®, however, subsequent information received from the Investigator indicated that the UE was not directly related to SonoVue® administration. For the remaining 2 participants, the causal role of SonoVue® could not be ruled out.
The most common side effects (≥ 0.5% of total reporting) in patients (n = 6179) were:

<table>
<thead>
<tr>
<th></th>
<th>related</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache</td>
<td>0.9 %</td>
<td>2.0 %</td>
</tr>
<tr>
<td>nausea</td>
<td>0.6 %</td>
<td>0.9 %</td>
</tr>
<tr>
<td>chest pain</td>
<td>0.2 %</td>
<td>0.8 %</td>
</tr>
<tr>
<td>chest discomfort</td>
<td>0.3 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>injection-site pain</td>
<td>0.3 %</td>
<td>0.4 %</td>
</tr>
</tbody>
</table>

Data from market experience

To date SonoVue® has been administered to over 2.7 million patients in routine clinical practice (status: September 2013, calculated on the basis of packages sold). Clinical practice has confirmed the good tolerability of SonoVue®.

Since its introduction to the market in 2001, adverse events have been reported in 824 patients in total (0.0295%). In 346 patients serious adverse events occurred (0.0124%), most of which were hypersensitivity reactions (n = 257, < 0.01%).

In total, a serious hypersensitivity reaction requiring immediate emergency treatment can be expected in about 1/10,000 patients. Accordingly trained personnel and the necessary medical equipment, including emergency medications, must be readily available when SonoVue® is administered.

Since its introduction to the market, a total of 13 patients who reported UEs had fatal outcome following the administration of SonoVue®. The association of the deaths with SonoVue® administration could not be ruled out in 8 of these cases. These patients were all severely ill with a high spontaneous risk for fatal outcome. In addition to these 13 patients, 5 other patients experienced serious adverse events after the administration of SonoVue® and subsequently died due to their underlying disease.
The total incidence of serious side effects with SonoVue® since its introduction to the market has been constant at about 0.01%.

According to current product information SonoVue® is contraindicated for use in patients with known hypersensitivity to sulphur hexafluoride microbubbles or to any of the excipients of SonoVue® as well as in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure > 90 mmHg), uncontrolled systemic hypertension, or acute respiratory distress syndrome. In these patients additional complications such as anaphylactoid reactions may arise, which could complicate the treatment of the associated symptoms. SonoVue® should not be used in combination with dobutamine in patients with conditions suggesting cardiovascular instability where dobutamine is contraindicated.

No data from clinical studies are available for pregnant women. Although data from animal experiments do not indicate any harmful effects, caution should be exercised when administering SonoVue® to pregnant women. It is not known if sulphur hexafluoride is excreted in human milk. Therefore, caution should also be exercised when SonoVue® is administered to breast-feeding women. The safety and innocuousness of SonoVue® in patients under 18 years old has not been established in clinical studies up to now. According to current product information SonoVue® should not be used in these patients.

Further product and safety information and details concerning indications and contraindications can be found in the current product information (Summary of Product Characteristics) for SonoVue® [50].
REFERENCES


(45) NICE diagnostics guidance 5: SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast enhanced ultrasound imaging of the live. Issued: August 2012 (www.nice.org.uk/idg5)


(50) SonoVue Summary of Product Characteristics (SPC). EMEA/MC/000303