

# Identification of Early Complications Following Liver Transplantation using Contrast Enhanced Ultrasound (CEUS). First Results

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## Abstract

**Aim:** Identification of complications following liver transplantation using CEUS in comparison with MRI, CT, DSA or US. The study evaluated whether CEUS could confirm the preliminary diagnosis or even provide additional information, relevant for the therapeutic strategy.

**Methods:** Retrospective evaluation of 23 patients (age 1 – 72 years) following liver transplantation. CEUS was used as an additional diagnostic method when obscure diagnostic findings occurred in US, CT, MRI or digital subtraction angiography (DSA). Fundamental B-scan, Color Doppler imaging and CEUS were performed in all patients by an experienced examiner using a multifrequency convex transducer (1-5 MHz). After a bolus injection of up to 5 ml SonoVue® digital raw data was stored as cine-loops.

**Results:** In all 23 patients, the pathological features and suspected diagnostic findings identified in the other imaging modalities could be confirmed using CEUS. In 12/23 patients, new clinically relevant findings were detected. In 22 patients, the diagnosis of CEUS was confirmed during surgery (4), DSA (6), follow-up CEUS (6), CT (2), MRI (5) and colonoscopy (1). In 4 patients, stenosis of the portal vein or hepatic artery were found, in 3 patients normal perfusion of the liver parenchyma and the hepatic vessels was diagnosed, 1 patient showed a local cholestasis and 1 patient intestinal bleeding. In 3 patients, a definite diagnosis of a benign tumor was possible. **Conclusion:** These first results show that CEUS can provide additional, clinically relevant information in patients with early complications following

liver transplantation. Thus, an early application within the diagnostic course seems useful.

## Key words

Contrast enhanced ultrasound (CEUS) – liver transplantation – early complications.

## Introduction

Important advances in operative techniques, postoperative care, and immunosuppression over the last 20 years have significantly improved patient outcomes following liver transplantation. However, these complex interventions are still associated with various complications that contribute to patient morbidity and mortality.

Studies have reviewed the long-term outcomes after liver transplantation and reported that approximately 5 to 30% of recipients are developing vascular or biliary complications following transplantation [1]. It is known that these complications might occur early (<3 months) or late (>3 months) after transplantation and can result from imperfect surgical techniques or due to protracted ischemic or immunogenic injury.

Due to the high rate of vascular complications, such as portal vein thrombosis, hepatic artery stenosis and thrombosis or ischemia, a close monitoring of the anastomotic vessels, the tissue perfusion and the microcirculation is necessary. Hepatic artery thrombosis is reported to occur in 4 to 15% and is generally more frequent after pediatric liver transplantation [2, 3]. Portal vein thrombosis complicates up to 7% of orthotopic liver transplantation and, equally in hepatic artery thrombosis, may be fatal for both the allograft and the patient [4].

The best available imaging method in case of an emergency is ultrasound (US) including Color Coded Doppler Sonography (CCDS) and Power Doppler (PD), especially in intensive care units. These techniques are established following renal transplantation [5, 6], however,

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examinations following liver transplantation can be demanding. Especially the interpretation of minor changes of the hemodynamic parameters, such as differentiation of structural abnormalities in the hepatic artery from low-flow hepatic arterial perfusion, might be difficult.

However, contrast enhanced ultrasound (CEUS) has become increasingly available in recent years. Using high resolution multifrequency transducers, CEUS allows a dynamic coverage of the microcirculation, from early arterial until late parenchymal period. According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), a dynamic evaluation of the organ microcirculation following renal transplantation is recommended [7].

The aim of this study was to evaluate the value of CEUS regarding the identification of acute and subacute complications following liver transplantation, compared to other imaging modalities such as contrast enhanced computed tomography (ceCT), contrast enhanced magnetic resonance imaging (ceMRI), digital subtraction angiography (DSA) and conventional non-contrast ultrasound (US).

## Material and methods

### Study design

From December 2010 until February 2012, 23 patients (10 male, age 1 – 72 years, mean 39.8 years) with clinical distinctive features following liver transplantation were included in this retrospective study. Before the procedures were conducted, written informed consent was obtained from each patient for MRI, CT and CEUS after the nature of the procedure was fully explained. Permission of the local Ethical Board was obtained for this study.

Exclusion criteria of this study were contraindications for application of contrast agent, such as impaired renal function, pre-existing severe allergic reactions and decompensated cardiac failure.

### Imaging techniques

#### *ceMRI*

MRI was performed on a 1.5-T whole body scanner (Avanto, Siemens Medical Solutions, Germany) equipped with a high-performance gradient (Quantum) system (maximum gradient strength, 30 mT/m; slew rate, 125 T/msec). A combination of the standard body phased-array coil with spine array coils was used for signal reception.

For MRI, 0.1 ml/kg body weight of the liver specific contrast agent Primovist® (Bayer HealthCare AG, Germany) was injected intravenously. T1-weighted VIBE (Volumetric Interpolated Breathhold Examination) transversal dynamic scans were acquired 20, 40, 120 and 600 sec after application of Primovist®.

In patients under the age of 18 years, 0.1 mmol/kg body weight Dotarem® (Guerbet, France) was injected intravenously. T1-weighted VIBE transversal dynamic scans were acquired 20, 40 and 120 sec after application of the contrast agent.

#### *ceCT*

The CT diagnosis was based on a triphasic contrast enhanced protocol using a Dual Source scanner (SOMATOM Definition Flash, Siemens, Germany), slice thickness 5 mm axial and 3 mm coronal MPR). The contrast bolus consisted of 1ml/kg Ultravist 370® i.v. (Bayer HealthCare AG, Germany) administered at a flow rate of 4 ml/s using a bolus trigger technique (positioning of the respective region of interest - ROI - in the abdominal aorta), threshold 100 Hounsfield Units (HU). The arterial phase started with a delay of 20-40 sec., the portal-venous phase with a delay of 60-70 sec. and the late phase >120 sec after reaching the threshold.

#### *US and CEUS*

Ultrasound examinations were performed by one experienced ultrasound examiner [more than 5000 examinations each year for more than 10 years] using a multifrequency convex transducer (1–5 MHz, LOGIQ E9, GE, USA).

First, a B-Scan sonography in sweep technology of the whole liver was conducted. Color Coded Doppler Sonography (CCDS) and Power Doppler (PD) ultrasound were used to evaluate native vascularization. Flow parameters were adjusted to the lowest possible pulse repetition frequency (PRF, < 1000 Hz) and the best possible color imaging without blooming artifacts.

The dynamic CEUS with separate bolus injections for each liver lobes of 1 - 2.4 ml SonoVue® (BRACCO, Italy) or less in children was conducted with a reduced mechanical index (MI < 0.2) applying the contrast harmonic imaging technique (CHI) using the true agent detection mode for real-time evaluation of the contrast-agent enhancement. A maximum of 5ml SonoVue® i.v. was administered through a 20-18 G peripheral cubital cannula, followed by a bolus injection of 10 mL NaCl. One turn of the scanner head examined the whole liver during intermittent breath holding using the sweep technique. The complete data of the contrast-agent examination was recorded up to 5 min. The second generation contrast medium SonoVue® is approved for human use within the European Union. In patients under 18 years, the use of SonoVue® was off-label. However, a recent study evaluated the effects of the US contrast agent upon children and found no adverse effects [8].

The liver microcirculation was evaluated continuously from an early arterial phase (beginning 15 sec after contrast application) until a late parenchymal phase (< 2 min). Special impact was placed on whether the microcirculation in the early post-transplantation stage was normal, delayed, diminished or not detectable.

#### *DSA*

In 1 patient, the procedure was performed via a common femoral artery approach in local anaesthesia using Seldinger technique and a 4-French angiographic catheter (Vertebral, Cook, USA) was positioned in the coeliacal trunc. A diagnostic angiography (Axium Artis, Siemens, Germany) was performed to visualize the suspected arterio-portal fistula

and the anastomotic vessels. The fistula was sealed using various Helix Axium coils (ev3 Neurovascular, USA).

In 3 patients, an ultrasound guided, transhepatic puncture of the portal vein was performed. Following a diagnostic angiography (Axium Artis, Siemens, Germany) and evaluation of the pressure difference between the distal and proximal section of the portal vein, 2 patients underwent a stent angioplasty and 1 patient a balloon angioplasty with good results.

### Imaging analysis

All CT, MRI, US, DSA and CEUS examinations were analyzed by two experienced radiologists in consensus. For each modality used, each observer recorded the diagnostic findings. Furthermore, the image quality was documented on a four point scale: 1 - excellent, 2 - minor diagnostic limitations, 3 - major diagnostic limitations, 4 - non-diagnostic.

Imaging modalities (ceCT, ceMRI, DSA, US, CEUS) were evaluated using a picture archiving and communication system (SyngoImaging; Siemens) and the data analyzing hard-/software of the ultrasound system (LOGIQ E9).

### Statistical analysis

All results were presented as the mean  $\pm$  standard deviation (SD). For data analysis, SPSS software (version 16.0, SPSS Inc., Chicago, USA) was used.

We evaluated, whether the pathological features and suspected diagnostic findings identified in the other imaging modalities (MRI, CT, US and DSA) could be confirmed using CEUS. Also, it was assessed if the CEUS could provide additional relevant information that might cause a change of the therapeutic strategy.

## Results

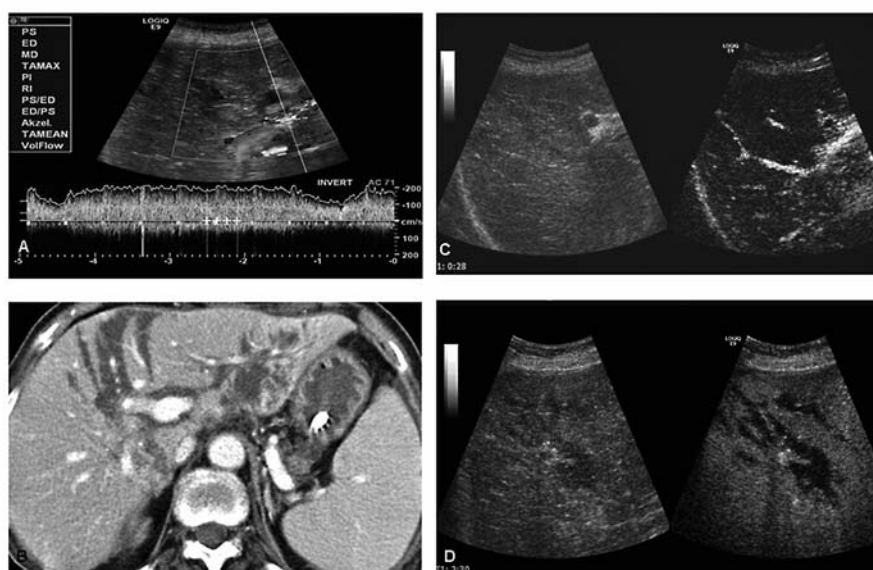
Twenty-three consecutive patients (10 male, age 1 – 72 years) following liver transplantation were included in the study. No adverse reactions were experienced in any of the patients who received Primovist®, Dotarem®, Ultravist 370® and SonoVue®.

The preliminary imaging modalities used were ceCT (12 patients) (Fig. 1), ceMRI (5 patients) (Fig. 2) and conventional non-contrast US (6 patients). Each patient underwent CEUS within 1 – 8 weeks following liver transplantation. In all patients, the pathological features and suspected diagnostic findings identified in the other imaging modalities could be confirmed using CEUS (100%).

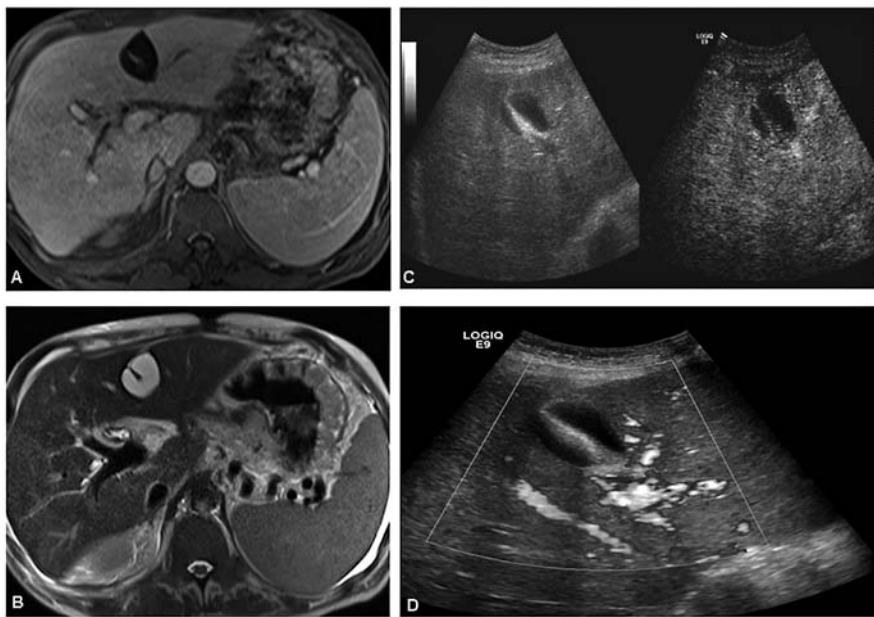
The underlying diseases are shown in Table I. In 12 out of 23 patients (52.17%), new clinically relevant findings were detected using CEUS. In 4 patients, a stenosis of either the portal vein or hepatic artery was found, in 3 patients normal perfusion of the liver parenchyma and the anastomotic arterial and venous vessels was diagnosed. One patient showed local cholestasis in the liver segment IV and 1 patient suffered sigmoidal bleeding. In 3 patients, a definite diagnosis of benign lesions with characteristic features (hemangioma and cyst) following liver transplantation was possible.

In 22 out of 23 patients (95.6%), the diagnosis of CEUS was confirmed during surgery (4), DSA (6) (Fig. 3), follow-up CEUS (6), CT (2), MRI (5) and colonoscopy in case of the sigmoidal bleeding.

All patients underwent follow up CEUS examinations up to 9 months after liver transplantation. If an interventional treatment was carried out in patients with arterial or venous



**Fig 1.** 63-year old female patient following liver transplantation. A: Color Coded Doppler Ultrasound revealed a dramatically increased flow velocity of the portal vein (up to 200cm/s) with central aliasing, marking a profound stenosis. B: CT scans showed a diminished parenchymal perfusion of the left liver segments with no evident graft vessel occlusion. C/D: CEUS confirmed the portal vein stenosis in the anastomotic region and the corresponding diminished parenchymal perfusion.



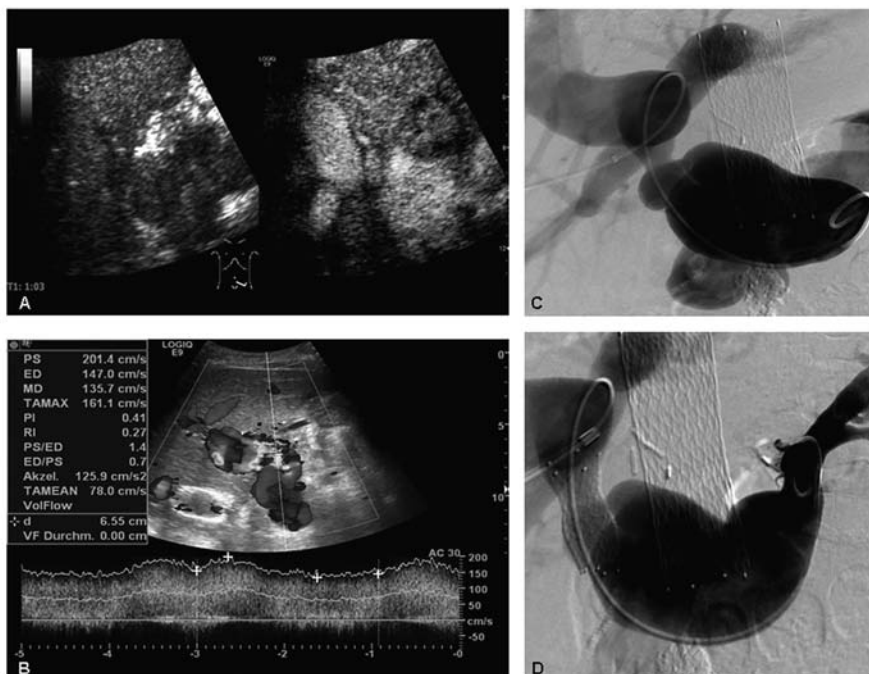
**Fig 2.** 47- year old male patient. A/B: T1-weighted VIBE following contrast application, T2 haste scans revealed a cystic lesion following liver transplantation with septations but no apparent enhancement. Primary diagnoses were either a complicated cyst or bilioma. C/D: CEUS and Power Doppler confirmed the septated cystic lesion which was found to be located within the liver with no detectable vascularization.

thrombosis, no residual findings were found in the follow up control.

In all 23 patients (100%) CEUS was feasible. The image quality in all modalities was excellent or had only minor

diagnostic limitations (1–2 in CEUS SD 0.476, 1–2 in ceMR SD 0.527, 1-2 in ceCT SD 0.426, 1-2 in non-contrast US SD 0.534, 1-2 in DSA SD 0.408).

In 3 out of 12 patients (25%) with a preliminary ceCT



**Fig 3.** 58-year old male patient. A: CEUS confirmed the diagnosis of the portal vein stenosis in the anastomotic region without thrombosis. Poststenotic dilatation of the portal vein. Parallel display of B-Scan (left) and CEUS (right). B: Color Coded Doppler Sonography (CCDS) shows a high systolic and diastolic flow with aliasing within the portal vein, consistent with a hemodynamically relevant stenosis. C/D: The patient was referred to angiography and underwent a stentangioplasty with good clinical results.

**Table I.** Evaluation of the new clinically relevant findings relative to the imaging method used

New findings	CEUS	ceCT	ceMRI	US
Normal perfusion	3	0	0	3
Benign lesion	3	2	1	0
Portal vein thrombosis/ stenosis	2	0	2	0
Hepatic artery stenosis/ occlusion	2	1	0	1
Local cholestasis	1	0	0	1
Sigmoidal bleeding	1	0	0	1

scan, new clinically relevant findings were detected using CEUS. As for patients with a preceding ceMRI or conventional non-contrast ultrasound, in 3 out of 5 patients (ceMRI – 60%) and in 4 out of 6 patients (US – 83.3%) new findings were diagnosed.

## Discussion

Since CEUS is increasingly available, a dynamic evaluation of the microcirculation from early arterial to late venous phase following liver transplantation is possible. As previous studies have shown, CEUS offers an important diagnostic potential for pre-operative evaluation of the donor organ and post-operative detection of complications [9-12].

The aim of this study was to identify acute and subacute complications following liver transplantation, comparing CEUS with other imaging modalities such as ceCT, ceMRI, DSA and fundamental B-Scan and non-contrast Doppler ultrasound (US). Our results indicate that CEUS seems to be especially helpful compared to a preliminary diagnosis with ceMRI or fundamental B-Scan with non-contrast Doppler Sonography alone. The differences regarding ceCT and ceMRI can be explained by the fact that most of the patients examined with ceMRI were children aged 4 years or less with very small vessels with associated modifications of the normal vessel anatomy, making a definite evaluation rather difficult.

Ultrasound contrast agents are stabilized microbubbles composed of galactose that contain air [(first generation contrast agents, e.g. Levovist® (Schering, Berlin, Germany)) or other gases, such as sulphur hexafluoride (SF<sub>6</sub>) [(second-generation contrast agents, SonoVue® (Bracco, Milan, Italy)) using the low mechanical index (MI) technique of contrast harmonic imaging (CHI). Membranes of second-generation contrast agents consist of phospholipids that serve as true blood-pool agents, which enable continuous real-time contrast sonography over an extended period of time. After being injected intravenously, the microbubbles are transported with the bloodstream and merely spread intravascularly. Thus, an artefact-free display of the vascular architecture that is independent of blood flow velocity and has a high spatial resolution, is possible [13].

Via contrast agents, which intensely enhance intravascular signals, CEUS has been used in various studies to evaluate

hemodynamic changes that occur in liver cirrhosis [14, 15]. The benefit of CEUS is that it allows a continuous, dynamic evaluation of the microcirculation of the parenchyma from early arterial to late portal venous period. Thus, subacute focal areas with diminished microvascularization (transplant rejection) can be distinguished from wedge shaped defects (infarction), round areas of absent microvascularization (possible septic embolism), arterio-venous malformations and fistulas, vascular stenosis and tumor lesions, necrotic parenchyma or abscesses.

Subtraction techniques using Pulse Inversion Harmonic Imaging (PIHI) reduce motion and pulsation artifacts compared to CCDS and PD. Also, there are no blooming artifacts or angle deviation. With low transmission power and reduced mechanical index (MI < 0.16), the oscillation of the microbubbles of the US contrast agent is used for evaluation of the capillary microcirculation. A selectively applied energy impulse of up to 100 % can be employed for evaluation of the flash-replenishment kinetics to determine the capillary microcirculation with the possibility of a quantitative time intensity curve (TIC)-analysis [16-18].

Due to the absence of flow artifacts, CEUS in combination with 3D-imaging is particularly suitable for display of arterial and venous stenosis and fistulas. Infarction and necrosis, tumor lesions, hematomas and acute bleeding, inflammation and abscesses are confidently identified using CEUS. As well as the measuring of hemodynamic parameters using CCDS, the evaluation of marginal changes associated with transplant rejection is possible. However, a final assessment is not feasible by imaging methods alone and a biopsy is necessary, though CEUS could be helpful for the detection of areas with diminished perfusion.

The limitations of this study are the small number of patients and a rather heterogeneous patient population. Prospective studies are necessary in order to ascertain the diagnostic reliability of CEUS compared to established methods for the diagnosis of acute and subacute complications following liver transplantation.

## Conclusion

Our study shows that CEUS can provide additional, clinically relevant information in patients with acute and subacute complications following liver transplantation. Thus, an early application within the diagnostic course seems useful.

## Conflicts of interest

None to declare.

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