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# Contrast-enhanced ultrasound using sulfur hexafluoride is safe in the pediatric setting

Torres, Alvaro; Koskinen, Seppo K; Gjertsen, Henrik; Fischler, Björn

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**Contrast-enhanced ultrasound using sulphur hexafluoride is safe in the pediatric setting**

## **Abstract**

**Background:** Contrast-enhanced ultrasound (CEUS) by using sulphur hexafluoride microbubbles is not licensed for use in children, but its off-label use is widespread.

**Purpose:** To outline our experience with the off-label use of CEUS in children, specifically with regards to safety.

**Material and Methods:** We retrieved all records of 10681 patients under 18 years of age who underwent abdominal ultrasound (US) January 2004– December 2014. We then identified those who underwent an abdominal CEUS using sulphur hexafluoride microbubbles. Electronic patient charts were used to verify the indication for contrast agent, dose, possible adverse effects as well as information on patient height, weight and age

**Results:** We identified 183 patients (mean age 11 yrs, range 0.1-18) who underwent a total of 287 CEUS exams. 46% of all exams were performed on the native liver, 31% on

a transplanted liver and 23% on other organs. The indications were; “circulatory status?” (40%), “characterization of lesion?” (40%) and miscellaneous (20%). Mean contrast dose was 2,3ml (range 0.1-8.1). No immediate adverse effects were recorded. One patient experienced itching the day after, but this was considered to be a reaction to concomitantly administered fentanyl.

**Conclusion:** The use of intravenous ultrasound contrast seems safe in patients under 18 years of age and our results do not support the current practice to restrict the use of CEUS in children.

**Keywords:** : Pediatrics, Ultrasound, Contrast Agents-Intravenous, safety

## **Introduction**

Contrast enhanced ultrasound (CEUS) exams are performed by administering micro-bubbles into the circulation, thereby visualizing the regional blood flow in the examined organ.

In its earliest form, CEUS was accomplished by agitating vials of saline solution right before i.v. administration (1). Since then, the concept has evolved and the microbubbles have been stabilized and their size standardized. Sulphur hexafluoride microbubbles (SonoVue®, Bracco Imaging, Milan, Italy) is currently the most commonly used

contrast agent approved for CEUS. Currently this agent is registered in Europe for cardiovascular and liver indications and for the assessment of focal lesions in the breast (2). The diagnostic benefits and safety of adding a microbubble contrast agent to ultrasonography (US) imaging in adults are well established and CEUS is a widely used diagnostic technique (3 - 5). However, none of the available US contrast agents are licensed for intravenous (i.v.) use in children under the age of 18 years (2). Consequently, the use of CEUS in children is to be considered off-label and for this reason its use by individual physicians in their everyday practice is restricted.

The majority of pediatric studies on sulphur hexafluoride are on the use of intravesical administration for voiding urosonography (6). Conversely i.v. use of sulphur hexafluoride is not equally well and thoroughly studied (3, 6).

In our institution, we have used CEUS with intravenous administration of sulphur hexafluoride contrast agent in both adults and children for more than a decade.

This retrospective study was conducted with the aim to outline our experience regarding clinical indications as well as the safety profile of sulfur hexafluoride i.v. administration on pediatric patients.

## **Material and Methods**

We retrieved all records of 10681 exams on patients younger than 18 years who underwent any US investigation 2004- 2014. We then identified those who underwent an abdominal CEUS using sulphur hexafluoride. Electronic patient charts were used to verify the indication for the exam, dose, and possible adverse effects. Adverse effects were defined as any unexpected reaction that was not explained by other medication or better explained in other ways. When available, information regarding weight, height and administered contrast dose were also collected. Sulphur hexafluoride is delivered in 5 ml vials and the standard dosage for pediatric patients in our institution is to administer 0.1 ml/kg body weight, up to 24 kg. Patients weighing 24 kg or more are given the full dose of 2.4 ml. When needed, repeated doses were given. The institutional review board (IRB) approved this study.

## **Results**

Of the initial 10681 US exams, we identified 173 patients (mean age 11 yrs, range 0..1-18 yrs) who underwent a total of 287 CEUS exams. 134 (46%) of these were on the native liver, 92 (31%) on transplanted liver, 30 (10%) on the spleen, 21 (7%) on the kidney, and 16 (6%) on other organs (Table 1).

Anthropometric and dosage data for each subgroup are presented in Table 2.

For 27 of the 287 exams, no height data of the patient was available. For 15 exams, no weight information was available and for 51 exams no data on administered contrast dose was available.

36 patients were  $\leq 1$  year of age. 41 patients weighed 10 kg or less and 32 measured 75 cm in height or less. Previously known clinically significant allergies, as identified in the electronic patient chart system, are presented in Table 3.

The indications for the examinations are described in Table 4.

No adverse effects were observed in any of the patients. One patient experienced itching the day after, but this was considered to be a reaction to concomitantly administered fentanyl.

## **Discussion**

Our data show that a large number of children, including a significant proportion of very young and ill children, could safely undergo CEUS. Our results are fully in accordance with the available literature on the subject.

The advantages of using sulfur hexafluoride microbubbles in children are many. Sulphur hexafluoride is exhaled after the destruction of the microbubbles and the kidneys are not involved in the elimination of the substance. The substance has no known nephrotoxicity (5). Further, it does not contain iodine, thereby not having any effect on the renal nor on the thyroid functions, hence it avoids the potential risks associated with iodinated and gadolinium-based contrast media used in computed tomography (CT) and MRI, respectively (7,8).

So far, there is no data supporting the need for follow up blood test or too perform other investigations after CEUS.

Although sulphur hexafluoride is considered nontoxic it can be regarded as a foreign material by the immune system; therefore, a hypersensitivity reaction is possible (4). The incidence of a severe hypersensitivity reaction was reported in about 0,2 % in available literature regarding pediatric CEUS (3). The overall reported incidence of the hypersensitivity reaction was less than that occurring with the use of an iodine contrast agent in CT and was similar to that of the use of a gadolinium chelate contrast agent in MRI (9,10).

As anaphylactic reactions are known to occur, and almost exclusively occur in the first minutes after contrast administration, a patent i.v. line should be kept until the end of



the examination for safety reasons as well as to allow the possibility to repeat injections when indicated.

Contrast related safety issues aside- the fact that CEUS is radiation free is of great importance in the pediatric population, since children are found to be significantly more vulnerable to ionizing radiation than adults (11,12). CEUS is non-invasive and it also eliminates the need for sedation that is often required in pediatric magnetic resonance imaging (MRI).

In addition to reporting on adverse effects after the administration of US contrast our study showed that several different organs and clinical questions could be studied with CEUS. This also is in accordance to the available literature in the matter.

In children CEUS is most commonly used in the characterization of focal liver lesions. Other uses, supported by official guidelines and recommendations are the follow up of solid organ injuries after trauma, follow up after transplantation, therapy outcome evaluation of inflammatory bowel disease as well as multiple other indications (3, 13).

The diagnostic accuracy of CEUS in children has been evaluated in some studies and there has been a high concordance between CEUS and the reference-standard imaging method. Positive and negative predictive values have been very high. Especially, this applies in the evaluation of solid organ injuries following blunt abdominal trauma and in the characterization of indeterminate focal liver lesions (3).

In the adult population, studies have been made that show CEUS to be relatively cheaper or equal to the cost of CT and significantly cheaper than MRI in the evaluation of liver lesions (14-16). There is reason to believe that the results transfer to the pediatric population as well.

Although the potential uses and indications for CEUS are several there are practical limitations to take in to consideration. The most important one is probably the relative scarcity of medical practitioners with sufficient knowledge and experience to correctly perform and interpret these exams.

Among pediatricians, the fact that a large part of the medications administered to patients are used off-label, is widely acknowledged. This means that pediatricians administer drugs that are not officially licensed for use in children, but none the less have some descriptive evidence from literature (17) .The same situation seems to apply to sulphur hexafluoride microbubbles.

Whether this or other similar substances is going to receive official labeling in the near future, equivalent to that of adults, remains unclear. Until this happens physicians will have to base their decisions on available data and collective experience.

Recommendations regarding the use of, as well as potential risks associated with CEUS in both adults and children are thoroughly outlined in the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guideline publications from 2012 (5) as well as the publication by the Society for Pediatric Radiology (SPR) together with the International Contrast Ultrasound Society (ICSU) from 2013 (4). These, alongside with our own study and multiple other reports indicate the relative safety of CEUS in the pediatric population (3,4,13,18,19) as well as its diagnostic capabilities, especially when compared to alternative imaging techniques as CT or MRI (7,8,11,12).

A recent update is that Bracco Imaging® has received FDA approval for a sulfur hexafluoride microbubble contrast agent by the name of Lumason ®. It appears as this is a rebranding of the same molecule from Sonovue ®. One important fact about this approval is that it has been approved for use in children. However, it is only approved for liver diagnostics (20).

The release and extended indications of Lumason ® is an important step in the right direction and will in our opinion undoubtedly have an impact on clinical practice worldwide, leading to increased use of CEUS as an alternative to CT and MRI. However, much work is still needed in order to expand the licensing of the use of US

contrast agents to include more organ systems and thereby increase the indications for its use.

In reaction to the release of Lumason ® the EFSUMB has issued an update with regard to the off-label use of CEUS, emphasizing the evidence for its use in multiple organs, not only liver, and advocating its further development (13).

The strength of our study is that we included a relatively large number of patients. Moreover, we had access to chart notations from the clinicians in charge of the patients which allowed us to search for possible adverse effects with relative accuracy.

The limitations of our study are those associated with its retrospective nature, primarily the risk of missing some adverse reactions not noted by healthcare personnel in charge of the patient, alternatively noted but not associated to the administration of sulphur hexafluoride. However serious adverse effects are not likely to have been missed.

In conclusion, our results strongly suggest that sulfur hexafluoride can be safely used for a large number of pediatric indications.

### **Conflicts of interest**

The Authors declare that there is no conflict of interest

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Table 1. Main focus of CEUS exams

	Number of exams	%
Native Liver	133	45.4%
Transplanted Liver	92	31.4%
Kidney	21	7.2%
Spleen	30	10.2%
Miscellaneous	17	5.8%
<b>Sum</b>	<b>293</b>	<b>100%</b>

Table 2 Anthropometric and dosage data for pediatric patients who underwent CEUS.

	Native liver	Transplanted liver	Spleen	Kidney	Misc
Mean height (cm)	134.4	127.5	151.0	150.6	134.2
Median height (cm)	148.0	138.0	156.0	158.0	147.0
Range height (cm)	41-184	63-189	114-184	140-186	63-187

Mean	40.0	36.3	48.0	47.9	39.5
weight (kg)					
Median	40.0	34.0	48.0	48.0	40.0
weight (kg)					
Range	1.5-126	6-72	19-87	33-90	8-80
weight (kg)					
Mean dose	2.2	2.1	2.2	2.2	2.1
(ml)					
Median	2.4	2.4	2.4	2.40	2.4
dose (ml)					
Range dose	0.3-8.1	0.1-5	0.8-4	0.6-5	1.8-5
(ml)					

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Table 3 Reported known allergies in patients subjected to CEUS

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Known allergies (per patient)	
No allergies	149
Any antibiotic	11
Other prescription drugs	8
Food stuff	3
Blood products	1
Iodinated contrast	3

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Table 4. Indications for CEUS sorted by examined organ (number of exams)

	Circulatory status	Lesion characterization	Surveillanc e of known lesion	Miscellaneous
All organs	116	115	16	42
Native liver	15	78	14	28
Transplanted liver	73	15	2	2
Kidney	12	9	0	0
Spleen	18	11	0	2
Miscellaneous	0	5	0	12

