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ORIGINAL ARTICLE

Application of a second-generation US contrast agent in infants and children—a European questionnaire-based survey

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Abstract
Background No US contrast agent (US-CA) is currently licensed for use in children.
Objective To survey the off-label use in children of a second-generation US-CA.
Materials and methods Questionnaires were e-mailed to European paediatric radiologists, who were asked about their experience with the second-generation US-CA Sonovue® (Bracco, Milan, Italy). Number of examinations per indication and adverse effects were recorded. Examinations were categorised by intravenous or intracavitary use of US-CA.
Results Out of 146 respondents, 88 stated that they did not perform contrast-enhanced US in children, but 36 of these (44%) would appreciate paediatric approval. Forty-five centres reported 5,079 examinations in children (age mean: 2.9 years; range: birth–18 years, M/F: 1/2.8). The majority (4,131 [81%] in 29 centres) were intravesical applications. The minority (948 [19%] in 30 centres) were intravenous applications. No adverse effects had been recorded from intravesical use. Six minor adverse effects (skin reaction, unusual taste, hyperventilation) had been recorded after five intravenous studies (0.52%).
Conclusion Responses suggest a favourable safety profile of this second-generation US-CA in children. It also demonstrates a demand for such US-CA from paediatric radiologists.

Keywords Contrast-enhanced ultrasound · Child · Voiding urosonography

Introduction

The recent worldwide efforts to reduce the radiation burden caused by diagnostic imaging, particularly in children, has created an increased need for alternative, reliable and non-ionising imaging tools. The well-documented hazards of diagnostic radiation, especially during the first decade(s) of life, add further importance to the need to optimally exploit the diagnostic potential of ultrasound (US) as a noninvasive and nonirradiating imaging tool; its potential can possibly be enhanced significantly by a US contrast agent (US-CA) for some selected queries and conditions.

In Europe, the use of US-CAs is approved for a limited number of indications in adults, i.e. echocardiography, large ("macro") blood vessels, breast and liver conditions. At present, there is no approved US-CA for

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paediatric use. The only US-CA (i.e. Levovist®, Schering, Berlin, Germany) approved for paediatric intravenous (IV) and intracavitary use in some European countries was taken off the market for economic reasons some years ago. As soon as an approved US-CA was available—despite the obstacle of lacking paediatric registration at present—US-CAs have been used in infants and children in many countries over the last 15 years, particularly in Europe. The most frequent paediatric application is contrast-enhanced voiding urosonography (ce-VUS) for assessment of vesicoureteral reflux (VUR) [1–24]. Levovist® was the agent most frequently used, since it had been approved for paediatric intravesical use in some countries. For this application, a procedural recommendation has been developed and issued by the Uroradiology Task Force of the European Society of Paediatric Radiology (ESPR) and the Paediatric Work Group of the European Society of Urogenital Radiology (ESUR) to promote standardised high-quality examinations [25]. All the experience with US-CAs led to recommendations by the World Federation of Ultrasound in Medicine and Biology (WFUMB) as well as the European Federation of Societies on Ultrasound in Medicine and Biology (EFSUMB) on the use of CE-US [26] which included paediatric applications, particularly in the 2008 and 2011 updates [27, 28]; the proposed indications include both IV and intracavitary applications. The recommended paediatric indications are assessment of focal lesions of parenchymal abdominal organs (e.g. in trauma or in oncology conditions) and the assessment of VUR by intravesical US-CA administration (= ce-VUS) [28, 29]. The list of indications will increase in the future as demonstrated by trials analysing the clinical potential and impact of CE-US, particularly in adult but also in paediatric oncology. All these experiences demonstrate that CE-US can contribute significantly to reducing the diagnostic radiation burden to the population.

But, at present, all paediatric US-CA applications remain off-label; a situation that does not match the clinical need. For instance, in the setting of mild blunt abdominal trauma, imaging (and follow-up) by CT would involve a significant radiation exposure and iodinated CA injection (potentially even repeatedly); this might partially be replaced by CE-US. However, physicians must obtain an informed consent for off-label use of US-CA. Similar reasoning holds for the assessment of VUR. These examples illustrate why approval for paediatric use is deemed urgently necessary.

To address this need, and to try to confirm the safety of US-CAs in children, the ESPR Uroradiology Task Force together with the ESUR Paediatric Working Group set out to help provide data and information on the use and safety of the most common second generation US-CA presently available in Europe, i.e. SonoVue® (Bracco, Milano, Italy), used for paediatric applications, by initiating a Europe-wide survey. Responses from this survey are presented.

Materials and Methods

Questionnaires were distributed in summer 2010 via e-mail to all members of the ESPR and the Society of German-speaking Paediatric Radiologists (Gesellschaft pädiatrische Radiologie [GPR]) as well as other physicians and groups who requested or offer to participate to support our efforts (partially also via personal and individual contacts), all being considered potential users of this US-CA in children, i.e. general radiologists, paediatricians, paediatric urologists, members of affiliated societies (e.g. ESUR, Austrian Society for Ultrasound in Medicine [OEGUM], Austrian Society for Radiology [OERG]), and customers known to the manufacturer Bracco (Milan, Italy). Replies were accepted until April 2011.

The questionnaire asked for specific information on number of paediatric applications, mean age and gender, on the individual application (IV or intracavitary), and on all observed adverse events associated with the US-CA. Furthermore, in IV CE-US, the targeted organ and the clinical query/indication were to be listed. The type and duration of US-CA usage in children needed to be filled out. The completed questionnaire could be returned by fax, regular mail or e-mail with identification of the submitting institution. It was promised that the submitted data would not be used for any undertaking or research other than this ongoing survey, and that the various nonrelevant details (name of institution, etc.) would be kept anonymous. Only reports on the use of SonoVue® were evaluated; data on Levovist® applications were not included. To avoid duplicate data and data overlap from one institution with several individuals filing the survey, only one completed survey per institution was used.

The central questions asked about experience with contrast-enhanced US in a questionnaire sent European paediatric radiologists

Questionnaire on contrast-enhanced ultrasound (CE-US) in children

Do you or have you used **US contrast agents in children**? ☐ Yes ☐ No

Do you or have you used **SonoVue® in infants and children**? ☐ Yes ☐ No

If Yes: Since when have you used SonoVue® ……

how many exams ……, how many exams / year ……

intravenous ……., intravesical (for VUR detection) ……

which other US contrast do / did you use ……

Have you performed or do you perform **contrast-enhanced voiding urosonography** (ce-VUS) for the detection vesicoureteral reflux in children using SonoVue® ☐ Yes ☐ No

If YES: Since when have you performed ce-VUS....., since when have you used SonoVue® …….

Number of exams …… number of exams / year……

Mean patient age ……(years), range ……(years), gender ratio ……..

Number of contrast agent related side effects …… …..

If YES, please give age and gender of affected patient(s) ……

Please describe adverse effects: ……

Have you performed or do you perform **intravenous SonoVue® applications** in children? ☐ Yes ☐ No

If YES: Since when have you performed CE-US ……., since when have you used SonoVue® …….

Number of exams / patients……., number of exams / year……

Mean patient age ……(years), range ……(years), gender ratio …….

Indications (number, age, gender):

Trauma ……

Tumors and mass lesions ……

Inflammation ……

Vessel patency ……

Others (please name) ……

Targeted organs (number, age, gender):

Liver ……

Spleen……

Pancreas ……

Kidney …… …… …….

Brain ……

Major vessels ……

Others …… …….

Number of contrast agent related side effects ……

If YES: please give age and gender of affected patient(s) ……

Please describe kind of reaction ……

Results

A total of 146 surveys were received, 88 of which simply stated that no CE-US was performed in children at the respective institution because of regulatory issues or availability. Nevertheless, 44% of the 88 (n=36) stated that they would appreciate paediatric approval to then start using US-CAs in children. Nine centres reported that they had been using Levovist®, but stopped CE-US after Levovist® became unavailable. Four data sets were incomplete or mixed with adult applications (without age information that would allow the paediatric cohort to be identified) and could not be used; however, in two of these surveys, two adverse events were reported in adolescents (one severe anaphylactic reaction and one urticaria, both after IV use of SonoVue®).

Forty-five centres from all over Europe reported on paediatric applications of SonoVue®, documenting 5,079 examinations in total. Thirty-one centres performed both IV and intracavitary CE-US, the others reported the use of either IV CE-US or ce-VUS. The number of patients could not be retrieved from these data, but appears to be less than the above number, as some patients may have undergone repeated examinations. The highest number of responses [23] came from Germany. The other countries were—in alphabetical order—Austria, Finland, France, Greece, Hungary, Italy, Norway, Poland, Romania, Slovenia, Spain, Sweden and Switzerland. Mean patient age was 2.9 years (range: birth to 18 years), gender distribution was 1 male to 2.8 females. Most centres started to use SonoVue® between 2006 and 2009, only a few reported using SonoVue® from 2001 onwards; i.e. when the agent was first introduced. This indicates a frequency of approximately 100 to 1,000 investigations per year in earlier years. In 2010—the last complete year covered and included in the survey—there were approximately 2,000 examinations. Twenty centres had been using Levovist® before switching to SonoVue®. For the other questionnaires, the respective answer (as to whether CE-US has been performed with Levovist before starting to use SonoVue) was partially missing in the respective field.

The most extensive experience with CE-US exists in centres that perform a large number of ce-VUS. Between 400 and 700 ce-VUS studies were reported in four centres; the majority of institutions reported 50–300 examinations (Table 1). IV applications of CE-US are used less frequently. Many reported only small series with up to 10 case studies, the rest between 10 and 80 patients, except for one large series of nearly 500 patients (Table 2). All six mild side effects of SonoVue® that could be attributed solely to the US-CA were reported in five patients with IV applications.

A total of 4,131 intracavitary applications (81.3%) was reported from 29 centres, nearly all intravesical (Table 1). Only three groups mentioned other intra-cavitary applications, such as assessment of drain position and function during or after percutaneous interventions—no exact number available (probably <1%). The mean patient age in the intra-cavitary use group was 2.5 years (range: newborn to 18 years, gender distribution = 1 male to 3 females). No side effect could be attributed solely to the US-CA for ce-VUS; the few complaints reported were most likely from catheterisation. This matches with the result from a literature meta-analysis, where no significant side effects could be attributed clearly to SonoVue®; the few minor symptoms reported with Levovist® were also probably due to the catheter itself.

Thirty centres reported 948 IV examinations (18.7%) (Table 2). The mean patient age was 5 years (range: newborn to 18 years, gender distribution: 1 male to 2 females). The most frequently targeted organ was the liver, rarer the spleen, less frequently the kidney and pancreas, with a few additional applications such as the ovary or vessels. The indications were mostly oncological, traumatic or inflammatory conditions—either lesion detection (e.g. in subacute or moderate trauma) or lesion characterisation (e.g. abscess vs tumour)—or some dedicated rare queries (such as transplant and vascular examinations). Five patients were reported to have had six minor side effects after IV US-CA administration, with one having two symptoms (i.e. strange taste and skin reaction). The symptoms were minor skin reaction (n=2, urticaria or rash), unusual taste (n=3) and hyperventilation (n=1). One severe anaphylactic reaction necessitating resuscitation measures was reported in an adolescent girl suffering form an oncological condition (not included in the survey population, as patients older than 18 years were not the target of the survey) after repeated US-CA application and with numerous other known allergies.

Discussion and conclusion

US-CAs were introduced initially for cardiac use about 25 years ago. At that time, they were not able not to pass the lung capillaries and thus were used mainly for assessment of (intracardiac or intrapulmonary) shunts [30–32]. Technical developments then created smaller micro-bubble carriers that enabled smaller and more stable US-CAs to pass the capillary bed, with a better signal response and constantly increasing contrast enhancement duration [30, 32, 33]. Basically, all US-CAs consist of some gas micro bubbles (e.g. air, perfluorocarbon, sulphur-hexafluoride, etc.) attached to a carrier molecule (either a protein-, a sugar- or a lipid-macromolecule) that acts as a shell, stabilised usually by palmitic acid. US-CAs not only increase US reflexion, but also emit additional US signals by their harmonic response [32–37]. These can be visualised by a

Table 1 Survey results: detailed results from responses concerning contrast-enhanced voiding urosonography (ce-VUS). *CA* Contrast agent

	Number of exams	Mean age (years)	Age range (years)	Male: female	SonoVue since	CA before	Adverse effects
	500	2	0–5	1: 2.5	2009	Levovist	None
	12	1	0–12	1: 11	2009	Levovist	None
	4	0.5	?	0: 7	2008	Levovist	None
	315	2	0–17	1: 1	2009	Levovist	None
	15	?	?	?	2004(−7)[a]	None	None
	700	1.5	0–16	?	2004	None	None
	120	1.6	0–18	1: 5	2007	Levovist	None
	10	0.5	0–1	?	2007	None	None
	40	4.5	0–15	1 t: 3	2003(−4)[a]	Levovist	None
	500	0.55	0–4	1: 1	2009	None	None
	450	?	0–15	1: 9	2006	None	None
	8	1	0–3	1: 2	2009	Levovist	None
	200	1	0–4	2: 8	2008	Levovist	None
	10	8	0–18	8: 2	2006	None	None
	160	4.6	0.5–16	2: 8	2008	Levovist	None
	25	1	0–2	?	2010	None	None
	50	12	7–16	1: 3	2009	None	None
	5	10	7–13	0: 1	2009	Levovist	None
	180	3.6	0–18.5	1: 2	2010	Levovist	None
	55	2	0–12	1: 1	2010	Levovist	None
	2	4	2–6	0: 2	2004	Levovist	None
	2	9.5	8–11	1: 1	2011	Levovist	None
	240	2	1–10	2.5: 1	2007	None	None
	33	7	0–10	2: 1	2009	None	None
	200	0.5	1–18	1: 1 0	2007	Levovist	None
	38	1.8	0–11	21: 17	2010	Levovist	None
	1	8	8	1	2011	Levovist	None
	76	5.7	0–19	1:2	2001	Levovist	None
	180	1	0.5–3	1:3	2007	Levovist	None
29 centres							
Total	4,131	2.5	0–19	ca. 1:3			None

[a] Data are provided only for the given time span (e.g. because not used before or since)

variety of US techniques, both with basic grey scale imaging or using more novel techniques such as harmonic imaging and pulse inversion, Doppler techniques and other dedicated contrast visualisation tools are presently incorporated in practically all high-end US systems, based partially on non-fundamental response [32, 38–40]. More recently, low mechanical index ("low-MI") contrast imaging techniques have enabled an even longer duration of adequate signal response with very little US-CA destruction, thus improving real-time assessment of enhancement dynamics.

In adults, numerous applications have been assessed and reported in the literature—particularly the use of US-CAs for lesion detection and characterisation in abdominal parenchymal organs (predominantly the liver) [32, 41–52]. These reports demonstrate not only a high diagnostic potential and reliability of CE-US, but also a high safety profile of US-CAs; in adults, anaphylactoid reactions have been reported at a low rate of less than 0.002% [53, 54]. The established indications are oncological, traumatic or inflammatory lesions, assessment of vascular patency or pathology, tissue perfusion, echocardiography, intraoperative guidance and transplant queries [32, 55–70].

So what is the actual evidence for using CE-US in children? It is clear that CE-US delivers reliable diagnostic information for a variety of conditions, particularly in adults. In children, the diagnostic value of ce-VUS has been studied extensively. These studies demonstrate that ce-VUS is a practical unique paediatric application of US-CAs that has gained widespread acceptance over the past few years after its introduction in the mid-1990s. Initial restrictions,

Table 2 Survey results: detailed results from responses concerning intravenous contrast-enhanced ultrasound (CE-US) data

	Number of exams	Mean age (years)	Age range (years)	Male: female	SonoVue since	CA before	Adverse effects
	13	5	1–16	5: 8	2009	Levovist	None
	43	7	0–18	1: 1	2007	None	1 × strange taste
	5	?	0–16	1: 1	2004(−7)[a]	None	None
	20	10	2–19	1: 2	2006	Levovist	None
	43	?	0–18	?	2007	Levovist	2 × strange taste, cutaneous reaction
	19	10.3	0–23	1.4: 1	2007	Levovist	None
	26	9.8	0–15	4: 22	2007	n.c.	None
	30	5	0–15	?	2008	None	None
	10	7	?	?	2009	n.c.	None
	20	9	0–15	1: 1	2008	Levovist	None
	30	12	0.2–18	19:11	2006	None	1 × cutaneous reaction
	6	2	0–4	?	only in 2009	n.c.	None
	2	16.5	16, 17	1: 1	2007(−10)[a]	None	None
	6	12	7–18	2: 8	2009	n.c.	None
	3	16	15–17	2: 1	2009	Levovist	None
	15	9	0–18	1: 1	2003	None	None
	14	15	10–17	?	2005	n.c.	None
	15	8	5–16	1: 1	2009	n.c.	None
	80	8	0–18	1: 1	2008	n.c.	1 × hyperventilation
	2	17	17	1: 1	2008	n.c.	None
	10	10	1–16	1: 1	2001	n.c.	None
	2	?	?	?	2002	n.c.	None
	4	14	10–18	1: 1	2007	n.c.	None
	10	12	−17	1: 3	2008	Levovist	None
	22	?	3–17	1: 1	2003	n.c.	None
	10	?	>6	?	2008	Levovist	None
	1	17	−17	0: 1	2009	n.c.	None
	7	10	10–17	3: 4	2010	n.c.	None
	5	7.8	1–17	?	2007	n.c.	None
	475	?	1–17	?	2002	n.c.	None
30 centres							
Total	948	5	0–19	ca 1:2			5 patients; 6 symptoms; 1 patient had 2 symptoms and strange taste)

[a] Data are provided only for the given time span (e.g. because not used before or since)

n.c. No comment given

such as assessment of the urethra, have been overcome, and the potential to combine ce-VUS with sonographic genitography has also been demonstrated [70–75]. A recent meta-analysis of the existing literature on comparative studies of ce-VUS with voiding cystourethrography (VCUG) and direct radionuclide cystography (DRNC) confirmed the high sensitivity and specificity of this elegant nonionising imaging modality [76]. The data included more than 2,549 children with more than 5,078 pelvi-ureteric units. Using VCUG as the reference method, ce-VUS had a sensitivity of 90% and specificity of 92%, with a high correlation of VUR grading. Compared to DRNC, ce-VUS yielded a sensitivity of 94% and a specificity of 95%. More, and up to 10% higher graded, VURs were detected on ce-VUS; intrarenal reflux can also be depicted by ce-VUS. Additionally, perineal ce-VUS of the urethra enables excellent imaging of urethral anatomy, as demonstrated in 880 patients. In more than 97% of these patients, urethral assessment was reported feasible and reliable. The diagnostic performance of ce-VUS with SonoVue®, the most widely used US-CA agent in

Europe, did not differ significantly from Levovist®; actually, SonoVue® performed slightly better. In some institutions, particularly when Levovist® was still available and registered for paediatric use, VCUG and DRNC are being gradually, or have been, replaced by ce-VUS, reducing the number of ionising studies significantly [77]. Less data are available on IV CE-US in children. The results of the few reports are similar to those from adults, and prove the high diagnostic potential of US-CAs in reducing the need for radiation-burdened imaging, particularly also in investigations of moderate blunt abdominal trauma [78–82].

In the United States, differences in practice and regulatory requirements have hampered the use of US-CAs. Nonetheless, two US-CAs (Definity®, [Lanthaeus Medical Imaging, N. Billerica, MA] and Optison® [General Electric, Princeton, NJ]) are approved, but only for echocardiography. Regarding noncardiac use, a phase III study is underway by Bracco (Milan, Italy) to evaluate the use of SonoVue® for focal liver lesion characterisation. There are also a few institutions conducting animal or clinical studies pertaining to paediatric applications. Additionally, the Society of Pediatric Radiology (SPR) recently established a Contrast-enhanced Ultrasound (CE-US) Task Force with the objective of raising awareness among paediatric radiologists of the use of CE-US in children and to advise the FDA with regards to approval of US-CAs for paediatric use.

On balance, it seems logical to recommend CE-US for specific indications, particularly as CE-US would reduce significantly the exposure of children to radiation and iodinated CA, and specifically taking into account the extremely low rate of drug-related adverse events reported to date [32, 53, 54, 83, 84]. This is even more important when compared with the potential long-term harmful effects of CT, particularly in children who have higher radiation sensitivity and a longer expected life span. This increasing awareness of the negative effects of radiation may spur the search for alternatives and suggests the use of US-CAs also in paediatric imaging.

The data from this Europe-wide questionnaire-based survey suggests a high safety profile of the US-CA SonoVue® and additionally demonstrates that there is not only a medical need, but also a potential market for paediatric US-CAs applications.

However, some restrictions of this survey have to be addressed. The response rate to the survey could not be properly assessed, as the number of recipients could not be tracked properly for many reasons: There was often more than one recipient per institution, no feedback of receipt of message, or different distribution pathways with partially significant overlaps between the various e-mail groups. However, as only one completed survey was submitted per institution, no data overlap in the CE-US application data appears to be present. It has to be additionally acknowledged that conventionally US is a primarily noninvasive study (that can be performed by radiographers, as it is standard for US in some parts of the world); performing a ce-US would make the investigation a more invasive study - by having to administer the US-CA either intravenously or into the respective cavity, mostly via catheter, which would require a physician to be present. However, if it helps reduce more threatening risks such as radiation hazards and does not exceed the invasiveness of the respective alternative technique (e.g. CT or MRI need IV-CA, too, VCUG requires catheterism and CA), CE-US appears justified. Still, proper precautions must be taken (i.e. one needs to have potentially necessary medication at hand, and staff who are qualified to administer the US-CA and to perform the examination, etc.), and adequate reimbursement has to be eventually granted.

Additionally, caution should be used with IV applications in patients who are prone to increased allergic risk (e.g. suffering from multiple other allergies, particularly after repeated US-CA applications), in particularly endangered organs (such as the brain and eye) or where gas interfaces may cause cavitation-induced damage (i.e. lung and intestines), as well as in neonates, because the potential side effects have not been studied in detail and, additionally, cellular effects from the US-CA have been observed in vitro. Furthermore, data from small animal models suggest that glomerular capillary haemorrhage and other microvascular rupture may occur upon exposure to high sound pressure [85]. But most of the presently applied contrast imaging techniques are “low MI” techniques that use low energy and low sound pressure, thus making these aspects unlikely to affect CE-US in clinical practice [86]. Nevertheless, further studies on the safety of intracavitary and, particularly, intravesical SonoVue® applications will be necessary, as these have been performed only for Levovist®—a different agent consisting of air microbubbles and a sugar macromolecule.

Finally, it must be acknowledged that only the data submitted could be analysed and used. Some data gaps are obvious on the sheets (e.g. incomplete age information, the date since when the US-CA was used how many and which abdominal organs were imaged for what indication, etc.), and no validation of the correctness of the submitted data could be performed. Also, other systemic bias deriving from such retrospective surveys has to be considered, e.g. the lack of a common standard of recording of adverse effects, and one might speculate that those who advocate and support CE-US in children might have been more eager to answer than others. However, this does not affect the total numbers of documented paediatric CE-US applications, and our results match those of existing literature reports [26–29, 76, 84].

Nevertheless, knowledge of existing experience might be valuable for discussion and to promote the use of US-CAs and research in this field. The data from this survey—together with the information available in literature—may support the undertaking to eventually achieve paediatric licensing for US-CAs, as these observations suggest and demonstrate a

good safety profile, clinically important and valuable applications, and a potentially reasonable market. There is also a first of its kind joint effort in pushing for licensing of US-CAs for paediatric use by a number of major societies (ESPR, ESUR, GPR, ESR Ultrasound Section, EFSUMB, WFUMB, SPR) [87, 88]. The manufacturer Bracco (Bracco, Milan, Italy) has agreed to start an internal assessment on the possible inclusion of new indications, i.e. the paediatric use of SonoVue®. This statement at the uroradiology task force session during the International Paediatric Radiology Meeting in London in June 2011 raises optimism [88, 89]. The data from this survey may help to bring together the aspects of clinical importance, safety and use of US-CAs in infants and children.

Conclusion

This questionnaire-based European survey demonstrates that there are important applications for CE-US throughout childhood. Particularly, VUR assessment by ce-VUS could contribute to significantly reduce the exposure of this group of patients to diagnostic radiation. Furthermore, the survey suggests a high safety profile of US-CA SonoVue® and a potential reasonable market, thus making approval also economically more interesting, particularly taking into account all the comments stating willingness and eagerness to use US-CAs once they are made available and are approved for paediatric application. Hopefully, all this will spur interest in discussing and re-evaluating the use and approval of CE-US in children. For the time being, these experiences and the information from this survey can serve as valuable objective information when discussing an informed consent for off-license use of US-CAs, particularly SonoVue®, with patients, parents and/or guardians.

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