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CONTRAST–ENHANCED ULTRASOUND IN CHILDREN

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Contrast-enhanced ultrasound in children
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By

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To Karin

To Vira

To Eli

Popular science summary of the thesis

Ultrasonography (US) is in many cases the method of choice for diagnostic imaging of children. The main reason for this is the fact that US, in contrast to x-ray exams, does not require ionizing radiation. Ionizing radiation can, in large doses, cause cancer. Also, US almost never requires sedation of the child, in contrast to magnetic resonance imaging (MRI) exams where sedation may be required to allow for good images in small children. Sedation of a child requires a lot of resources and time and is associated with some risk of side effects.

Sometimes, however, you need more information than what is available through the regular (B-mode) US image. In those cases, an additional layer of information can be added to the image by using an ultrasound contrast-agent. The contrast-agent consists of gas microbubbles, as large as red blood cells, suspended in a liquid. The contrast agent is administered intravenously and almost instantly after administration you can see the glittering echo from the bubbles as they pass through the blood vessels in the area investigated with your ultrasonography system. The ultrasound waves omitted from the system make the passing microbubbles in the contrast-agent oscillate. This oscillation is what produces the "glittering" in the image.

This combination of ultrasound with a contrast-agent is called contrast-enhanced ultrasound (CEUS) and provides important real time information on the blood circulation, or the lack thereof, in the area of interest.

In most parts of the world the use of these contrast-agents in children is considered "off-label" use. This means that there is no official licensing for its use in children. The lack of official licensing does not mean that the contrast-agent or drug has been proven to be toxic or harmful in children, but rather that the manufacturer has not performed the necessary studies in children required for the drug to receive official licensing. This "off-label"-use is widespread and is the case for many other medications regularly used in pediatric clinics and hospitals around the world. The use of CEUS varies greatly from hospital to hospital and from country to country. At Karolinska University Hospital, Huddinge contrast- enhanced ultrasound has been used in children for a long time.

The aim of this thesis was to analyze and share the pediatric CEUS experience from Karolinska University Hospital, Huddinge and also to survey the use of CEUS in the Nordic countries.

Study 1 suggests that CEUS is safe to use with no serious adverse effects among our cases.

Study 2 suggests that CEUS can be used for the detection of vascular complications after liver transplantations, and that it can be used as a problem solver when B-mode US is inconclusive.

Study 3 suggests that CEUS can be used for the differentiation between malignant and benign focal liver lesions. In select cases, CEUS is the only exam needed to rule out a

malignant lesion.

Study 4 provides insight into the current use of pediatric CEUS in Nordic hospitals. The main advantage reported was the potential to reduce alternative imaging and hence reduce the amount of radiation and/or sedation for the child. The main obstacles were reported to be lack of experience and of official approval.

In conclusion, contrast-enhanced ultrasound has many uses in adults and children alike and can be an important diagnostic tool with the potential to reduce possibly harmful radiation and avoid sedation in small children. However, among other things, the lack of official licensing for children in Europe serves as an obstacle for its use. Efforts should be made to grant it official pediatric licensing as is the case in the United States since 2016.

Populärvetenskaplig sammanfattning

Närhelst ett barn ska genomgå någon bilddiagnostik är ultraljud ofta den mest använda undersökningsmetoden. En av anledningarna är att ultraljud, till skillnad från röntgenundersökningar inte använder sig av joniserande strålning. Joniserande strålning kan i höga doser orsaka cancer. Vidare kräver ultraljudsundersökningar inte att man söver barnet, till skillnad från magnetkameraundersökningar där i alla fall små barn måste sövas för att kunna ligga stilla under undersökningen.

Men ibland räcker inte det vanliga ultraljudet till för att kunna ge en bra diagnos, i dessa fall kan man lägga på ett ytterligare lager av information på ultraljudsbilden. Detta genom att använda sig av en kontrastvätska. Denna vätska består av mikrobubblor av gas, stora som röda blodkroppar, upplösta i vätska. Denna vätska injiceras intravenöst och nästan omedelbart kan man på ultraljudsbilden se de "glittrande" mikrobubblorna när dom passerar i blodkärlen. Detta "glitter" uppstår som följd utav att ultraljudsvågorna träffar mikrobubblorna och får dem att oscillera.

Denna kombination utav ultraljud ihop med ultraljudskontrast kallas kontrastförstärkt ultraljud (contrast-enhanced ultrasound, CEUS). CEUS tillför direkt information om blodflödet, eller avsaknad av detsamma i det undersökta området.

I många delar av världen räknas användandet av ultraljudskontrast hos barn som "off-label"-bruk. Detta innebär att det inte finns officiellt godkännande för att använda detta hos barn. Det innebär inte att kontrasten eller läkemedlet har bedömts vara farligt eller riskabelt hos barn, däremot att läkemedelsföretaget inte ansökt om godkännande för användning hos barn. Detta "off-label"-bruk är vanligt inom barnmedicin och omfattar en stor andel av de läkemedel som dagligen används för barn.

CEUS användandet hos barn är utbrett i varierande grad i världen och varierar lokalt från sjukhus till sjukhus. På Karolinska sjukhuset i Huddinge har man lång erfarenhet av att använda CEUS hos barn.

Målet med denna avhandling var att analysera och dela med oss av våra erfarenheten från Karolinska universitetssjukhuset Huddinge samt att försöka kartlägga användandet av CEUS i de nordiska länderna.

Studie 1 antyder att CEUS är säkert hos barn, inga allvarliga biverkningar sågs bland de undersökta fallen.

Studie 2 antyder att CEUS väl kan användas för bedömning av kärlrelaterade komplikationer efter levertransplantation och har en roll som problemlösare när vanligt ultraljud inte räcker till.

Studie 3 antyder att CEUS har en plats för att skilja ut godartade från elakartade förändringar i levern. I utvalda fall kan CEUS ensamt räcka för att utesluta elakartade förändringar i levern.

Studie 4 belyser det aktuella användande av CEUS hos barn i nordiska sjukhus. Den

främsta fördelen som rapporteras är att CEUS har potential att undvika alternativa undersökningar så som skiktröntgen eller magnetkameraundersökningar och därmed minska mängden joniserande strålning och/eller minska behovet av sövning. De främsta hinder som rapporterades var brist på erfarenhet/vana och att CEUS inte har officiellt godkännande för användning hos barn.

Sammanfattningsvis har CEUS många möjliga användningsområdet hos både vuxna som hos barn och är ett viktigt diagnostiskt verktyg fritt från joniserande strålning och utan behov av att söva barnet. Däremot hindras mer utbredd användning bland annat av att det inte finns officiellt godkännande för användning av CEUS hos barn. Förhoppningsvis görs ansträngningar för att ge CEUS officiellt godkännande så som fallet är i USA, där det är godkänt hos barn sedan 2016.

Abstract

Background: Contrast-enhanced ultrasound (CEUS) is a diagnostic tool that is used for many applications in adults. Many of these applications are considered "off-label" use but still play an important role in diagnostic imaging. In Europe, and most other countries worldwide, all pediatric CEUS use is 'off-label', regardless of the specific application. However, there is mounting experience and documentation to support its safe and effective use in children and adults alike. Nonetheless, there may be some apprehension among physicians when considering CEUS for children, partly due to the lack of official licensing. In Karolinska University Hospital, Huddinge, CEUS has successfully been utilized in children for over two decades.

Aims: To analyze and present our experience with pediatric CEUS at Karolinska University Hospital, Huddinge and to survey the use of pediatric CEUS in Nordic hospitals.

Material and methods: Studies 1–3: We retrieved the records of 10681 patients under the age of 18 who underwent abdominal ultrasonography (US) January 2004 to December 2014. We then identified those who underwent CEUS using sulfur hexafluoride microbubbles. Electronic patient charts were used to gather clinical information on the cases such as indication for the exam, lab results, patho-histologic results etc. Also, anthropometric data was collected. The hospital Picture archiving and communication systems (PACS) was used to retrieve relevant radiology reports and information on administered contrast dose.

Study 4: Radiologists in Nordic hospitals in 2022 were surveyed trough a web questionnaire.

Results: Study 1 suggests that CEUS is safe in the pediatric population with no severe adverse effects recorded. Study 2 suggests that CEUS can be used to identify circulatory complications after liver transplantation. Moreover, CEUS may be valuable as a "problem solving – tool", particularly when the unenhanced ultrasonography is inconclusive. Study 3 suggests that CEUS has a place in the characterization of focal liver lesions and in select cases it can rule out a malignant lesion without the need for further workup.

Study 4 suggests that CEUS is widely used in many Nordic countries and the main reasons for its use was reported to be that CEUS could result in fewer alternative exams such as Computed tomography (CT) and Magnetic resonance imaging (MRI) and hence decrease the amount of ionizing radiation and sedation. The main obstacle for its use was reported to be lack of experience and of official licensing.

Conclusions: Our findings support the continued use of CEUS in children and further reinforces its place as a safe alternative and/or compliment to CT and MRI. It also highlights the perceived advantages and obstacles for its continued use in the Nordic countries. Much could be gained from allowing official licensing for pediatric CEUS.

List of scientific papers

I. **Torres A**, Koskinen SK, Gjertsen H, Fischler B. Contrast-enhanced ultrasound using sulfur hexafluoride is safe in the pediatric setting. Acta Radiol 2017;58:1395–9. https://doi.org/10.1177/0284185117690423.

II. **Torres A**, Koskinen SK, Gjertsen H, Fischler B. Contrast-Enhanced Ultrasound for identifying circulatory complications after liver transplants in children. Pediatr Transplant 2019;23:e13327. https://doi.org/10.1111/petr.13327.

III. **Torres A**, Koskinen SK, Gjertsen H, Fischler B. Contrast-enhanced ultrasound is useful for the evaluation of focal liver lesions in children. Australas J Ultrasound Med. 2021;24(3):143–50

IV. **Torres A**, Fischler B, Koskinen SK. Pediatric contrast-enhanced ultrasound in Nordic hospitals. WFUMB Ultrasound Open 2023;1:100024. https://doi.org/10.1016/j.wfumbo.2023.100024.

Contents

List of abbreviations

US	Ultrasonography/Ultrasound (the terms are often used interchangeably)
CEUS	Contrast-enhanced ultrasound
CT	Computed tomography
MRI	Magnetic resonance imaging
FLL	Focal liver lesions
i.v	Intravenous
UCA	Ultrasound contrast agent
FLL	Focal liver lesion
HCC	Hepatocellular carcinoma
FNH	Focal nodular hypeplasia
VUR	Vesico-urethral reflux
ceVUS	Contrast-enhanced voiding urosonography
PPV	Positive predictive value
NPV	Negative predictive value
CI	Confidence interval

Introduction

During my ultrasonography rotation within my radiology residency there was some apprehension and worry amongst the nurses who assisted in the pediatric CEUS exams. The cause for this worry was that it had come the nurses' attention that the contrast agent used for these exams was not officially licensed for pediatric use and they worried about the possible medicolegal consequences of such use. Inspired by this issue, one of the senior doctors proposed a systematic review of the cumulated local experience within our institution– in order to hopefully reassure any insecurities among the staff regarding the safety of pediatric CEUS. I saw the practical value of such a study and agreed to undertake it. As it turned out, the data we collected contained a wealth of information, more than what was needed for a single paper. This strongly supported the rationale to expand this into a thesis – and here we are.

In diagnostic imaging there are a variety of imaging modalities available depending on the indication for the exam. For detailed differentiation between different tissues within the body, mainly three modalities are used; Computed tomography (CT), Magnetic resonance imaging (MRI) and Ultrasonography (US)

A CT scan produces a 3D image by way of rotating x-ray tubes and the patient is moved through the "gantry" to achieve the image. The image can be enhanced by the addition of an iodinated intravenous (i.v.) contrast agent.

MRI uses an advanced combination of magnetic fields and radio waves to produce an image and hence does not require x-rays to produce an image and is free of ionizing radiation. However, MRI exams usually require the patient to be very still during the time of the scan, or else the images will become blurred and difficult to review. Sedation of the child may therefore be necessary. Similarly, MRI exams can be enhanced through incorporation of an intravenous contrast agent, typically utilizing a gadolinium-based contrast agent.

Both CT contrast agents and MRI contrast agents are eliminated from the body through the kidneys and therefore both require the patient to have a certain degree of remaining renal function in order to be eligible to receive the contrast agent.

Modern ultrasonography uses high frequency sound waves that are sent into the body through an ultrasound transducer connected to an ultrasound system. The sound waves "bounce off" the different tissues in its path and the returning sound waves, "the echoes" return to the transducer– which acts as both a transmitter and as a receiver of sound waves. These returning echoes are processed by the ultrasound machine and converted into images almost instantly. This technique of both sending and receiving

through the same transducer is called the "pulse-echo method" and is used in A-, B-and M-mode imaging.

A-mode imaging provides limited information presented through a one-dimensional graph depicting depth and dimension of an object and has very limited clinical use.

B-mode (Brightness-mode) ultrasonography on the other hand provides the 2-dimensional image that most people recognize (Figure 1). This technique was first developed in the early 1950´s (1,2) and has since then rapidly evolved in terms of image quality and speed.

Figure 1 Example of a B-mode image from a liver ultrasound
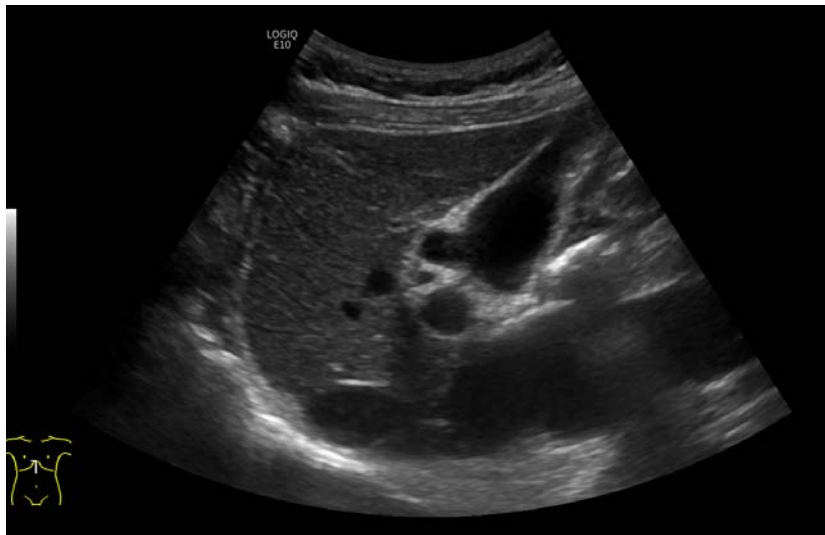
M-mode (motion-mode) US, similar to A-mode imaging, also provides a one-dimensional graph but instead the graph depicts amplitude over time, where non-moving structures create flat lines, whereas moving structures create upward and downward inflections of the line (Figure 2). M-mode has some clinical applications, primarily in echocardiography (3) and in lung ultrasound (4).

Figure 2 Example of a M-mode image from a cardiac ultrasound
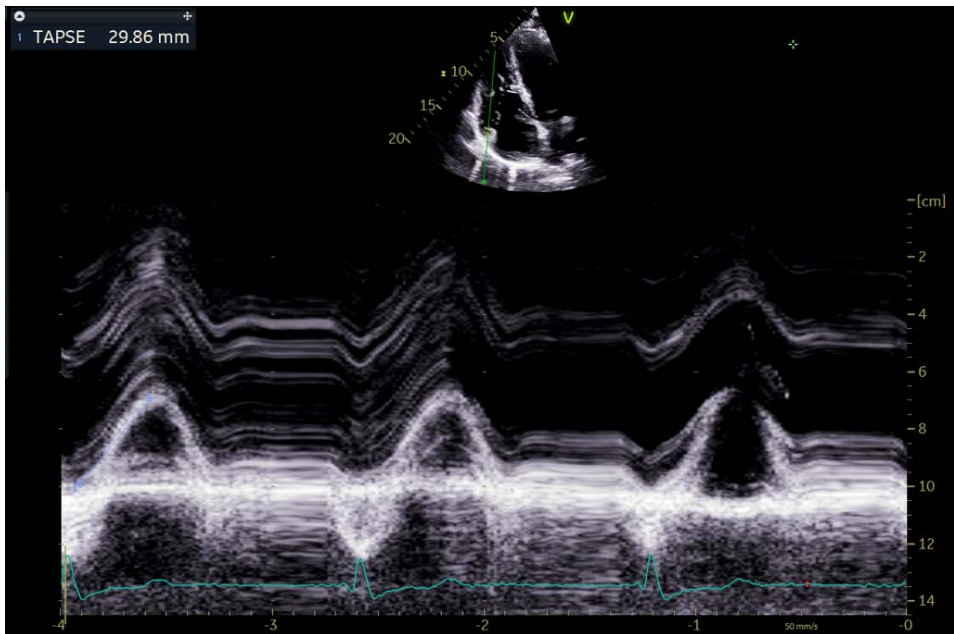
Doppler imaging is a feature that together with B-mode imaging can be considered the "workhorse" of modern US. Doppler imaging takes in to account the change of the signal frequency going out compared to the signal coming back to the transducer (Doppler shift). This change is then transformed this into an image. This property within doppler imaging is used to visualize blood flow within tissues and having doppler information overlayered on a B- mode image provides valuable real time information acquired through a non-interventional manner. Doppler imaging has since its development in the mid 1950's (5) experienced important improvements, including the development of power doppler and spectral doppler techniques.

US exams have the possibility to be enhanced even further by administering a contrast agent which allows for real time visualization of the vascular flow within the area of interest.

SonoVue® (Sulphur hexafluoride) by Bracco is by far the most commonly used ultrasound contrast agent in Europe. In the United States, SonoVue is marketed as Lumason®, which is identical to Sonovue®. The second most used contrast agent in the world is Sonazoid® (Perfurobutane microbubbles), approved in Japan, Korea, Taiwan and Norway. (Daiishi-Sankyo/GE Healthcare). For the purposes of this thesis, I will hereon refer to Sonvue®/Lumason® when using the term "ultrasound contrast agent" (UCA).

SonoVue® Microbubbles consist of a gas within a phospholipid shell (Figure 3). The microbubbles are slightly smaller than red blood cells, with each microbubble having a

mean diameter of 2.5 µm. In contrast, red blood cells typically measure 7–8 µm in diameter.

When subjected to ultrasound waves, each microbubble compresses and then expands, i.e., oscillates. The phospholipid shell allows the microbubble to do so without bursting. It is this motion of compression and expansion–or oscillation–, that gives rise to the characteristic "glittering" image seen on the ultrasonography system screen.

Figure 3. Graphical representation of the structure of a Sulphur hexafluoride (SF6) microbubble (Reprinted from Greis C. Ultrasound contrast agents as markers of vascularity and microcirculation. Clinical Hemorheology and Microcirculation. 2009 Jan 1;43(1–2):1–9., reprinted with permission from IOS Press and the author).
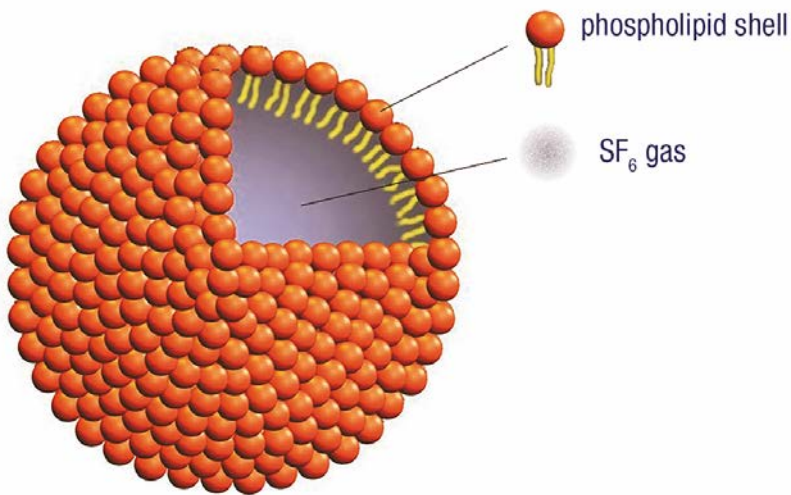
Unlike MRI and CT contrast agents, sulfurhexafluoride UCA's remain completely intravascular, but do pass through to the pulmonary system. This means that it is available for diffusion through the alveoli, out into the expiratory air. According to the manufacturer, more than 80% of the contrast agent is exhaled within 2 minutes and 100% within 15 minutes (6)

An example image of a CEUS examination of the liver is shown in Figure 4.

Figure 4. A CEUS image of the liver. The image shows a split screen, with the contrast enhanced image on the right and the non-enhanced ultrasonography image on the left. The orange arrow points to a hepatic hemangioma.
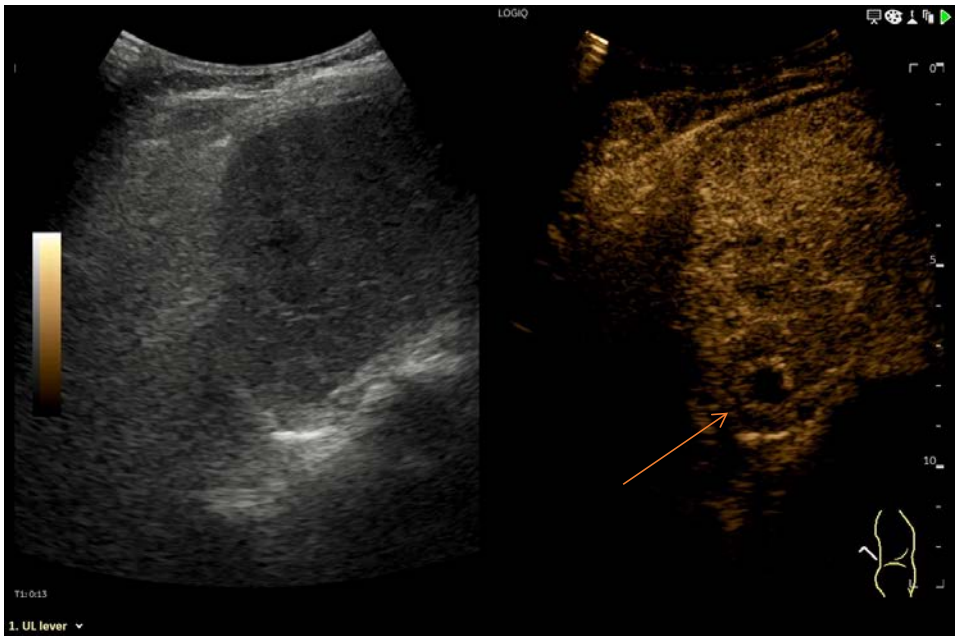
1   Literature review

1.1   Off-label

In Europe, Sonovue® is officially approved for echocardiography and vessel examinations in adults as well as for liver and breast examinations in adults. Additionally, it has been approved for intravesical use in children aged 0 to 18 years.

This means that all other examinations are considered "off-label". This very rigid definition can sometimes seem to lack logic. For instance, if you administer the UCA to an 18-year-old and perform a CEUS of the liver, you are fine- you are covered by the official approval. However, if you slip on the ultrasound gel and move the transducer just a few centimeters in another direction you may stumble upon the kidney, the pancreas, the bowel, or the spleen, and none of these organs are covered by the official license and you find yourself performing an off-label examination.

Consequently, many physicians around the world have slipped on the ultrasound gel to find that CEUS can provide very useful information in a vast variety of ways not listed in the official licensing and there is ample documentation and research on this. The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) has published various guidelines and recommendations for CEUS, summarizing the existing evidence for various indications (7,7,8).

By comparison, off-label use of drugs is not limited to CEUS- according to a report from 2017, published by the department of health and food safety of the European Commission (9), the prevalence of off-label use, for both children and adults, receiving in-hospital care is as high as 69%.

In 2016, Lumason® was officially approved by the US Food and drug administration (FDA), for the characterization of focal liver lesions in both adults and children. This was accomplished by a series of efforts witch are summarized in a paper from 2021 by K. Darge et al. (10). This approval was the first approval for i.v. pediatric use of CEUS in the world and still is to this date.

1.2   Safety

Safety is a critical factor to consider when evaluating the use of a drug, whether in adults or children. Regarding contrast agents, adverse effects are primarily associated with allergic or allergic-like reactions, which can range from severe anaphylactic reactions to mild itching sensations.

Regarding CEUS, the sulfur hexafluoride bubbles are suspended in a solution containing a variety of compounds. Allergic reaction can occur in response to any of these. Specifically the component "polyethylene glycol" (PEG) has been identified as a possible trigger for anaphylaxis (11).

1.2.1 Adults

The safety profile of UCA' in adults is well documented and there are several very large studies on the subject. Four large studies on the safety of intravenous administration of sulfur hexafluoride were identified. They included 23 188 (12), 30 222 (13), 34 478 (14) and 463 434 (15) CEUS examinations. The reported incidence of any adverse effect ranged between 0.02% to 0.13%. The incidence of any treatment-requiring adverse effect ranged between 0.004% to 0.017%.

1.2.2 Children

One recent review paper summarizes the existing research in the topic of UCA safety in children (16). This review included 51 studies in which 4533 i.v. exams with sulfur hexafluoride were performed on 4306 children and reported an overall incidence of 1.25% adverse events of which 0.2% were considered serious and were of anaphylactic origin. It is not specified how many of these patients that required any treatment.

Gadolinium-based contrast agents in children:

Two large studies have evaluated the safety of gadolinium-based contrast agents in children. In a 2007 study of 13,344 children (17), the incidence of adverse events was 0.04%, with 0.02% being severe. In a 2013 study of 15,706 children (18), the incidence of adverse events was 0.05%, but no data on the severity of these events was available.

Iodinated contrast agents in children:

Two large studies have evaluated the safety of iodinated contrast agents in children. In a 2007 study of 11,306 children (19) the incidence of adverse events was 0.18%, with 0.07% requiring treatment. In a 2009 study of 12,494 children (up to 21 years of age) (20), the incidence of any adverse event was 0.46% (57 of 12,494). The incidence of a moderate adverse event was 0.08% (10 of 12,494), and most of these cases required treatment. There were no severe adverse events in this study.

The difference between the different kinds of contrast agents in relation to the incidence of adverse events are presented in Table 1.

Table 1 Incidence of adverse events in children by type of contrast agent. US, ultrasound. "?" means no data is available

	Incidence of adverse events (All/Serious)	Number of children included in study	Reference

US contrast-agents	1.25%/0.2%	4,533	(16)
Gadolinium contrast-agents	0.04%/0.02%	13,344	(17)
	0.05%/?	15,706	(18)
Iodinated contrast-agents	0.18%/0.07%	11,306	(19)
	0.46%/0%	12,494	(20)

1.2.3   Pregnancy

The EFSUMB Guidelines and Recommendations from 2017 (8) do not endorse the use of CEUS during pregnancy due to the lack of research regarding possible harmful effects. There are, however, no indications of CEUS having a negative impact on the pregnancy or the development of the fetus. For instance the manufacturer states, in the documentation that accompanies the contrast agent, that animal studies have not indicated any harmful effect (6). A review from 2020 (21) concludes that although not enough data exists to definitively say that CEUS is safe in pregnancy, all data so far encourage continued research to generate clinically relevant quantitative data in human pregnancies.

Regarding iodinated contrast and gadolinium-based contrast agents during pregnancy, the European society of urogenital radiology (ESUR) recommend its use if the indication is strong and the examination is essential. Following administration of iodinated contrast media the thyroid function of the neonate is recommended to be checked within one week post-partum due to the risk of thyroid dysfunction related to the iodine in the contrast media (22).

1.3   Clinical applications

Compared to CEUS in adults, pediatric CEUS presents some key differences that have to be considered. Some of these are taking in to account the age span and hence the body size span, ranging from premature babies to adolescents. This also means considering age dependent organ changes. Also, the dosage of the UCE has to be adjusted to the body size of the child. Another consideration is the fact that the transit time of the contrast agent is also a bit faster in children compared to adults. However, the most important difference is that the disease panorama is different in children compared to adults. All these differences have to be considered in order to ensure adequate exams and diagnoses.

The possible clinical applications of CEUS are limitless, i.e. wherever you can point a US transducer, you can also perform an CEUS examination. Many of the potential uses, and their respective level of evidence and recommendations for their use can be found in guidelines and recommendations from regional organizations around the world. For the purpose of this thesis, mainly the EFSUMB (European federation of societies for ultrasound in medicine and biology) guidelines and recommendations are used.
It is not my intention to cover all of the possible clinical applications in this literature review, instead I have mainly focused on the applications relevant for the understanding of the studies included in this thesis.

1.3.1 Focal liver lesions

The liver is the only organ were CEUS is officially licensed, therefore it is not surprising that the most common indication for a CEUS exam is the characterization of focal liver lesions (FLLs) (23–27).

In practice, the target of interest, usually a suspected lesion found on US or other imaging modality, is scanned through all vascular phases – arterial-, portal venous- and late phase and the lesion is analyzed depending on its specific enhancement characteristics. Image loops of the different vascular phases are stored for secondary inspection.

1.3.1.1 Malignant vs. benign differentiation

The key CEUS-imaging feature for malignant lesions is washout in the later vascular phases- i.e. a hypo-enhancing lesion compared to the surrounding liver parenchyma (7,28,29). To my understanding the pathophysiology of this imaging feature is not clearly understood but related to the alterations in the vascular biology associated with malignant tumor transformation.
In a 2018 review paper (30), CEUS was suggested to have significantly better diagnostic sensitivity and specificity compared to unenhanced US for malignant vs. benign characterization. For sensitivity the difference for CEUS vs. US was 81–85% vs. 52–54% and for specificity 95% vs 40-43%. This same review paper compared the sensitivity and specificity of CEUS in comparison with CECT for malignant vs benign differentiation were CEUS seemed to outperform CECT with a sensitivity of 95.3% vs 90.7% and a specificity of 83.7% vs 81.6%.
Another study found CEUS to perform as well as CEMRI for malignant vs benign differentiation (31).
The EFSUMB guidelines gives strong support for the use of CEUS in these instances (7). There is also support in the guidelines for the use of CEUS in the detection of metastatic lesions, in patients with a known malignancy. However, the role of CEUS in these cases appears to be less strong than for the characterization of lesions. This is due to the fact that the scanning conditions have to allow for complete examination of all liver

segments, something that is not always the case. One pitfall of CEUS is that hypo-enhancing lesions can be mistaken for malignant lesions, when in fact they can represent small cysts, adenomas, focal nodular hyperplasia (FNH), or even small abscesses not originally seen on the US scan. This is because these benign lesions may also have reduced blood flow. Therefore, if a CEUS is performed as the first surveillance exam and a possibly malignant lesions is suggested you should consider using another modality, preferably CEMRI to confirm your findings.

CEUS is not recommended for surveillance of patients at risk for hepatocellular carcinoma (HCC). This is due to the very variable CEUS appearance of HCC and the fact that not all HCC demonstrate washout in the late phase, limiting the sensitivity of CEUS.

The EFSUMB guidelines note that although the majority of the studies are adult studies, the available pediatric studies and collective experience of physicians, all recommendations for adults apply to the child as well (29).

1.3.1.2   Benign liver lesions

CEUS also performs well when characterizing specific benign lesions.

Focal fatty sparing for instance, which can resemble a lesion, will enhance just like the rest of the liver parenchyma. Here CEUS outperforms B-mode US and is comparable to CECT for the correct diagnosis (32).

Hemangiomas, on the other hand, can very accurately be diagnosed with B-mode US alone if the patient is at low risk for malignant liver lesions. In these cases no CEUS is needed for the diagnosis (33). In the setting of chronic liver disease however B-mode US performs poorly and is insufficient for the task (34). In these cases, and in other cases where B-mode US is inconclusive, CEUS can very accurately identify a hemangioma (35–37), with a diagnostic accuracy of around 90%.

Focal Nodular Hyperplasia (FNH) can be diagnosed with CEUS with an overall sensitivity of 88% according to a meta-analysis from 2013 (38). However, if not all the enhancement hallmarks of an FNH are present in the exam other modalities are needed. The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on the management of benign liver tumors from 2016 recommend a combination of CEUS and CEMRI for these difficult cases (39).

Liver cysts, as expected show no enhancement at all, and are easily identified with CEUS.

1.3.2   Transplantation

1.3.2.1   Liver transplantation

Sometimes the only treatment for end stage liver disease is liver transplantation. It is a major surgical procedure and the recipient is often very ill, therefore complications are potentially deleterious, both for the patient and for the liver graft.

One of the most feared complications, a complication that potentially leads to complete graft failure, is hepatic artery thrombosis (HAT). HAT complicates between 0- 19% of all liver transplants (40–45). Another possible complication is portal venous thrombosis (PVT), a complication that occurs in 2-17 % of all transplantations (40,42–44). Both HAT and PVT occurs more frequently in children than in adults (46).

In our institution- with the aim of quickly identifying said complications, along with other complications such as bleeding and biliary leaks- ultrasonography is usually performed within the first 12–24 hours after transplantation.

Often, HAT or PVT are readily visible with US doppler. However, sometimes, the diagnosis is not so easy, especially in children with vessel diameters that can be as small as 2mm in diameter and in an immediate post-operative setting where surgical dressings and post-operative changes can obscure the view and produce artifacts. In these cases, performing CEUS can in most cases give a definitive answer. Studies show specificity, sensitivity and diagnostic accuracy numbers for detection of vascular complications as high as 100% (47). For HAT specifically, PPV and NPV have ranged between 77%-92.9% and 99%-100% respectively (48,49). The EFSUMB guidelines and recommendations from 2012 (50) support the use of CEUS for confirmation of a suspected vascular thrombosis or stenosis after liver transplantation. Most studies building the basis for the recommendations are performed on adult patients, or a mix of adults and children. All experience so far supports its use in children. For instance, the EFSUMB position statement on pediatric use of CEUS from 2017 (29), states that "The application of CEUS in the child following transplantation is likely to be similar to the adult, with vascular patency, areas of necrosis, assessment of new focal lesions and the assessment of post-operative complications (e. g. fluid collections) most likely the areas of use." One recent and comprehensive review article on the subject of pediatric liver- and kidney transplantations outlines the various uses of CEUS in this setting (51).

1.3.3 Kidney Transplantation

Renal artery or vein stenosis is a feared post-operative complication of kidney transplantation. US is the method of choice for the evaluation of transplanted kidneys, but adding contrast to your US exam has been shown to increase the diagnostic performance for the detection of vascular complications and CEUS is also superior in visualizing the microcirculation in the kidney- and in the setting of vascular thrombosis/stenosis- visualize areas of poor perfusion (8,51,52).

1.3.4 Abdominal trauma

Trauma is an important and significant cause for injury and death in children, and blunt force abdominal trauma represents a significant part of these cases (53,54). After blunt

force abdominal trauma, the liver and the spleen are the most commonly injured organs (Holmes et al., 2002).

In the emergency setting there are two main diagnostic imaging options for identifying injuries to the abdomen, US and CT (55).
US has a place in the initial evaluation in a hemodynamically unstable patient in order to identify hemoperitoneum (55,56). However, if one would want to expand the use of US, and also evaluate organ injuries, there is an up to 30% risk of missing such an injury (57,58).
CECT on the other hand, as the gold standard in trauma imaging, has excellent diagnostic capabilities for identifying organ injuries. However, a downside with CT is that it requires potentially harmful radiation (Brenner et al., 2001; Pearce et al., 2012). For unstable patients with potentially life-threatening injuries, radiation exposure is a secondary consideration, but hemodynamically stable patients may gain from an alternative imaging method if sufficiently accurate.

CEUS for detection of organ injury after blunt abdominal trauma has been shown to perform in line with- or slightly below CECT, only missing small, clinically insignificant injuries (59–62). In hemodynamically unstable patients, CECT should always be done, but in hemodynamically stable children after mild- to moderate abdominal trauma CEUS can be used as a primary investigation. CEUS also can be used to follow up injuries and hence has the potential to significantly decrease the need for additional CT scans and hence avoiding harmful radiation (28,29,63).

1.3.5   Other organ applications

CEUS is used in many applications besides the above mentioned, and new applications are continuously being developed.

CEUS can be used to visualize and characterize pathology in most organs in the abdomen, as for example the kidneys, pancreas, spleen and adrenals. CEUS can also be applied to the lung adjacent to the pleura and the pleural space in order to differentiate between viable and necrotic consolidations or to diagnose lung abscesses amongst other uses.

CEUS is useful for bowel diagnostics as well, where the bowel wall enhancement patterns can be used in order to determine disease activity and treatment response in patients with inflammatory bowel disease. CEUS has also been used for diagnosis of focal changes or circulatory pathology in the testes and ovaries.

All these applications and more, as well as the specifics for their use are outlined in the EFSUMB guidelines and recommendations (8,64). As is the case with most CEUS applications, the recommendations and the studies that they are based on come from

mainly adult patients. However, there is accumulating evidence and guidelines that suggest that the same applies for children as well (28,29,63,65).

1.3.6   Intravesical administration

Intravesical administration, i.e. administering sulfur hexafluoride through an intravesical catheter in order to diagnose vesico-urethral reflux (VUR) is actually an officially licensed use of sulfur hexafluoride in Europe for children ages 0-18 years of age. It is also one of the best documented uses for CEUS in children, with good diagnostic capabilities (66–73) and favorable safety profile (74). All evidence suggests that contrast enhanced voiding urosonography (ceVUS) performs as well as its traditional counterpart conventional voiding cystourethrography which requires radiation. The EFSUMB recommends that ceVUS should be the initial investigation for suspected VUR in children (8).

1.3.7   Interventional CEUS

CEUS can be helpful in US guided interventional procedures. There is strong consensus (8) for using CEUS as guidance when doing biopsies of tumors. The enhancement pattern on CEUS can help to focus the biopsy location to perfused parts of the tumor and avoid necrotic parts of the tumor. According to studies this practice can help improve the diagnostic accuracy of the biopsy compared with non-enhanced US biopsy methods, and hence reduce the need for new biopsies and reduce the time to adequate treatment (75–79).
There is equally strong consensus for the use of CEUS guided biopsy or drainage, when the lesion is hard to see on unenhanced ultrasonography (8).

1.4   Use of- and attitudes toward pediatric CEUS

Although not much is written on this subject there are ongoing efforts to explore the actual use of CEUS in children.
One such effort is the "EFSUMB Pediatric Registry" created by the EFSUMB. This registry was created with the purpose of collecting data related to pediatric CEUS with SonoVue. Its aim is to document the range of use of pediatric CEUS in the European countries and to assess its safety in children. One study from 2021 summarizes the data from the registry and gives us an insight into its use in Europe. The study was on iv. use only and reported that the focus of exam for the 1463 cases included was liver (62.3 %), spleen (13.0 %), kidney (10.0 %), gastrointestinal tract (3.9 %), testis (2.4 %) and chest (1.7 %). Less frequently reported uses included superficial structures (1.6 %), adrenal gland (1.5 %), gallbladder (0.5 %), pancreas (0.8 %), urogenital pelvis (1.4 %), vessels (0.4 %) and head and neck (0.5 %)
The data was submitted from the UK (49%), Germany (35%), Poland (10%), Lithuania (3%), Hungary (1%) and Italy (1%).

Apart from this study, there are to our knowledge only two other studies that survey some aspect of pediatric CEUS in Europe. One surveyed Germany only (80). The majority only used CEUS in adults, but about 12 % also reported to use CEUS in children. Among these the most common indication was for liver lesion diagnosis followed by ceVUS exams. The other survey study from 2012 was aimed at all of Europe and surveyed pediatric CEUS specifically. (25). The majority of the respondents (88/146) did not perform CEUS on children. The ones that did reported the largest volume of exams to be ceVUS. The main iv. indication for CEUS in this study was liver lesion diagnosis.

2 Research aims

Overall aim:

To analyze and share the pediatric CEUS experience from Karolinska University hospital, Huddinge and to survey its use in the Nordic countries.

Specific aims for each paper:

I. To evaluate the safety of CEUS in children.
II. To evaluate the usefulness of CEUS in diagnosing vascular complication after liver transplantations in children.
III. To evaluate the usefullnes of CEUS in the carachterization of focal liver lesion in children.
IV. To survey the use of- and the attitudes toward pediatric CEUS in the Nordic countries.

3 Materials and methods

3.1 Study design and data collection

3.1.1 Papers I–III

Papers I–III were papers based on retrospective data from the Karolinska University Hospital, Huddinge.

In our institution, all ultrasonography exams, including CEUS-exams are performed in our radiology department and are reported through the hospital RIS/PACS system.

All persons younger than 18 years at the time of the exam who had performed a CEUS exam during the period January 1, 2004 to December 31, 2014 were eligible for inclusion. During these 11 years, there were RIS/PACS records for 10'681 US exams performed on patients less than 18 yrs. of age. Of these 10'681 exams, 287 where CEUS exams (2.7%). These 287 exams were performed on 173 individual patients. Through the RIS/PACS we retrieved data on administered contrast dose and relevant radiology reports.

Electronic patient charts were used to retrieve anthropometric data; weight, height, age and gender. Also, information on known allergies, as well as information on medical background relevant for the indication of the CEUS exam was retrieved.

3.1.1.1 **Paper 1**. *All 287 exams were eligible for inclusion in this study. For the sake of identifying adverse effects from the UCA, the patient charts were searched for mentions of adverse effects from 0 to 10 days after the CEUS exam.*

3.1.1.2 **Paper 2**. *All exams performed on a transplanted liver with the aim to assess the circulatory status of the liver graft were included. There were 74 exams performed on 34 patients. Patients charts were searched for vascular complications after liver transplantation for 30 days after the CEUS exam.*

3.1.1.3 **Paper 3**. *Figure 5 demonstrates the selection process of included CEUS exams. With regards to focal liver lesions characterization, radiology reports and available pathohistological reports as well as relevant patient records were searched for as long as the patients had follow-up for his/her liver lesion or until a clear pathohistological diagnosis was achieved.*

Figure 5. Flow chart of the selection process. FLL, Focal Liver Lesion (Reprinted with permission from Wiley journals)
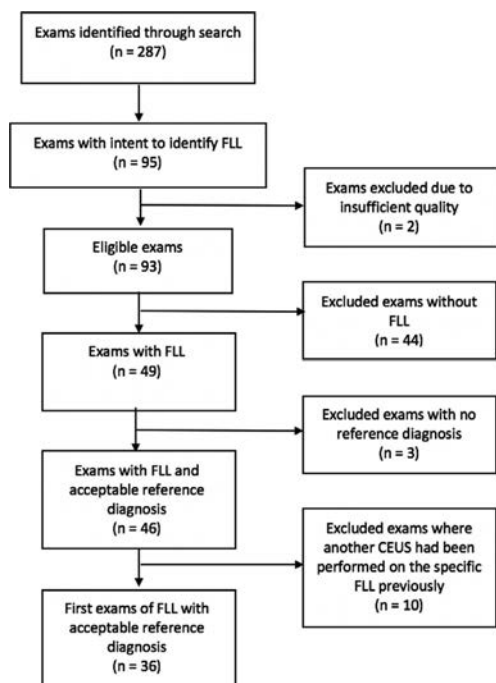
3.1.2 Paper IV

The authors created a 12-question web survey using Survey Monkey® (SurveyMonkey Inc., San Mateo, CA). The questionnaire in its original form is available as an appendix. We did not have a list of contact information for the radiologic departments in Nordic hospitals. Therefore, a manual search consisting of a combination of web-searches and personal contacts was used to find the contact information to radiologists in as many hospitals as possible. We specifically asked for the contact information to a pediatric radiologist or an ultrasonography radiologist, preferably with special pediatric interest. Especially helpful in the search for contact information were the representatives from the Swedish Society of Radiology's division for medical ultrasound and pediatric radiology, the Danish society of diagnostic ultrasound as well as the Norwegian society of radiology's division for pediatric radiology. The contact persons were asked to forward the email with the survey link to colleagues in other hospitals.

The web survey was sent in an email together witch a short explanatory text and information that the survey was completely anonymous and no personal information would be collected. We wanted only one answer per hospital and therefore each respondent was asked to respond for his/her department.

Not all respondents were required to answer all 12 questions. Respondents who did not use CEUS in children skipped questions 2-5, which were questions on the specific use of

CEUS and therefore irrelevant to these respondents.

Questions 2,5,7 and 8 had multiple answer options. For these questions we enabled a randomization function which made sure that the order of the answer options (except the last option, which was an "other (please specify)"-option) were randomized for each respondent. This to remove the possibility of "answer option bias". In questions 7 and 8, regarding advantages and barriers to the use of CEUS in children, the number of answers were limited to between and 1 and 3.

3.2 Definition of reference standards

3.2.1 Paper 1

Our reference standard for any adverse event was any mention of allergic or allergic-like reactions in the patient charts, from the time of administration of the UCA up until 10 days post administration. An adverse event was defined as any unexpected reaction not accounted for by other sources.

3.2.2 Paper 2

Our reference standard for any vascular complication was the necessity for specific surgical intervention in response to a suspected vascular complication.

3.2.3 Paper 3

Our reference standard for focal liver lesions was dependent on the available information. In falling order of priority, the standards used were: Histopathology of the lesion, follow-up of at least two years with radiological imaging, clinical follow-up without radiologic imaging of at least two years or follow-up with radiologic imaging of less than two years.

3.3 Data analysis

3.3.1 Papers I–III

All descriptive statistics as well as calculations for positive predictive value (PPV), negative predictive value (NPV) and specificity were calculated using Microsoft excel for Mac, version 16.16.27 and PRISM 9, version 9.5.0 for mac OS.

The formulas used for the calculations:

$$Sensitivity = \frac{true\ positive}{true\ positive + false\ negative}$$

$$Specificity = \frac{true\ negative}{true\ negative + false\ positive}$$

$$NPV = \frac{true\ negative}{true\ negative + false\ negative}$$

$$PPV = \frac{true\ positive}{true\ positive + false\ positive}$$

3.3.2 Paper IV

All descriptive statistics was extracted from the survey monkey website and reformatted in Microsoft excel for Mac, version 16.16.27. For Fisher's exact test PRISM 9, Version 9.5.0 for Mac OS was used.

3.4 Ethical considerations

3.4.1 Studies 1–3

The studies were performed in accordance with the Declaration of Helsinki and were approved by the Ethical review board in Stockholm, Sweden.

Risks Since there is no intervention performed, there is no risk for immediate harm or injury. However, there is the possibility of harm related to the invasion of individuals right to self-determination and integrity. The research subjects have not been informed of the use of their data for the purposes of these studies and hence there is no informed consent. According to the Declaration of Helsinki there are exceptions to when this may an acceptable practice, provided that the research in all other aspects is carefully considered and planned, and the importance of the objective outweighs the associated risks and burdens. From the declaration of Helsinki, under "informed consent", "... There may be exceptional situations where obtaining consent would be impossible or impracticable for such research. In such situations the research may be done only after consideration and approval of a research ethics committee."
In our application, we argued that all data we collected was retrospective and hence did not in any way affect the care of the patient and that the data represented the routine every day care of the patients in our institution.

Benefits
Although the research will not benefit the research subjects directly, it has the potential to benefit children in general, and specially children who are ill and in need for medical imaging. They will hopefully be exposed to less radiation and require less sedation if CEUS is used more often. Also, the research can decrease the burden many health care personnel experience regarding the absence of official licensing for CEUS. This "off-label" makes many people apprehensive about using it, and hopefully the knowledge gathered in this thesis will help relieve some of that apprehension.

Vulnerable groups
Children as a group are considered vulnerable and the declaration of Helsinki states that if possible, the research should be performed on other populations if the research question can be answered this way.

However, in this particular case, children are the necessary subjects to answer the research questions.

Conclusion

The possible benefits from this research outweigh the burdens and harms associated with not gathering informed consent.

3.4.2 Study 4

Throughout this study, we did not collect any personal or sensitive data from either the respondents or the patients under their care. As a result, there was no requirement for ethical considerations, and we did not submit an application to the Ethics Review Board.

4 Results

4.1 Paper 1

The distribution of CEUS exam focus across various organs is presented in Table 2. In absolute numbers, a total of 293 organs were examined, which exceeds the total number of CEUS exams which was 287. This discrepancy is explained by the fact that six CEUS exams involved two organs each.

The patients ranged in age from 0.1 y/o to almost 18 y/o. In height the patients ranged between 41 to 189 cm, in weight from 1.5 to 126 kg. Throughout the study period, the standard contrast dose calculation used was 0.1 ml/kg body weight for children up to 24 kg. Beyond this weight threshold, patients were given the full dose of 2.4 ml. When deemed necessary, additional doses were administered. The range for contrast dose was 0.3 to 8.1 ml. It is worth noting that the dose of 8.1 ml is more than 3 times the full dose. There were also a few other cases were the contrast dose was 7 ml and quite a few instances where the dose was 4.8 ml, i.e. double the full dose. There was no documentation to explain the reasoning behind the administered contrast dose in these cases.

Table 2 Focus of CEUS exams

	Exams (n)	%
Total	293	100%
Native liver	133	45.4%
Transplanted Liver	92	31.4%
Kidney	21	7.2%
Spleen	30	10.2%
Miscellaneous	17	5.8%

No serious adverse effects were recorded. Only one case of itching the day after the exam was noted, but this was considered to be a reaction from intravenous fentanyl which was concomitantly administered.

4.2 Paper 2

During the study period, a total of 74 CEUS exams were conducted on 34 patients with the objective of assessing the circulatory status of transplanted livers.
All but 13 (18%) of these were performed within 30 days after the transplantation surgery. 53% of the exams were performed on children 2 y/o. or younger. Arterial or portal venous complications were observed in six (11%) out of the 34.

Table 3 Cause for transplantation in relation to transplantation technique and in relation to confirmed vascular complications within 30 d from surgery (Reprinted with permission from Wiley journals)

Cause for transplantation		Cholestatic condition[b]	Metabolic Disease[c]	Re-transplantation due to graft failure	Other[d]
No. of patients	37 total	23 (62%)	4 (11%)	3 (8%)	7 (19%)
Transplantation technique	Diseased Donor (DD), split liver	10 (44%)	2 (50%)	0	3 (43%)
	DD, whole liver	7 (30%)	2 (50%)	1 (33%)	4 (57%)
	LD (left lateral segment)	6 (26%)	0	2 (67%)	0
Circulatory status	No circulatory problem	17 (74%)	4 (100%)	2 (67%)	6 (86%)
	Arterial problem	2[a] (9%)	0	0	0
	Arterial and portal vein problem	1 (4%)	0	0	1 (14%)
	Portal vein problem	0	0	0	0
	Perfusion problem	4[a] (17%)	0	1 (33%)	0

[a]One patient had both an arterial and perfusion problem
[b]Biliary Atresia, Alagille syndrome, Primary sclerosing cholangitis, Progressive Familial Intrahepatic Cholestasis, Intrahepatic cholestasis of unknown origin.
[c]Alfa-1- antitrypsin deficiency, Cystic Fibrosis, Primary hyperoxaluria, Crigler-Najjar syndrome.
[d]Caroli syndrome, Cryptogenic cirrhosis, Fulminant hepatic failure, Hepatitis C, Hepatopulmonary syndrome related to Adams-Oliver syndrome.

Table 3 provides a summary of the confirmed vascular complications in relation to liver-specific details such as liver disease and transplantations technique.
In all cases CEUS accurately diagnosed the vascular complication, however, there were two false positives– one where CEUS reported no arterial circulation and one where CEUS reported reduced portal vein flow. Both these cases turned out to have adequate circulation by the reference standard.

Table 4 Contingency table for the calculations of PPV and NPV for arterial complications

	Arterial complication	No arterial complication	Total	Calculation
CEUS positive	4	1	5	PPV: 4 / (4+1) = 80%

| CEUS negative | 0 | 69 | 69 | NPV: 69/ (69+0) = 100% |

Table 5 Contingency table for the calculations of PPV and NPV for portal vein complications

	Portal vein complication	No portal vein complication	Total	Calculation
CEUS positive	2	1	3	PPV: 2/ (2+1) = 67%
CEUS negative	0	71	71	NPV: 71/ (71+0) = 100%

Table 6 Contingency table for the calculations of PPV and NPV for arterial– or portal vein complication.

	Arterial– or portal vein complication	No arterial– or portal vein complication	Total	Calculation
CEUS positive	6	2	8	PPV: 6/ (6+2) = 75%
CEUS negative	0	74	74	NPV: 74/ (74+0) = 100%

PPV and NPV for arterial complications was 80% and 100%. For portal vein complications the PPV and NPV was 67% and 100%. For arterial– or portal venous complications the PPV and NPV was 75% and 100% respectively. Tables 4–6 show the contingency tables used for the calculations of PPV and NPV for vascular complications.

In 28% of cases, the radiologist could not see the arterial blood flow without CEUS. In 4% of cases, the same was true for portal venous blood flow.

4.3 Paper 3

36 exams, performed on 35 patients were included in this study. The distribution of the reference standard for the 36 exams included in this study is summarized in Table 7.

Table 7 Reference standard for diagnosis

Reference standard	N (%)
Patho-histology	10 (28%)
Radiologic follow-up ≥ 2 years	13 (36%)
Clinical follow-up ≥ 2 years	5 (14%)
Radiologic follow-up < 2 years	8 (22%)

The reference diagnoses are presented in table 8 and subgrouped into a cirrhotic group and non-cirrhotic group because the general panorama of focal liver lesions differs between these two groups. 35 of 36 lesions were determined to be benign by the reference standard. One lesion was malignant.

Table 8 Distribution of reference diagnosis for all examinations, subdivided into cirrhotic and no-cirrhotic groups (reprinted with permission from Wiley journals)

Reference diagnosis	Cirrhotic liver (n = 6)		Non-Cirrhotic liver (n = 30)		Total (n = 36)	
	n	%	n	%	n	%
Benign						
Benign, uncharacterisable	2	33	11	37	13	36
FNH	1	17	10	34	11	30
Regenerative nodule	2	33	2	7	4	11
Cyst	0	0	4	13	4	11
Adenoma	1	17	0	0	1	3
Hematoma	0	0	1	3	1	3
Haemangiondothelioma	0	0	1	3	1	3
Malignant						
Klatskin tumour	0	0	1	3	1	3

FNH, Focal Nodular Hyperplasia.
Distribution of reference diagnosis for all examinations, subdivided into cirrhotic and non-cirrhotic groups.

4.3.1 Benign vs malignant differentiation

In 27 /36 cases (75%) there was agreement between the CEUS exam and the reference standard in regard to being able to differentiate a benign from a malignant lesion. The 9 cases where there was disagreement between CEUS and reference standard are summarized in table 9.

Table 9 CEUS vs Reference diagnosis (number of exams in parenthesis)

CEUS diagnosis (total = 9)	Reference diagnosis (total = 9)
Malignant (1)	Benign (1)
Inconclusive (4)	Benign (4)
No FLL visualized (4)	Benign (3), Malignant (1)

The malignant case was a Klatskin tumor (hilar cholangiocarcinoma) and the patient had performed multiple diagnostic imaging exams previously, none of which allowed for a definitive diagnosis. The CEUS exam that was included in our paper was performed with the primary aim to help guide the radiologist in securing a representative core biopsy from the lesion. Characterization of the lesion was a secondary objective. Since no FLL was seen with CEUS, no biopsy was taken at that time. An intraoperative liver biopsy was performed 2 weeks after the CEUS exam which led to the definitive diagnosis.
The stored images, which apart from non-enhanced US images and cine-loops and only included arterial phase CEUS cine-loops were re-examined in 2021 by a senior US and CEUS radiologist. His report stated that, given the limitations from only having arterial phase images, no pathological enhancement could be seen in the hilar region of the liver.

When removing the four CEUS exams where a FLL could not be seen, the overall agreement between CEUS and reference was 84% (27/32). Also removing the four inconclusive CEUS exams, and hence only keeping the exams resulting in a dichotomous "benign" or "malignant" report, resulted in 96% (27/28) agreement.

4.3.2   Diagnostic agreement for specific diagnoses

When looking specifically at the three most common diagnoses in our material the agreement between CEUS and reference diagnosis was as follows (Table 10).

Table 10 (reprinted with permission from Wiley journals)

Reference diagnosis	Agreement between CEUS and reference diagnosis (%)
FNH	91 (10/11)
Regenerative nodule	75 (3/4)
Cyst	100 (4/4)

FNH, Focal Nodular Hyperplasia.
Agreement between CEUS diagnosis and reference diagnosis for the three most common diagnoses. Presented as percentage with absolute numbers within parenthesis.

4.3.3 Sensitivity, Specificity, PPV and NPV

For the calculation of sensitivity, specificity, PPV and NPV of a diagnostic test, a contingency table is needed. In our case for malignant vs benign differentiation, only the cases where the test– the CEUS exam, could provide an answer were included– hence removing the four inconclusive cases and the four cases where an FLL could not be seen. A table with the remaining 29 cases is presented in Table 11.

Table 11 Contingency table for calculations of PPV, NPV, Sensitivity and Specificity of CEUS as a diagnostic tool for differentiation between malignant and benign lesions. PPV, positive predictive value, NPV, negative predictive value, CI, confidence intervals, N/A, not applicable

	Disease (Malignant)	No disease (Benign)	Total	Calculation
CEUS positive (Malignant)	0	1	1	PPV: N/A
CEUS negative (Benign)	0	28	28	NPV: 28/ (28+0) = 100% (95% CI: 0.88 to 1.00)
Total (n)	0	29	29	
Calculation	Sensitivity: N/A	Specificity: 28/ (28+1) = 97% (95% CI: 0.83 to 1.00)		

4.4 Paper 4

We sent out 119 surveys and received a total of 48 responses of which 45 were complete and included in the results, yielding a response rate of 38%.
In the survey, there were questions that included a response option for "other, please specify". Whenever possible, any free-text responses fitting into the predefined answer categories were categorized accordingly. Otherwise, they were grouped in a "other" category.

4.4.1 Demographics

There was equal distribution between respondents working in a university hospital (49%) and those in a non-university hospital (51%). 44% of respondents worked in a hospital that had a specialized pediatric radiology department whereas 53% provided pediatric radiology services from within their general radiology department. Most responses where from Sweden (Table 12).

Table 12 Distribution of responses per country in falling order of quantity (reprinted with permission from Elsevier).

| Country	n (%)
Sweden	21 (47%)
Finland	11 (24%)
Norway	9 (20%)
Denmark	3 (7%)
Iceland	1 (2%)

4.4.2 Use of pediatric CEUS

22 (49%) of the institutions used CEUS in children. All 22 used Sonovue® as contrast agent and none used any of the alternatives.

65% (13/20) of institutions with a specialized pediatric radiology department performed pediatric CEUS compared to 37.5% (9/24) of institutions without. Radiology departments within a university hospital were slightly more likely to perform CEUS in children– 64% (14/22) in university hospitals vs 35% (8/23) in non-university hospitals. However, this difference was not statistically significant (P-value 0.13 using a two-sided Fisher's exact test).

The indications for use are presented in figure 6.

Figure 6. Summary of indications for the 22 institutions that used CEUS in children. Total number of respondents n and percentage of total in parenthesis (%). The "other (please specify)"- answers were:

"ovarian torsion", "intracavitary/fistula use", "other vascular indications", "subcutaneous nodes" and "kidney anomalies". (Reprinted with permission from Elsevier)
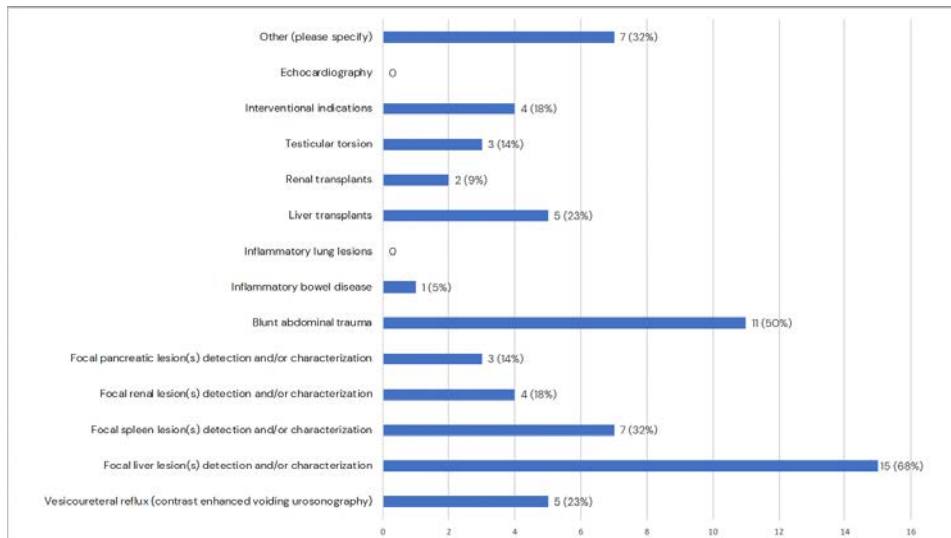
4.4.3   Advantages and barriers

The distribution of the respondent's opinions regarding advantages and barriers for pediatric CEUS is presented in figures 7 and 8.

Figure 7. Summary of advantages for all 45 respondents. 1–3 answers per respondent was allowed, therefore the sum is larger than 45. (Reprinted with permission from Elsevier)
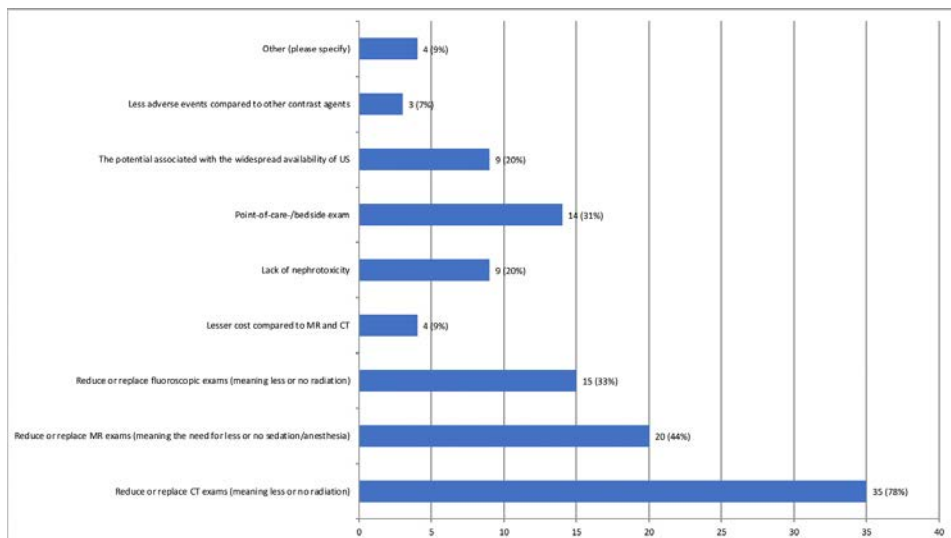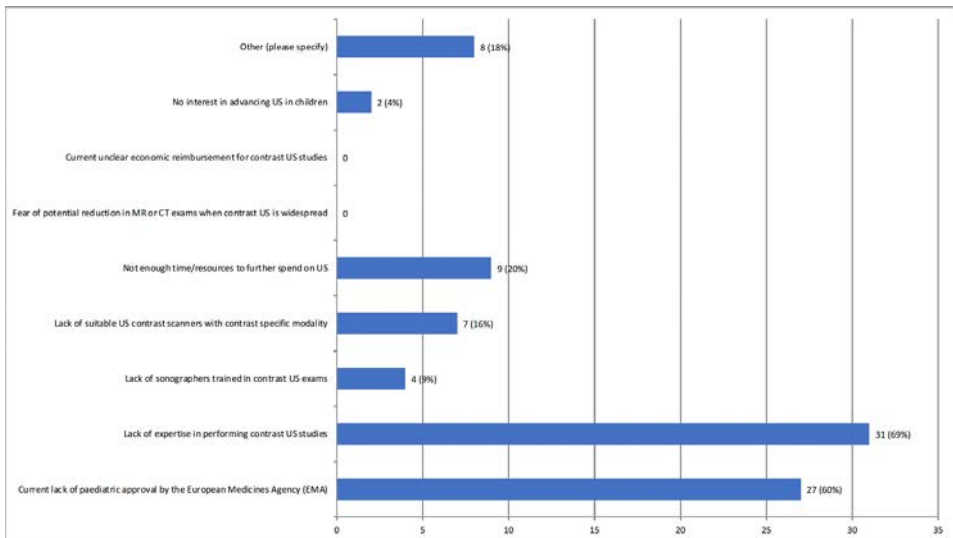
Figure 8. Summary of barriers for all 45 respondents. 1–3 answers per respondent was allowed, therefore the sum is larger than 45. (Reprinted with permission from Elsevier)

10 respondents (43.5%) of the 23 that did not use CEUS in children stated that they were considering using it.

5 Discussion

5.1 General aspects

The four papers included in this thesis help illuminate the width of use that CEUS has in children. Papers 1–3 display the specific uses of pediatric CEUS in our institution, which as a tertiary liver center has strong focus on liver diagnostics. The results imply safety and useful diagnostic capabilities in the characterization of vascular complications after liver transplantation as well as for the characterization of FLL's. Interestingly enough, in our institution we did not use CEUS for voiding urosonography which in general is one of the most widespread uses of pediatric CEUS and the only officially approved pediatric use of CEUS in Europe. The reasons for this are unknown, but one can speculate that local routines, habits and preferences govern the decisions in diagnostic medicine, (as would be expected in a workplace ecosystem).

Paper no 4 widens the perspective on CEUS and tries to survey its use in the whole country and our neighboring Nordic countries. This study highlights the perceived advantages and barriers for pediatric CEUS among the respondents, were the most important advantage was the possibility to avoid alternative diagnostic exams. The greatest barriers to its use were reported as lack of expertise and lack of official licensing.

5.2 Paper 1 – Safety

Our paper (81) did not find any serious adverse effects from i.v. use of sulfur hexafluoride.

Considering the incidence of 1.25% for any adverse event, reported by Ntoulia et. al. from the 2021 review paper (16) it is plausible that we may have detected some non-treatment-requiring adverse events had we conducted a prospective study or had access to comprehensive adverse event surveillance data for retrospective analysis. In our study, we relied on the information recorded in electronic patient charts, which may have led to the potential oversight of subtle and transient adverse events. However, we have to assume that any adverse events requiring treatment would have been documented in the patient's chart and subsequently identified during our retrospective analysis. With this assumption, we can confidently conclude that no serious adverse events occurred in any of the cases we reviewed.

In retrospect, we should have made clear what we defined to be an adverse effect, for instance using the definition from the World Health Organization (82). These definitions aligned closely to the criteria we were looking for in our retrospective analysis, especially in regards to serious adverse events. While the inclusion of these definitions would not have changed our results, it would have contributed to the reproducibility of the study, which might have been a more appropriate approach.

Overall, intravenous hexafluoride use in children appears to be safe, but so far appears to provoke adverse events slightly more often (16) than iodinated-contrast agents (19) and gadolinium-based contrast agents do (17,18).

It is worth noting that the larger adult studies (12–15) in general show a lower percentage of adverse events compared to the smaller pediatric studies. It is plausible that as the sample size increases the rate of adverse events decreases – approaching the true rate of such adverse events. Or, it could be that children are more prone to react to Sonovue/Lumason than adults are.

In the assessment of the safety of CT and MRI scans, it's important to also account for other, non-allergy related adverse events.

One of the greatest concerns is the elevated cancer risk associated with ionizing radiation. Children are more sensitive to radiation than adults are and therefore there are conscious and continuous efforts to lower the doses emitted from diagnostic exams. However, there still appears to be an elevated risk for the development of certain cancer forms, especially from CT exams (83).

Other risks include contrast-induced nephropathy from iodinated contrast agents (84,85) and nephrogenic systemic fibrosis from gadolinium based contrast agents (86). Therefore, patients with reduced renal capacity should not undergo any of these exams due to the risk for permanent renal damage.

Another possible hazard associated with gadolinium based contrasts is that the contrast has been shown to deposit in the body of patients (87–89) It´s long term effects are however, still unknown (90).

Furthermore, MRI exams can in some instances require the child to be rendered immobile though sedation, which, in turn, carries some associated risks and is associated with allocation of extra resources and time. Nonetheless, there are continuous developments in MRI protocols and sequences to minimize the need for sedation (91).

When considering potential non-allergy related risks associated with CEUS, it's important to account for the field of research exploring the potential bioeffects of CEUS on tissue. These studies reveal that under specific conditions, CEUS can induce tissue damage, particularly in-vivo microvascular damage. It is to be noted that these studies have been performed on small animal models and there is still uncertainty regarding if these results can be transferred to the human setting, and if so, what the possible implications are (92–96).

All in all, the low rate of adverse events together with the facts that CEUS is free of ionizing radiation, that it can be administered independently on renal function and that it does not require sedation makes it a very safe method to use. Nevertheless, allergic

reaction will occur and it is important that the exams are performed in a setting equipped to manage such reactions.

5.3   Paper 2 – Vascular complications after liver transplantation

Our paper (97) found that PPV and NPV for arterial complications was 80% and 100%, for portal venous complications 67% and 100 % and for either arterial or portal venous complications the PPV and NPV was 75 and 100% respectively.

A high NPV is desirable in a setting like this, where the disease diagnosed is serious, but treatable if addressed early in its course. A moderate PPV in this case can be argued to be acceptable– in those cases where a circulatory issue is noted on CEUS, but there really is none, unless there are clinical signs to say that there is a circulatory issue, it is unlikely that the patient will undergo surgery without any other diagnostic confirmation. That was the case in our study, where one patient with a positive CEUS exam underwent a follow-up CECT, which revealed no circulatory complication, and the patient did not require surgery.

Our sample size of 74 exams was not large enough to allow for adequate sensitivity– and specificity calculations (98), therefore only PPV and NPV were calculated.

Furthermore, when it comes to making decisions about individual patients, sensitivity and specificity are generally not the most practical parameters to use. For this purpose, NPV and PPV prove to be much more useful (99).

Now, for calculations of PPV and NPV, a reference standard is required. In a prospective study, such reference standard could have been angiography or CECT. In our case, the reference standard was a practical one. Our assumption was that any significant vascular complication – a positive reference standard– would be observed by the treating physicians and acted upon usually through surgery. Conversely, the absence of clinical suspicion and the absence of surgery would represent a negative reference standard.

I consider this to be an adequate reference standard given the fact that such serious complication such as arterial- or portal venous thrombosis or stenosis are never left untreated.

Another interesting finding in our study was the fact that in 28% of the cases, the radiologist performing the postoperative CEUS exam could not identify arterial blood flow without the help of CEUS and in 4% of the cases the portal venous blood flow could not be identified without CEUS. The practical implications of this are even easier to appreciate than the PPV and NPV: the radiologist could, in the same setting, administer CEUS, visualize adequate circulation and provide a positive report to the treating

physicians and worried parents. Even more so, the radiologist could scan the liver for a couple of more minutes and give a report on the other vessels as well as the general perfusion of the liver transplant. Without CEUS and in absence of clear clinical signs of a complication, these cases would have probably needed a CECT to confirm the patency of the hepatic artery or the portal vein. In these cases, CEUS saves the patients from harmful ionizing radiation.

5.4 Paper 3 – Characterization of focal liver lesions

In our paper (100) diagnostic agreement between the CEUS exam and the reference standard was 75% for differentiation between benign and malignant lesions for all 36 cases. We then removed the 8 cases where CEUS was inconclusive or CEUS could not find an FLL and adjusted the diagnostic agreement accordingly to 96%. In retrospect I think that removing the four cases where an FLL could not be seen is appropriate since FLL characterization using CEUS is dependent on being able to evaluate the enhancement patterns of the specific FLL, something that could not be done in these four cases. However, it could be argued that if the FLL could be visualized but the CEUS still was inconclusive – that this is just part of clinical reality and that these four cases should have been included in the adjusted calculation. A revised calculation of diagnostic agreement would therefore, adding these four inconclusive cases to the calculation, be 84% (27/32).

For reference, the largest pediatric only study on this subject included 44 children (23). Among these cases, diagnostic agreement for benign versus malignant differentiation, was calculated for the 34 cases where reference imaging was available, yielding an 85% agreement rate.

We also presented results for specificity (96%) and NPV (100%) for correctly characterizing a lesion as benign. 95 % confidence intervals (CI) were also calculated for the purposes of this thesis– however CI's were not part of the original paper (100). For these calculations we used the 28 patients remaining after the removal of the 8 inconclusive cases and the cases where an FLL was not visualized. In this situation however, I think that removing all these cases from the calculation was adequate. Specificity and NPV, as well as sensitivity and PPV, require dichotomous results, both from the reference standard and from the test that is evaluated. Therefore, we removed the non–dichotomous values from the equation.

It is to be noted however, that our data only included one malignant case. This is a limitation regarding the external validity of the test.

Again, comparing against the largest pediatric study, results remain very similar, this study reporting specificity of 98% and NPV of 100% (23).

However, there are concerns about whether specificity should have been calculated at

all. It can be argued that 28 cases are too few to allow for accurate specificity calculations (98). Nevertheless, the 95% confidence intervals for specificity and NPV provide an estimated range of these diagnostic characteristics.

For reference standard, i.e. the "true" diagnosis that CEUS is compared against, we used different measures according to availability. As shown in table 6, four distinct types of reference standards were used: Histopathology, radiologic follow up of ≥ 2 years, clinical follow up of ≥ 2 years and radiologic follow up of < than 2 years, in falling order of priority. There are arguments both against and for the decision to include various reference standards.

The argument against is mainly that this weakens the robustness of our reference standard. In a perfect world, all exams would be compared against a histopathologic diagnosis.

Conversely, the rationale behind the decision to utilize multiple reference standards is rooted in the complex nature of investigating FLLs. In clinical practice, the reference standard typically involves contrast-enhanced MRI (CEMRI) or contrast-enhanced CT (CECT) because in cases where a radiologist classifies a lesion as benign, biopsy is often deemed unnecessary. In other cases, clinical follow-up is the most appropriate course of action for the individual patient. By including all these cases, we can argue that this approach more closely reflects the true clinical reality and potentially offers a more accurate representation of the population under study.

One important factor that may influence the frequency of use of reference standard exams/procedures is the "verification bias". This is a measurement bias in which the results of a preliminary test (CEUS in this case) affects whether or not the reference standard is used to verify the test results. This is especially true for situations where the reference standard is costly, invasive, risky or otherwise cumbersome and clinicians therefore may be reluctant to let the patients go through further exams. In this setting, it may very well be the case that a patient whose CEUS exam reports a benign lesion is not sent to CT or MRI and definitively not sent to perform a liver biopsy. It would thus seem evident that the distribution of reference standards in our study is in part affected by verification bias. The magnitude and direction of the effect that the verification bias has on our results is unclear.

5.5   Paper 4 – Survey of use- and attitudes towards CEUS

This study is as far as I know, the first of its kind to survey the routine use and the attitudes towards pediatric CEUS in the Nordic countries. For comparison there exists only three other studies from other parts of Europe (25,80,101) and one from USA (102).

In our survey (103), half (22/45) of the respondents stated that their institutions performed pediatric CEUS which is higher than percentage from the other surveys, 30.8% (25), 26.6% (80) and 13.5% (102) respectively. In our sample 49% of respondents

worked in a university hospital and our results suggest that radiology departments in university hospitals are more likely to perform pediatric CEUS. There are no data from other studies on this correlation. It is possible that respondents from university hospitals are overrepresented in our sample. However, in the 2018 study by Back et al. a larger proportion of all respondents (73%) compared to our study worked in a university-hospital.

The distribution of indications of use are similar to those from the other studies where the liver is the most examined organ (25,80,101,102). However, regarding ceVUS, in our sample only 23% reported this as an indication of use compared to 32–81% from other surveys (25,80,102).

Regarding the attitudes towards pediatric CEUS, it was very clear from our results that the main advantages reported were the potential associated with CEUS in decreasing alternative exams such as CT's, MRI's and fluoroscopies. Considering the elevated cancer risks associated with CT exams this inherent property of CEUS is an important one and one that has the potential to significantly reduce the morbidity and mortality amongst the most vulnerable children.

However, there are barriers towards it use, and the most commonly reported barrier was "lack of experience" closely followed by "lack of official licensing". It is possible that it is the lack of official licensing that leads to the lack of experience, and addressing the regulatory issues regarding pediatric CEUS could simultaneously result in the elimination of many barriers.

The major weakness of our study is the low response rate and uneven distribution of respondents by nationality. In hindsight we should have assured to have a clearer contact pathway to radiologists in all countries.

The response rate, at 38%, aligns with findings from previous studies, such as 26.7% (102) and 42.3% (80). However, it falls below our desired level. The low response rate has implications for the representativeness of our sample. For instance, it raises the possibility that those who responded may have had a generally more favorable attitude towards pediatric CEUS compared to those who did not participate.

Despite its limitations, I am of the opinion that this study still offers valuable insights into the perspectives of Nordic radiologists regarding pediatric CEUS.

In conclusion, the knowledge mined from this study is expected to increase understanding of the current use of CEUS and may serve as a platform to further its continued implementation amongst radiologist and clinicians.

6 Conclusions

    I.   The short term (up to 10 days post exam) safety of CEUS in children is excellent.
    II.   CEUS is a useful tool in the post-transplant evaluation of vascular complications in children.
    III.   CEUS is a useful tool in the focal liver lesion work-up in children, especially for correctly classifying a lesion as benign.
    IV.   There is interest for pediatric CEUS within radiologic departmets in Nordic hospitals, but also obstacles for its use- primarily lack of experience and lack of official-licensing.

7 Points of perspective

Although there are many studies, guidelines and recommendations that speak for the capabilities of CEUS as a diagnostic tool in children, there still is a sizeable gap between adult use and pediatric use. There still exists apprehension amongst clinicians to perform CEUS in children due to its lack of official pediatric licensing, which probably explains a portion of this gap.

In the US, through the combined efforts from researchers, clinicians and lawmakers, in 2016 sulfur hexafluoride (Lumason) was accredited official FDA licensing for pediatric use in focal liver lesions. The effects of this decision remain to be seen, but one can speculate that the development of pediatric CEUS will increase rapidly and as a secondary effect the use of CT will decrease.

I believe that working towards an official European licensing is the sole most important change that can be made in order to allow for a more widespread use of CEUS in European children.

To achieve this goal, more pediatric-only research is needed and most importantly, more institutions should encourage the careful and deliberate use of CEUS in children.

I think that future studies in Europe should focus on the ongoing evaluation and validation of CEUS in areas where it has the potential to reduce radiation exposure, such as comparing CEUS to CT for diagnosing focal liver lesions or voiding urosonography vs standard voiding cystourethrography.

Additionally, research should focus on situations where CEUS can minimize complications compared to alternative methods, such as CEUS-guided biopsies versus non-CEUS-guided biopsies.

Furthermore, I think it is crucial to assess the cost-effectiveness of integrating CEUS into the routine diagnostic toolkit of hospitals and clinics.

All these areas of focus—radiation reduction, complication reduction, and cost-effectiveness—can be important factors in driving changes in institutional diagnostic protocols. Of these, I believe well-conducted studies on the cost-effectiveness of CEUS compared to alternative methods, hold the potential for the most practical impact.

8 Acknowledgements

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10 Appendix

1.

In Europe, no ultrasound (US) contrast agent has been approved by the European Medicines Agency (EMA) for use in children below 18 years of age. However, US contrast agents are widely used in adults and off-label in children. In the USA, paediatric use of a contrast agent (Lumason) has been approved by the FDA since 2019.

We want to assess current interest and usage of contrast US in children in the Nordic countries.

The survey will not take longer than 5 minutes to complete.

You will not be asked to share any identifying information about yourself, your patients or your institution.

Thank you very much for your cooperation

* 1. Does your radiologic department use US contrast agents in children?

◯ Yes

◯ No

2.

* 2. Which of the following contrast agents do you use? (select all applicable)

☐ Sonovue

☐ Optison

☐ Sonazoid

☐ Other (please specify)

[   ]

* 3. How long has your institution performed CEUS exams on children? Please specify in years

[   ]

4. How often do you use CEUS in Children?

○ Every day

○ About once a week

○ A few times a month

○ Once a month

○ Less than once a month

○ A few times a year

○ Once a year

○ Less than once a year

○ Other (please specify)

[   ]

* 5. Please check the indication(s) for your use of US contrast agents. Select all applicable answers

☐ Vesicoureteral reflux (contrast enhanced voiding urosonography)

☐ Focal liver lesion(s) detection and/or characterization

☐ Focal spleen lesion(s) detection and/or characterization

☐ Focal renal lesion(s) detection and/or characterization

☐ Focal pancreatic lesion(s) detection and/or characterization

☐ Blunt abdominal trauma

☐ Inflammatory bowel disease

☐ Inflammatory lung lesions

☐ Liver transplants

☐ Renal transplants

☐ Testicular torsion

☐ Interventional indications

☐ Echocardiography

☐ Other (please specify)

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3.

* 6. If you are not using US contrast agents in your institution, are you considering using it?

○ Yes

○ No (please specify why)

[   ]

4.

* 7. In your own professional opinion - what do you consider to be the most important advantages of the use of US contrast agents in children? (select 1-3 answers)

☐ Reduce or replace CT exams (meaning less or no radiation)

☐ Reduce or replace MR exams (meaning the need for less or no sedation/anesthesia)

☐ Reduce or replace fluoroscopic exams (meaning less or no radiation)

☐ Lesser cost compared to MR and CT

☐ Lack of nephrotoxicity

☐ Point-of-care-/bedside exam

☐ The potential associated with the widespread availability of US

☐ Less adverse events compared to other contrast agents

☐ Other (please specify)

[   ]

* 8. In your own professional opinion - what do you consider to be the most important barriers to the use of US contrast agents in children? (select 1-3 answers)

☐ Current lack of paediatric approval by the European Medicines Agency (EMA)

☐ Lack of expertise in performing contrast US studies

☐ Lack of sonographers trained in contrast US exams

☐ Lack of suitable US contrast scanners with contrast specific modality

☐ Not enough time/resources to further spend on US

☐ Fear of potential reduction in MR or CT exams when contrast US is widespread

☐ Current unclear economic reimbursement for contrast US studies

☐ No interest in advancing US in children

☐ Other (please specify)

[   ]

5.

* 9. Which of the following best describes your practice setting?

○ University hospital

○ Other hospital

○ Other (please specify)

[   ]

* 10. Which of the following statements corresponds with the radiologic department in your hospital?

○ Our department is a specialist paediatric imaging department and offers full paediatric imaging services, including but not limited to CT, MRI and paediatric fluoroscopy.

○ Our department provides at least plain radiography, ultrasound and CT for children.

○ Our department provides plain radiography and ultrasound services for children, but no other imaging for children is performed.

○ Our department provides no diagnostic imaging of children at all.

○ Other (please specify)

[   ]

* 11. Which of the following statements correspond best with the radiologic department i your hospital

○ Our department offers specific paediatric staff including paediatric radiologists

○ Our department is not a specialist paediatric imaging department but rather we provide paediatric imaging services from within our general radiology department.

○ Other (please specify)

[   ]

* 12. In what country is your hospital located?

○ Sweden

○ Denmark

○ Norway

○ Finland

○ Iceland