Title: The "humble" bubble: contrast-enhanced ultrasound.

Authors: Prof. Gill Marshall[1], Anne Sykes[2], Dr Jonathan Berry[3], Dr Leon Jonker[1]

1: University of Cumbria, Faculty of Health and Wellbeing, Lancaster LA1 3JD, UK

2: University of Salford, Directorate of Radiography, Salford, M5 4WT, UK

3: North Cumbria University Hospitals NHS Trust, Radiology Department, Carlisle CA2 7HY, UK

Corresponding author: Professor Gill Marshall

Research Development Lead

Faculty of Health and Wellbeing

University of Cumbria

Lancaster, LA1 3JD.

Telephone: 01524 384384, extension 2446

E mail: gill.marshall@cumbria.ac.uk

Running title: Emergence of contrast-enhanced ultrasound

Key words: sonographer; ultrasound; contrast agents; microbubbles; vasculature; side effects

Abstract [148 words, 150 max]

The use of contrast-enhanced ultrasound (CEUS) is increasing within the field of medical imaging. Ultrasonic contrast agent (UCA) contains gas microbubbles similar in size to red corpuscles which provide highly reflective interfaces, enabling dynamic demonstration of echogenic streams of the contrast within the anatomical area of interest on real-time greyscale ultrasound. Longevity of the microbubbles has been improved by changing their composition. The application of CEUS in the UK continues to grow, bringing it into territories historically occupied by computerised tomography (CT) scanning and magnetic resonance imaging (MRI). Hence, the role of CEUS may be of interest to all diagnostic imaging practitioners. Here we summarise the mode of action and use of CEUS, and its role within a range of applications. The potential risks of CEUS are compared to other contrast enhanced imaging techniques. The benefits of CEUS and its implications for diagnostic imaging practice are also covered.

The "humble" bubble: contrast-enhanced ultrasound.

Introduction

Contrast-enhanced ultrasound (CEUS) is a diagnostic technique that utilizes the physical attributes of microbubbles, and chemical properties of gases contained within them, enabling dynamic demonstration of echogenic streams of the contrast within the anatomical area of interest on Real-time greyscale ultrasound to gain detailed information about blood flow and perfusion, or for endoluminal evaluation, for example of uterine tube patency.[1] In addition to improving diagnostic capability within existing ultrasound practice, it has brought the application of ultrasound technology into territories historically occupied by computerised tomography (CT) scanning and magnetic resonance imaging (MRI).[2] Hence, the role of CEUS may be of interest to all diagnostic imaging practitioners. Unlike CT, CEUS does not involve any ionizing radiation, nor the potentially fatal side-effects of CT and MRI contrast agents. These are: contrast induced nephrotoxicity associated with iodinated agents used in CT and nephrogenic systemic fibrosis associated with gadolinium based MRI agents.[3,4] Given these factors, it would be reasonable to expect the use of CEUS, and interest in the topic to continue to increase within the field of medical imaging. This article provides an overview of CEUS in terms its mode of action, diagnostic applications and also barriers to and risks associated with its use, from both a patient and health professional perspective. Finally, the implications for practice of this rapidly developing area within diagnostic imaging are identified.

Properties of ultrasound contrast agents

Mode of action of microbubbles

The ability of ultrasound to detect microbubbles was first reported on during the 1960's and 1970's.[5,6] The actual routine application of microbubbles as contrast agents in medical diagnostics took place around the turn of the millennium.[7] Microbubbles enhance the ultrasound signal because of the way they respond to the ultrasound waves encountered. The microbubbles provide many tiny reflecting interfaces that produce non-linear echogenic signals, allowing visualisation of the contrast agent on real-time grey scale imaging.[8] Also, the microbubbles resonate in response to the changes within the ultrasound beam; they are compressed by each ultrasound pressure peak and expand during an ultrasound pressure trough and Resonance occurs at frequencies of approximately 3 MHz.[8] Because of this change in diameter of the bubbles, the microbubbles exhibit strong echogenic behaviour and hence the signal to noise (SNR) ratio is improved further. When insonated with low acoustic pressure and at low mechanical index (MI), the microbubbles provide strong non-linear harmonic responses and, without being destroyed, generate specific signals enabling continuous real-time imaging.[9] Therefore, the image is further optimised by selecting appropriate MI values and by use of ultrasound harmonics, where all nonlinear signals are collected within the entire broadband spectrum, including the fundamentals.[1] Ultimately this leads to images that enable improved discernment of areas of pathology, e.g. metastases within the parenchyma of organs.[9] The typical size of each microbubble is 1-8 microns, a size small enough to avoid risk of blocking capillary vessels or causing tissue ischaemia.[10,11] When ultrasound contrast agent in injected intravenously, the microbubbles remain purely intravascular both in macro- and microvascularity; they remain in the vascular compartment for several minutes, since they are small enough to avoid filtration by the lungs, but too large to enter the interstitial fluid.[9] They must be able to withstand the pressures of the left side of the heart and require transpulmonary stability to be able to reach the area being examined.[12] It can be seen then, that the properties of the microbubbles are key to the efficacy of the ultrasonic contrast agent.

Ultrasound contrast agents have been further developed for improved efficacy. The choice of microbubble gas and shell will determine the microbubbles' degree of echogenicity, longevity once in circulation and also capacity to absorb ultrasound wave energy before bursting.[1, 11] First generation ultrasound contrast agents (UCA) contained air within the microbubbles; an example is Levovist®. Current generation ultrasound contrast agents, e.g. Sonovue, contain an inert gas rather than air. Inert gases used to fill the microbubbles include octafluoropropane and sulphur hexafluoride. They are not absorbed in the blood and are removed from the body through the pulmonary circulation. This means that the half-life of the UCA is improved and a smaller amount needs to be injected into the patient. [1,11,13] For example, Sonovue® has a mean half-life of 1 minute (Bracco, Italy; Sonovue summary of product characteristics). Microbubble shells can be made from albumin, phospholipid or polysaccharides.[1,11,13] Current generation shells around the microbubbles are more resistant to the ultrasound wave energy, further prolonging the use of agent once injected into a patient; the phospholipid shell is metabolised in the liver.[1]

Thus, selection of appropriate ultrasound system settings for the detection of and for processing of the produced echo signals, together with the imaging properties of microbubbles (owed to gas and shell composition) promote improved quality of the acquired image. Background signal can be suppressed even better and the resolution of the image is further improved by applying contrast pulse sequencing.[14,15] For those seeking further information, Ultrasound contrast agent detection and visualisation is covered extensively in a supplement of European Radiology.[16]

[Table 1 to be inserted here]

Applications of CEUS

Cardiology

UCA are licensed solely for use in echocardiography in the United States and are used extensively throughout the world for this indication and others. Cardiac applications such as stress echocardiography are undertaken in patients with resting regional wall motion abnormalities, plus ischaemic heart disease, stable chest pain and suspected acute coronary syndrome.[17,18,19,20] CEUS echocardiography is used to assess left ventricular function in particular, by measuring ventricular volume and ejection fraction, and has been shown to be a better method than unenhanced echocardiography and equal to MRI.[21,22] It has also proved to be of added value in detecting left ventricle pseudoaneurysms, improving detection rates and thereby reducing the number of unnecessary emergency operations performed on patients.[23] One distinct advantage of CEUS echocardiography is that immobile patients and those who are attached to a ventilator can be investigated because of the mobility of the ultrasound equipment. This is of value in intensive care units.[24]

Non-cardiac applications

Currently, only Sonovue (Bracco, Italy) is approved and licensed - in the UK and Europe only - for use in non-cardiac imaging procedures. Guidelines and Good Clinical Practice Recommendations for CEUS have been developed to guide sonographers, radiographers and radiologists.[25] The areas in which CEUS is applied include the liver, kidney, pancreas, vesico-ureteric reflux, blunt abdominal trauma and transcranial scanning. In abdominal imaging, contrast enhancement enables improved detection of and characterization of liver lesions.[9] Further, it has been suggested that there may be a role for CEUS in the planning of liver metastatic tumour ablation.[26] Sonovue's strength in hepatic imaging was demonstrated in a study by Trillaud and colleagues[27], as well as other studies[28], in which CEUS was compared to CT and MRI to classify liver lesions as being benign, malignant, or intermediate. When compared to confirmative histology, sensitivity & specificity were 95.5% / 75.0% (CEUS), 72.2% / 37.5% (CT), and 81.8% / 42.9% (MRI) respectively.[27] Liver transplantation is an example where CEUS can have multiple applications. Pre-transplant the portal vein can be assessed for presence of thrombosis. Other vessels, such as the hepatic veins and the inferior vena cava may also be investigated to ensure they are not occluded. The patient's liver may also be checked for neoplasia (see Figure 1). Post-transplant, vessel potency, particularly of the hepatic artery, is critical and visualisation of these vessels is improved by CEUS. The newly transplanted liver can also be assessed for presence of fluid or abscesses.[29]

[Figure 1 to be inserted here]

Investigations of the spleen, kidneys and major abdominal vessels are also undertaken but are rarer.[30] Due to risks of contrast induced nephrotoxicity with contrast enhanced CT and nephrogenic systemic fibrosis in MRI imaging, there is an unmet need for optimal renal imaging, particularly in patients with compromised/ insufficient renal function where the use of CT and MRI contrast agents is contraindicated. Renal insufficiency is defined as severe renal impairment (ie, GFR [glomerular filtration rate] or eGFR [estimated GFR] 30mL/min/1·73m^2) or in patients with renal dysfunction who have had, or who are awaiting, kidney transplantation.[31] Ultrasonography of kidneys is often suboptimal, without contrast enhancement, because of poor resolution of images and low sensitivity to smaller arteries and segments deeper within the kidney. CEUS improves detection of pseudo lesions, such as cystic renal masses, but is less successful at detecting solid tumours.[32]

The potential applications of Sonovue, and UCA in general, stretch beyond those described above. This can be illustrated by highlighting a few published studies. A small study compared CEUS with grey scale ultrasound to measure the size of nine ductal breast carcinomas, using pathology laboratory tumour measurements as a control. CEUS was found to be more accurate in determining the size of the tumours than conventional ultrasound.[33] Vascular surgery is another specialty that is exploring the use of CEUS in its practice. In patients with peripheral arterial disease, characterised by claudication pain in the calf muscles, CEUS can be used to demonstrate the degree of impaired calf muscle perfusion.[34]

All of the applications above, both vascular and non-vascular, involve the injection of contrast agent into the patient's vein. A third application exists for contrast enhanced ultrasound: endoluminal sonography. CEUS is helpful in assessing fertility problems e.g. tubal patency via hysterosalpingo contrast enhanced sonography (HyCoSy). This involves instilling the contrast agent into the uterine cavity and then to visualize the passage of the microbubbles through the uterine (or Fallopian) tubes and into the pelvis in real time.[35] Administration into the bladder cavity enhances the signal during urosonography and helps to identify any potential vesico-ureteric reflux in children.[36]

Risks, contraindications and barriers

Safety profile of CEUS contrast agent.

In the US it is generally accepted that UCA are safe with a low incidence of side effects. They are not nephrotoxic or cardiotoxic and their use does not require renal function tests to be performed prior to administration.[37] The actual gas volume injected intravenously into a patient is usually less than 200 μl and the gases do not react with any substances inside the body. A large-scale retrospective analysis showed that SonoVue has a good safety profile in abdominal applications, with an adverse event reporting rate lower than or similar to that reported for radiologic and magnetic resonance contrast agents.[30] It was reported that the use of contrast during dobutamine stress ECGs was not associated with an increase in side effects even in patients with a high prevalence of ischaemic heart disease and resting regional wall motion abnormalities.[18] Timperley's findings[18] were congruent with those of Aggeli and colleagues[19] which reported that stress contrast-echocardiography was found to be an exceptionally safe technique in a large series of subjects. Furthermore, Ananthram *et al*[20] also reported that the administration of ultrasound contrast agents for stress echocardiography in those with stable chest pain and suspected acute coronary syndrome was not associated with an excess risk of excess adverse events.

However, in 2004 the European Medicines Agency (EMEA) put on hold an on- going clinical studies involving Sonovue. This followed on from three serious events resulting in death for three patients for cardiac imaging who had coronary artery disease, which occurred at a time similar to when they had been injected with Sonovue. An extensive investigation concluded that the reactions were idiosyncratic hypersensitivity reactions which are not unusual for injectables as observed earlier.[38] The EMEA removed the safety restrictions on Sonovue in 2005 but extended the contraindications to those with acute coronary syndrome or other unstable ischaemic conditions.[39]

A large independent retrospective study assessed the incidence of adverse events for SonoVue®, drawing from a total of 23 188 investigations. Data was collected from 28 centres in Italy. No fatal event occurred and adverse events were reported in 29 cases, of which only two were graded as serious; the rest, 27, were non-serious (23 mild, three moderate and one severe). The overall reporting rate of serious adverse events was 0.0086%. Overall, only four adverse events required treatment; two serious, two non-serious including one moderate and one severe adverse event that could be associated with the UCA.[30] Such a profile is comparable or below the number of adverse events of CT and MRI agents and most analgesics and antibiotics.[30] In the study there were some adverse events which had the characteristics of anaphylactic/anaphylactoid reactions. The overall reporting of this reaction was 0.013%, lower than reported for other contrast agents and similar to those associated with analgesics and antibiotics.[38] This trial was retrospective so it is likely reaction rates classified as mild or moderate are underestimated due to lack of documentation of all such reactions which is an acknowledged outcome of this trial.[30] However, it is less likely that severe or serious or severe adverse events were missed in this study.

Risks: comparison of CEUS with other imaging techniques

Although CEUS may not be without risk, it does not carry some of the risks associated with the other contrast enhanced imaging techniques. Most obviously, the specific risk associated with CT scanning is the exposure of the patient to ionizing radiation, a recognised drawback of this application when compared to ultrasound.[40] Furthermore, often contrast agent is indicated for CT diagnostics and some patients will have contraindications to the iodine-based contrast agents used, including patients with moderate to severe renal failure because of the risk of contrast induced nephrotoxicity, including subsequent nephropathy.[3,41] Although MRI scans do not involve radiation, other aspects need to be taken into consideration. Because of the magnetic forces involved in MRI scans, patients with most pacemakers and defibrillators cannot undergo an MRI. Furthermore, patients who are claustrophobic may be much more receptive to undergoing CEUS compared to MRI.[42] As with CT-scans, often MRI scans require contrast agent to be applied to allow a diagnosis to be made. The gadolinium-based contrast agents have been shown to be contraindicated in patients with renal problems. NSF is a potentially lethal disorder occurring in patients with renal failure.[4] Other studies cite acute non-renal adverse reactions e.g. anaphylactoid reactions, dizziness, nausea, pancreatitis and local necrosis of the injection site.[38,41]

Considerations before applying CEUS

As with any other medical imaging modality, several aspects need to be considered before CEUS can be implemented in a radiology department and potentially be sonographer or radiographer-led. First and foremost, there should be a clinical requisite for the application of CEUS. If there is indeed a clinical need then financial reimbursement and commissioning needs to be addressed, and equipment needs to be purchased, which will involve liaising with business managers and procurement activities. CEUS will not only involve the expert use of a high specification ultrasound system, but also requires injection or administration of UCA. There is a requirement for competence in preparing contrast agent solution – Sonovue for instance arrives freeze-dried and needs to be prepared on site – and also injection of UCA into patients. In addition to all the above, the usual aspects of delivering medical imaging services apply: consent of patients and adherence to safety policies, including risk assessments, and reporting guidelines.

In order to be able to deliver the CEUS service and to ensure patient safety, training requirements need to be met. The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) offers training courses through its EUROSON school programme. Currently there are three skill levels for CEUS: level 1, Training and Practice; level 2, Knowledge Base; and level 3, Training and Practice.[43] A competent CEUS practitioner should be able to perform a CEUS examination to EFSUMB Minimum Requirements, to recognise focal lesions and vascular disorders, be aware of the effects of UCA, be competent to compare CEUS to other imaging modalities such as CT and MRI, and to write an appropriate report.[43] Continued professional development should then be applied to keep up to date with the latest developments.

Conclusions

Technology has improved the stability of microbubbles used in CEUS and the number of applications for this diagnostic technique has increased. Non-cardiology specialties have adopted CEUS and, in addition to conventional venous administration, applications have been introduced which require the contrast agent to be instilled endoluminally. CEUS has a favourable safety profile but practitioners should be aware of patients' past medical history and co-morbidities, particularly acute cardiovascular disease. The increased incorporation of CEUS within diagnostic imaging services may mean that more radiographers are potentially exposed to this technique and radiographer-led clinics may in due course become more commonplace in radiology departments. It can be seen that good deal of groundwork sits behind the introduction of what may at first glance appear to be a fairly simple addition to the diagnostic imaging repertoire. For such integral changes to be effective, teamwork with the supportive leadership of radiologists and service managers will undoubtedly be required.

References:

1. Cosgrove DO, Eckersley R. Contrast-enhanced ultrasound: basic physics and technology overview. In: Lencioni R. Enhancing the role of ultrasound with ultrasound contrast agents. Pisa: Springer, 2006: 3-14.

2. Madsen H. Ultrasound Contrast: The Most Important Innovation in Ultrasound in Recent Decades. *Acta Radiologica*. 2008; 49: 247-248.

3. Barrett B, Katzberg R, Thomsen H, Chen N, Sahani D, Soulez G, et al. Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease Undergoing Computed Tomography. A Double-Blind Comparison of Iodixanol and Iopamidol. *Radiology* 2006; 41: 815-840

4. Broome D *et al* (2007). Gadodiamide-Associated Nephrogenic Systemic Fibrosis: Why Radiologists Should Be Concerned. *Am J Roentgenol.* 2007;**18:**586-592.

5. Gramiak R, Shah, PM. Echocardiography of the aortic root. *Invest Radiol*. 1968;3:356-366.

6. Crosby BC, Mackay RS. Some effects of time post-mortem on ultrasonic transmission through tissue under different modes of handling*. IEEE Trans Biomed Eng* 1978; 25: 91-92

7. Feinstein SB. The powerful microbubble: from bench to bedside, from intravascular indicator to therapeutic delivery system. *Am J Physiol Heart Circ Physiol* 2004;287: H450-H457.

8. Stride E, Saffari N. Microbubble ultrasound contrast agents: a review. *Proc Inst Mech Eng.* 2003;217:429-447.

9. Ariff B, Lloyd CR, et al. Imaging of liver cancer. *World J Gastroenterol* 2009; 15: 1289-1300.

10. Kaufmann BA, Lindner JR. Molecular imaging with targeted contrast ultrasound. *Curr Opin Biotechnol* 2007; 18:11-16

11. Furlow B. Contrast-enhanced ultrasound. *Radiol Techn*. 2009; 80: 547S-561S.

12. Saracco A, Aspelin P, Leifland K, Themudo R, Wilczek B, Axelsson R. Bolus Compared with Continuous Infusion of Microbubble Contrast Agent Using Real-Time Contrast Harmonic Imaging Ultrasound in Breast Tumors. *Acta Radiologica* 2009; 8: 854-859.

13. Berry JA, Sidhu PS. Microbubble ultrasound contrast agents. In: Allan P, Dubbins Pa, McDicken WN,Pozniak MA, eds. Clinical Doppler ultrasound. Philadelphia, Churchill Livingston. 2006:337-355.

14. Korpisalo P, Rissanen TT, Karvinen H et al. Contrast pulse sequence ultrasound is a novel imaging modality of regional perfusion in skeletal muscle and myocardium after proangiogenic gene therapy [meeting abstract]. *Circulation* 2006; 114:580.

15. Wilson SR, Jang HJ, Kim TK, Ijima H, Kamiyama N, Burns PN. Real-time temporal maximum-intensity-projection imaging of hepatic lesions with contrast-enhanced sonography. *AJR*

2008;190:691-95

16. Phillips P, Gardner E. Contrast-agent detection and quantification. *Eur Radiol*. 2004; 14 [Suppl8]:4-10.

17. Wei K. Detection and quantification of coronary stenosis severity with myocardial contrast echocardiography. *Prog Cardiovasc Dis*. 2001; 44: 81-100

18. Timpereley, JMitchell A, Thibault H,Mirza I and Becher H (2005) Safety of contrast dobutamine stress echocardiography:a single center experience *J Am Soc Echocard* 18 2 163-7

19. Aggeli C, Giannopoulos G, et al. Safety of myocardial flash-contrast echocardiography in combination with dobutamine stress testing for detection of ischaemia in 5250 studies *Heart* 2008;94: 1571-1577

20. Anantharam B, Chahal N, Chelliah R, Ramzy I, Gani F, Senior R. Safety of contrast in stress echocardiography in stable patients and in patients with suspected acute coronary syndrome but negative 12-hour troponin. *Am J Cardiol* 2009; 104: 14-18

21. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. *J Am Coll Cardiol* 2004; 44: 1030-5.

22. Hoffmann R, von Bardeleben S et al. Analysis of regional left ventricular function by cineventriculography, cardiac magnetic resonance imaging, and unenhanced and contrast-enhanced echocardiography: a multicenter comparison of methods*. J Am Coll Cardiol* 2006;47: 121-8

23. Garcia-Fernandez MA, Macchioli RO et al. use of contrast echocardiography in the diagnosis of subacute myocardial rupture after myocardial infarction. *J Am Soc Echocardiogr* 2001; 14: 945-7

24. Yong Y, Wu D et al. Diagnostic accuracy and cost-effectiveness of contrast echocardiography on evaluation of cardiac function in technically very difficult patients in the intensive care unit. *Am J Cardiol* 2002; 89: 711-8

25. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and Good Clinical Practice recommendations for contrast enhanced ultrasound (CEUS) – update 2008. *Ultraschall in Med* 2008; 29: 28-44.

26. Andreano A, Meneghel E, Bovo G, Ippolito D,Salvioni A, Filice C, Sironi S, Meloni MF. Contrast-enhanced ultrasound in planning thermal ablation of liver metastases: Should the hypervascular halo be included in the ablation volume? *Journal of Ultrasound* 2010; 13: 158-163.

27. Trillaud H, Bruel J-M et al. Characterisation of focal liver lesions with Sonovue – enhanced sonography: international multicentre-study in comparison to CT and MRI. 2009;15:3748-3756.

28. Diettrich CF, Kratzer W et al. Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT and MRI. *World J Gastroenterol* 2006; 12: 1699-1705

29. Berry JD, Sidhu PS. Microbubble contrast-enhanced ultrasound in liver transplantation. *Eur Radiol Suppl*. 2004;14[Suppl 8]:96-103.

30. Piscalia F and Bolondi L. The safety of Sonovue® in abdominal applications: Retrospective analysis of 23188 investigations *Ultrasound in Medicine and Biology* 2006;32:1369- 1375

31. Royal College of Radiologists 2007 Gadolinium Based Contrast Media and Nephrogenic Systemic Fibrosis London: Royal College of Radiologists.

32. Robbin ML, Lockhart ME, Barr RG. Renal imaging with ultrasound contrast: current status. *Radiol Clin North Am* 2003; 41: 963-978.

33. Van Esser S, Veldhuis WB, et al. Accuracy of contrast-enhanced breast ultrasound for pre-operative tumor size assessment in patients diagnosed with invasive ductal carcinoma of the breast. *Cancer Imaging* 2007; 7: 63-68.

34. Duerschmied D, Zhou Q. Simplified contrast ultrasound accurately reveals muscle perfusion deficits and reflects collateralization in PAD. *Atherosclerosis* 2009; 202: 505-12.

35. Ayida G, Harris P, Kennedy S, et al. Hysterosalpingo-contrast sonography (HyCoSy) using Echovist200 in the outpatient investigation of infertility patients. Br J Radiol. 1996;69:910-913.

36. Darge K. Contrast-enhanced voiding urosonography for diagnosis of vesicoureteral reflux in children. Pediatr Radiol. 2007;38:40-63.

37. Jakobsen JA, Oyen R, Thomsen HS, Morcos SK. Safety of ultrasound contrast agents. *Eur Radiol* 2005;15:941-945.

38. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med.* 2001;161:15-21.

39. EMEA website, http://www.ema.europa.eu/ (last accessed Dec 2010)

40. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med* 2007; 357: 2277-2284.

41. Bellin M and Van Der Molen A extra-cellular gadolinium-based contrast media: an overview. *Eur J Radiol* 2008;66**:** 160-7

42. Marshall G, Kasap C. Adverse events caused by MRI contrast agents: Implications for radiographers who inject. *Radiography* 2010; DOI: 10.1016/j.radi.2010.09.007

43. EFSUMB Newsletter section in the Ultraschall in der Medizin/European Journal of Ultrasound, 2010 31, http://www.efsumb.org/guidelines/ (last accessed Dec 2010)

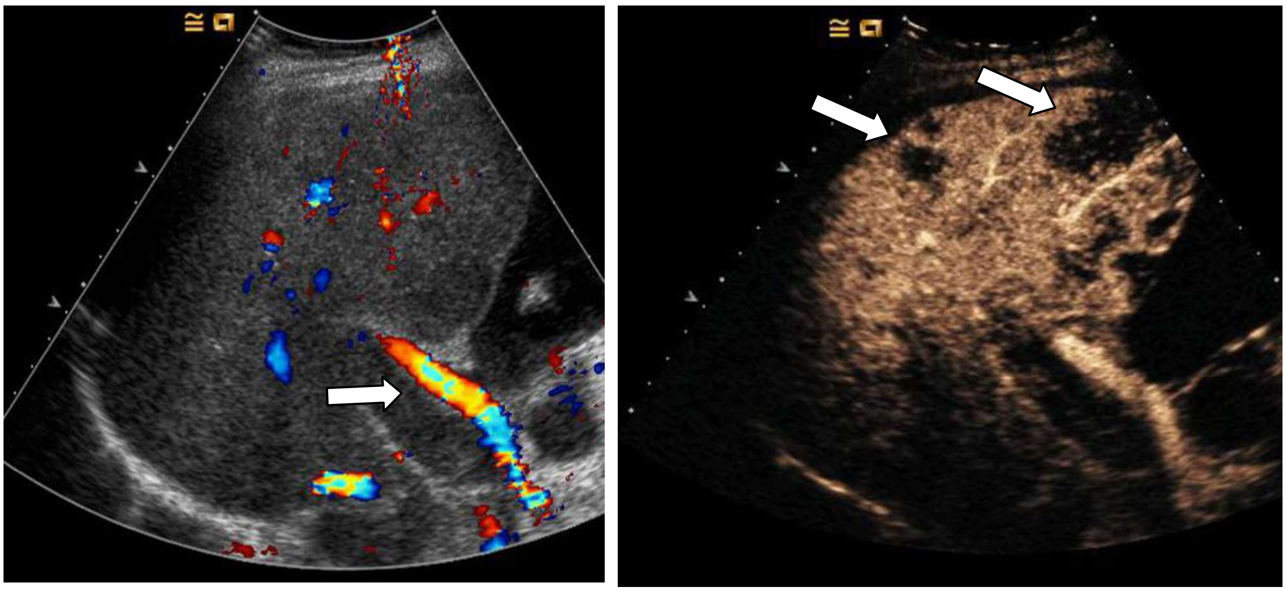

Figure 1. Colour Doppler imaging (left) reveals an occluded portal vein (arrow). Post contrast Low Mechanical Index (CPS) imaging (right) again shows the occluded portal vein but also previously unseen liver metastases (arrows) in a transplant candidate.

Table 1, Summary of ultrasound contrast agents

Brand Name	Gas/shell	Gen	Producer	Indication
Sonovue®	sulphurhexafluoride / phospholipid	2nd	Bracco, Italy	Echocardiography, Doppler
Luminity® / Definity®	octafluoropropane / phospholipids	2nd	Bristol-Myers Squibb	Echocardiography
Optison®	octafluoropropane / albumin	2nd	GE Healthcare	Echocardiography
Levovist®	air / lipid & galactose	1st	Schering	Echocardiography, Doppler
Albunex®	air/ albumin	1st	Mallinkrodt Medical	Echocardiography, Doppler