Contrast-enhanced ultrasonography: does it have a role in developing countries?

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Abstract

Contrast-enhanced ultrasonography (CEUS) has become an extremely useful adjunct to conventional ultrasound, and in many clinical situations it may replace or obviate the need for CT or MRI. Its use in developed countries has been variable, but it is suggested that in developing countries where CT and MRI have more limited availability, CEUS has great potential. This article explains why the author believes this to be the case, introduces the technique and describes the clinical roles to which CEUS may be applied.

Keywords: Ultrasonography; contrast media; microbubbles; diagnostic imaging; countries, developing

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Introduction

Contrast-enhanced Ultrasonography (CEUS) has been in clinical use for many years, its most widespread application having been in cardiology. Advances in the contrast agents have led to the ability of modern generation of the microbubbles to transit from peripheral veins, through the lung vasculature to the systemic circulation, and to recirculate for several minutes. This has resulted in the clinical roles to widen markedly. Only the non-cardiological roles will be discussed in this article.

CEUS has become an extremely useful adjunct to conventional ultrasound^{1,2} and, in many scenarios, may replace contrast-enhanced CT or MRI, particularly in the examination of the solid viscera of the abdomen. Despite this, its uptake in developed countries has been variable. CEUS is widely used in parts of Europe. However, in Australia, for example, CEUS is essentially confined to major public health centres³, partly due to the fee structure for medical procedures, partly due to the lack of incentive (and possibly the presence of a disincentive in private radiology practice) to the use of CEUS when CT and MRI are liberally available, and perhaps also partly due to the diminishing 'hands-on' experience of radiologists in US examinations. In the USA, while similar factors may apply, a major issue is that the recent generation of contrast agents has not been approved by the Food and Drugs Administration. The causes for this patchy uptake in the developed world was excellently summarized by Sidhu⁴ in 2008. Since then the impression is that progress has been slow.

However, there is a huge untapped potential for CEUS in the developing world and this

article discusses the advantages of CEUS in the context of the health system of those countries where access to CT and, in particular, MRI is limited. It is my understanding that in Sri Lanka, for example, outside the major population centres, CT and MRI are present in the minority of sites, whereas US is second only to plain radiography in availability.

When CEUS is a viable clinical alternative to CT and MRI, its advantages include:

- 1). Lack of need for transport of patients to major centers for CT/MRI
- 2). Less cost to the health system:
 - Less requirement for capital outlay on CT/MR machines, building infrastructure and staffing
 - Less maintenance costs
 - No requirement for strict oversight of ionizing radiation by regulation authorities
- 3). CEUS can be performed on existing modern US machines, updated with appropriate software (see below)
- 4). CEUS can be performed immediately – at the same attendance as the conventional US
- 5). CEUS can be undertaken at the bedside, in the Emergency Room or clinic
- 6). The contrast agents are safe, even in the presence of renal impairment, with no need for preliminary laboratory testing.
- 7). The contrast is relatively cheap.
- 8). Lack of ionizing radiation (*cf* CT)
- 9). The contrast medium is administered by peripheral intravenous injection.

Ultrasound Contrast and Technique

Latest generation US contrast agents consist

of microbubbles of stable perfluorocarbon or sulfur hexafluoride gas in a tough shell of albumen or phospholipids. They are administered by peripheral intravenous injection and are predominantly blood pool agents - that is they remain within the intravascular space, unlike the majority of CT and MRI contrast agents. The encapsulated microbubbles measure $<10\ \mu\text{m}$ and thus pass through the pulmonary and systemic circulation and are durable enough to re-circulate for several minutes. The limited diffusion of the inert gas, as well as its low solubility, contribute to the persistence of the microspheres in the blood. The gas is inert, is not metabolised and is eliminated through the lungs within 10 minutes of administration.

US contrast agents work by increasing the strength of the backscattered signals from blood by several orders of magnitude. Imaging is acquired in real time as the agent enhances the vascular structures within normal and pathological structures. Effectively a 'real-time' US angiogram is obtained over several minutes, if required, during multiple vascular phases.

Contrast-specific scanning modes are required on the US machine⁵. These modes use a low mechanical index (MI) to avoid bursting the bubbles on insonation and are usually a variant of contrast harmonic imaging /phase inversion techniques. 'Flash' imaging can be used as an adjunct; this entails transiently increasing the MI to deliberately disrupt the microbubbles within the insonated area, and then returning to low MI to visualize contrast replenishment within the area of interest.

Images can be interpreted qualitatively (Figs 1 -3) and quantitatively (Fig 4). Quantitative assessment is achieved by prescribing regions of interest (ROI) in the image⁶. The software then plots Time *versus* Intensity curves (TICs) that it displays graphically. TICs are very useful to measure various objective parameters, such as time-to-peak intensity, maximum intensity, area-under-the-curve, wash-out, etc. This helps to characterise lesions, particularly when ROIs from a lesion (and even from different parts of a lesion) and surrounding normal tissue are compared.

Fig.1 A,B,C._Serial images after IV US contrast agent of a liver haemangioma showing typical 'filling-in' of lesion from rim extending centrally.

Fig.2 A,B._Serial images - early (A) and delayed (b) - after IV US contrast agent of hepatic Focal Nodular Hyperplasia, (FNH) showing early hyper-enhancement of the lesion with persistence of enhancement in (B). Note central 'scar' in (B)

Fig.3._Another patient with hepatic FNH, showing early (23 second) hyper-enhancement of the lesion becoming iso-echoic to liver at 50 seconds. Note prominent feeding vessels (arrowed)

Complications and contra-indications

US contrast agents are very safe. There is no requirement for laboratory tests of renal or

thyroid function prior to administration. Hypersensitivity reactions are rare, with an incidence of life-threatening anaphylaxis reported as 0.001%².

Fig.4 A, B. Same patients as Fig.1 and Fig.2, respectively. Time Intensity Curves (TICs) confirming graphically the enhancement of the lesion (yellow line) relative to normal liver (green line).

There is a theoretical risk that US with contrast agents could result in bioeffects. Experimental data from their use in small animals indicate that rupture of microvessels could occur when gas bodies are insonated. If this is a real risk it is likely only to be clinically significant when CEUS is used for ocular roles and when insonating brain without an intact skull⁷.

US contrast agents are not licensed in pregnancy. The question of use in paediatrics is complex; CEUS should provide a very beneficial modality in children in view of its lack of ionizing radiation. However, in many jurisdictions the agents are not yet registered for paediatric use. Further developments are awaited, but in the meantime clinical judgement must remain important. A potentially important role of CEUS is the investigation of vesico-ureteric reflux after the intracavitary instillation of the contrast agent into the bladder.

Side effects of US contrast agents are unusual and almost always mild. Headache is the most frequent followed by nausea and/or vomiting, a warm sensation or flushing, dizziness and back pain.

With regard to contraindications, it was previously considered that patients with right-to-left cardiac shunts should not be given US contrast agents. However, recent data suggest that this should no longer be considered to be the case in adults^{8,9}.

Caution should be taken when considering CEUS in patients with pulmonary hypertension and “unstable cardiopulmonary conditions”, although in cardiology patients requiring echocardiography, the benefits of using US contrast agents may over-ride the risks¹⁰.

For the contrast agents in which the shell of the microbubble is albumin, a history of allergy to albumin or blood products should be sought as a contraindication.

Technical limitations

EUS is subject to the limitations of conventional US, including unfavourable body habitus and interposition of gas or bone between the skin surface and the target lesion. In addition, due to the nature of the CEUS scanning modes, deep lesions may not be able to be adequately examined with CEUS.

Clinical roles

CEUS provides a good alternative to CT and MRI in the examination of many solid organs, especially in the abdomen, and of vascular structures. The enhancement patterns of lesions can be studied during multiple vascular phases -arterial, portal venous, late and post-vascular phases - in a similar fashion to contrast-enhanced CT and contrast-enhanced MRI, but in real time with a resultant much higher temporal resolution than is possible with CT or MRI. The real-time nature of CEUS allows depiction of early arterial phase enhancement, which is sometimes missed on CT and MRI because of their lower 'frame rates'. The following is a non-comprehensive list of the applications of CEUS in various organs and clinical scenarios.

Liver²

1). CEUS has proven useful in the characterization of focal liver lesions (FLLs). It is particularly useful for differentiating benign and malignant nodules^{11,12}. CEUS shows tissue perfusion analogous to that shown on contrast-enhanced CT and MRI in which patterns of enhancement in the arterial and portal venous phases predict the diagnoses of

FLLs^{2,13-16} and has been shown to be comparable to CT and MRI¹⁷ and useful as a first line investigation of FLLs¹⁵. Most malignant lesions show 'wash-out' of contrast agent on portal venous or later phases (Fig 5).

2). For metastasis detection in patients with non-hepatic primary tumours, CEUS is better than conventional ultrasound¹⁸, but probably less sensitive than multi-detector CT on a lesion-by-lesion analysis^{19,20}

3). The use of CEUS is cost-efficient in the first-line diagnosis of FLLs compared to CT and MRI²¹. CEUS can often establish a definitive diagnosis or otherwise aid in deciding whether a liver lesion needs further investigation.

4). Simple algorithms allow diagnosis of most liver masses²².

5). CEUS has been found to improve the characterisation of focal liver lesions with enhancement patterns observed during the arterial, portal venous and late phases generally similar to CECT and CEMRI.

6). CEUS is valuable for the evaluation of nodules in the patient at risk for hepatocellular carcinoma^{23,24}.

7). CEUS can differentiate between adenoma and focal nodular hyperplasia in asymptomatic young women^{25,26} (Fig 6).

Renal applications

CEUS provides information on tissue perfusion and may play a role in kidney mass characterization similar to the role of contrast-enhanced CT and MRI^{1,27}.

Specific roles in the kidney include:

1). Differentiation of solid and cystic lesions in hypovascular masses.

2). CEUS significantly improves diagnostic confidence for solid renal masses.

Fig.5. TIC of hepatocellular cancer. The TIC shows arterial enhancement of the lesion, similar to surrounding liver, followed by ‘wash-out’ of contrast from the lesion i.e. lesion becomes iso-echoic to liver

The overall accuracy for renal carcinoma has been shown to be 90%²⁸.

3). CEUS is useful for the diagnosis of renal pseudo-tumours, reducing the need for CT²⁹.

4). CEUS enables Bosniak classification of complex renal cysts without the need for CT³⁰.

5). Investigation of suspected renal infarction – total or segmental

6). Vesico-ureteric reflux in girls after introduction of US contrast material into the bladder.

Scrotal imaging

CEUS is useful in patients with acute scrotal pain³¹ and trauma³².

1). In the differentiation of hypovascular and avascular lesions, the latter being indicative of benign disease

2). Discrimination of areas of non-viable tissue in cases of testicular trauma

3). Discrimination of abscess formation in severe epididymo-orchitis.

4). Detection of segmental infarction.

Pancreas

CEUS has been shown to be effective in:

1). The characterisation, delineation and local staging of adenocarcinoma³³.

2). The discrimination of mass-forming chronic pancreatitis and adenocarcinoma³⁴.

3). The differentiation of cystic tumours from pseudocysts³⁵.

4). Assessing hypervascular masses such as neuroendocrine tumours of the pancreas^{36,37}.

Fig.6 A,B. FNH (a) and adenoma (b). TICs from rim of lesion, central lesion and normal liver, showing different patterns of enhancement. FNH shows early enhancement of central portion followed by rim. Adenoma tends to show opposite pattern

Trauma

CEUS has been shown to be an accurate technique for evaluating traumatic lesions of solid abdominal organs^{38,39}. However, it has been suggested that its use should be as a first-line approach in patients with low-energy isolated abdominal trauma, as it shows a high sensitivity both in lesion detection and grading, but that CT should be performed in CEUS-positive patients to exclude active bleeding and urinomas⁴⁰. It is also useful for monitoring patients undergoing conservative treatment in mild degrees of liver and spleen trauma⁴¹.

Non-cardiological vascular roles

CEUS may be used in a variety of vascular applications, including:

1). Improving US visualization of

technically difficult vessels, such as the renal arteries in suspected renal artery stenosis⁴².

2). Differentiation between severe stenosis and complete occlusion of major vessels, including visceral and cerebral arteries. In the carotid arteries CEUS improves the sensitivity of Doppler US and can be used for differentiating complete occlusion from residual flow in tight stenosis. CEUS can be also be utilised to improve the delineation of the inner vascular wall, enabling detection of the configuration of pre-stenotic, intra-stenotic and post-stenotic segments and evaluation of neovascularization of plaque (which may be a precursor of plaque rupture)⁴³.

3). Assessment of vascular dissections

4). Evaluation of endoleaks following aortic

aneurysm repair.

Other applications

There are many other potential roles for CEUS, many of which await sufficient evidence of efficacy for clinical application. Examples include the investigation of gynaecological masses, assessment of renal transplants and intracavitary uses, such as voiding urosonography and imaging of Fallopian tube patency.

Conclusion

Contrast-enhanced ultrasonography is a procedure that holds great potential in the context of the health system of a developing country, where access to CT and MRI is limited. It is safe, relatively inexpensive, to a large extent can be applied with only relatively minor modification to existing resources, has a wide range of common clinical applications and may obviate the need in many patients for transfer to a major centre for CT or MRI.

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