Contrast-Enhanced Ultrasound (CEUS): an imaging modality with the wind in its sails

The introduction of contrast agents in ultrasound examinations has significantly extended the applicability and clinical value of conventional ultrasound Contrast Enhanced Ultrasound. CEUS is often cheaper, safer, better, faster and more convenient than other forms of diagnostic imaging, and is of course performed without ionizing radiation. At a time of heightened concerns regarding overall health care costs and the cumulative impact of ionizing radiation due to medical diagnostic testing, CEUS is often an equivalent or superior means of establishing diagnoses in many conditions such as heart disease, detection of tumors, and the characterization of many other pathologies.

This article summarizes some of the most pertinent applications of the technique, which seems set for a period of widespread expansion.

**CONTRAST ENHANCED ECHOCARDIOGRAPHY**

In a seminal paper published in 2008 outlining the evidence for clinical use of contrast echocardiography, a UK group highlighted the fact that echocardiography had, at that time long been accepted as a practical, cost-effective, and non-invasive method for examining cardiac structure and function at rest and during stress [1]. Stress echocardiography at the time was widely used to assess patients with suspected or known coronary artery disease (CAD). However, Bhatia and Senior [1] pointed out that, in a significant proportion of patients, echocardiography failed to produce diagnostically useful images. The main impediments to satisfactory imaging were obesity and lung disease. Suboptimal images could be seen in 10% to 15% of patients undergoing echocardiography. This problem was even greater in patients referred for stress echocardiography. It was estimated that images were suboptimal in as many as 33% of cases, with poor imaging of the endocardial border. The consequence of this shortfall was the suboptimal evaluation of left ventricular (LV) function. Until then, myocardial perfusion could not be reliably assessed by an echocardiographic technique.

In the light of this situation, Bhatia and Senior [1] set out the desirable properties of contrast media for echocardiography [Table 1]. Even at that time (2008), Bhatia & Senior concluded that the use of contrast “significantly enhanced imaging in routine echo-cardiography and stress echocardiography, frequently allowing the rescue of procedures that did not provide results of diagnostic quality. Contrast enhancement can reduce the need for additional expensive tests, thereby reducing costs and, perhaps more importantly, may spare the patient further invasive investigations. The authors predicted that "the benefits of a greater familiarity and use of contrast in echocardiography will become even more apparent when the measurement of myocardial perfusion by the technique is routinely performed. Finally, recent safety concerns need to be methodically evaluated and in the meantime, patient care may be best served by assessing the risk and benefits of using contrast agents on an individual case basis”.

Fast forwarding, it is apparent that the properties desired by Bhatia and Senior [1] six years ago have been broadly fulfilled. As summarized recently by Seol and Lindner [2], contrast echocardiography is now considered an essential component of any state-of-the-art echocardiography laboratory because of its ability to provide unique and/or more accurate information to the interpreter. There are particular situations and clinical questions where the use of contrast for of contrast for left ventricular opacification (LVO) is particularly useful, including stress echo, serial assessment of Left Ventricular function and the assessment for ventricular thrombi. While Myocardial Contrast Echocardiography perfusion imaging for the assessment of coronary artery disease (CAD) is not yet mainstream there are still niche applications where the assessment of perfusion with micro-bubbles has a high impact.

As Seol and Lindner point out however, as always the optimization of the use of ultrasound contrast agent in any hospital or clinic requires unique knowledge of contrast-specific imaging protocols, knowledge of microbubble administration techniques and a sound laboratory policy that promotes the use of microbubbles in a safe fashion in
patients who are most likely to gain benefit. In general however the safety profile of ultrasound contrast agents has been shown to be extremely high.

LIVER METASTASES

In a recent paper, Cantisani et al. [3] point out that enhanced ultrasound has completely changed ultrasound liver imaging of the colorectal cancer patient, notably through an increase in the sensitivity and accuracy in the detection of metastases. Clinical studies have reported that, compared to baseline-ultrasound, the use of contrast agents enables the visualization of more metastases with significantly improved sensitivity and specificity [Figure 1].

Furthermore, studies have shown that contrast enhanced ultrasound yields sensitivities comparable to computed tomography. In their review, Cantisani et al. described the state of the art of the technique, but did issue the caution, that although CEUS may be considered an effective technique, it still presents the same risk of the important drawbacks of every US examination, such as operator dependency. The approach also has limitations in obese patients, non-compliant subjects, and in cases with intestinal interposition. For these reasons, if the B-mode US is unsatisfactory, a subsequent CEUS examination will be suboptimal too.

LIVER TUMORS

Contrast enhanced ultrasound has been proven to be helpful in the diagnosis, differential diagnosis and follow-up of patients with focal liver lesions (FLLs). In a review of the literature concerning liver tumor characterization, a group from Würzburg, Germany described the recent advances in contrast-enhanced techniques which have improved the rate of detection of focal liver lesions to at least that obtainable with CT or MRI [4]. The analysis was based on the findings from important multi-center trials. Of these, the DEGUM (German Society for Utrasound in Medicine) trial was a large, multicenter prospective study that evaluated the diagnostic capability of CEUS using Sonovue, which is a preparation of sulfur hexafluoride lipid type A microspheres (Bracco Diagnostics). Specifically, the objective of the DEGUM trial was to characterize Focal Liver Lesions in daily clinical practice, compared primarily to histology and secondarily to contrast-enhanced computed tomography (CE-CT) and contrast-enhanced magnetic resonance imaging (CE-MRI).

In total, the trial involved 1349 patients. The result of the study confirmed the excellent performance of real-time CEUS using Sonovue for the characterization of focal liver lesions and the superiority of the technique over unenhanced ultrasound. The role that CEUS played in the diagnostic imaging of focal liver lesions was considered to be at least equal to, and in some ways superior to CE-CT and CE-MRI as a diagnostic tool.

NEPHROLOGY

The advantages of the diagnostic role of traditional gray-scale ultrasound in nephrology were pointed out in a very recent paper by Granata and co-workers [5]. The advantages cited are the absence of ionizing radiation and of nephrotoxicity, the rapidity of execution and immediate feed-back, excellent reproducibility, not to mention the possibility of actually carrying out the examination at the patient’s bedside and the low cost of the technique. On top of this already impressive performance, Granata et al. recognize that contrast enhanced ultrasound, by improving on the amount of information available from conventional Doppler and magnetic resonance and so represents a major step in the evolution of clinical ultrasound. They recognise that there can be several situations in which contrast-enhanced CT and MRI are indicated (such as evaluation of cystic or ischemic lesions, trauma and ablative therapies of the native and transplanted kidney), but point out that the use of CT contrast media can present a risk of contrast-induced nephropathy (e.g. in elderly patients or those with co-morbidities, and/or renal dysfunction). Likewise, since gadolinium-based MRI contrast agents are also contraindicated in cases of severe renal dysfunction on account of the risk of nephrogenic systemic fibrosis, CEUS may be a viable alternative.

“... the role that CEUS played in the diagnostic imaging of focal liver lesions was equal to, or superior than, that of CE-CT or CE-MR as a diagnostic tool...”

Thus a better knowledge of CEUS and a rigorous codification of the indications for its use may help to reduce the side-effects of traditional imaging techniques. The authors however emphasize the fact that although the safety record of the contrast agents used in ultrasound is well established, as always, whenever a technique is associated with the infusion of pharmacologically active substances, the potential advantages and risks of CEUS should always be borne in mind. For this reason the guidelines recently published by the European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) should always be consulted.[6]. In addition to the purely diagnostic uses of contrast enhanced ultrasound, Granata et al., suggest that a promising application of the technique comes from the ability of ultrasound contrast microbubbles to be targeted to spe-
cific endothelial cell ligands via the use of monoclonal antibodies. Such labelled microbubbles could transport bioactive materials e.g. drugs or genes that could be delivered inside the cell using specific mechanisms such as sonoporation, i.e. ultrasound-induced formation of pores in cell membranes.

CAROTID ARTERIAL DISEASES

A research group from Munich investigated the imaging of carotid arterial disease using contrast-enhanced ultrasound [7]. Carotid duplex ultrasound is the standard of care for the initial diagnosis of carotid artery bifurcation diseases. However in difficult examinations carotid abnormalities are commonly encountered and represent a diagnostic challenge. The objective of the work presented by Clevert et al. was to evaluate the potential of CEUS to improve or add extra information on carotid arterial disease. The conclusion was that CEUS with SonoVue enabled the detection and evaluation of carotid diseases. It is an additional examination to duplex sonography which remains the first-line imaging modality. The use of CEUS for carotid atherosclerosis could be helpful in the pre-operative risk stratification of patients with asymptomatic stenoses.

TECHNICAL ASPECTS OF CEUS: TIPS AND TRICKS

A recent paper from C Greis [8] deals with the technical aspects of CEUS. Greis reminds us that the break-through technical innovation in CEUS was the introduction of contrast-specific imaging modes on ultrasound scanners, which allow the direct visualization of signals emitted by contrast-agent microbubbles. Thanks to the specific characteristics of microbubble signals, which are fundamentally different from those of signals back-scattered from tissue, it is possible to create a microbubble-specific (i.e. contrast-only) image. However, the creation of such microbubble-specific signals requires a well-defined interaction between the contrast agent microbubbles and the insonated ultrasound beam. Thus, to obtain an optimal response signal, the insonation parameters (e.g. intensity and type of stimulation of the microbubbles) should be understood and well controlled together with an understanding of the post-processing parameters on the receiver side (e.g. separation of contrast and tissue signal, log compression, attenuation correction and noise suppression). The parameters involved in the above phenomena are all inter-related. As Greis indicates, it is a matter of experience to establish the optimal balance between the parameters. Although standard settings from instrument manufacturers or by contrast agent manufacturers can be sufficient to obtain good images even for a beginner in the field, a full understanding of the main parameters and settings is important to enable the optimal configuration of the machine and the examination strategy as a function of the individual patient and precise clinical objective.

OTHER APPLICATION OF CEUS

The references cited above are only selected examples of the use of CEUS. Many other papers describe the use of CEUS in areas such as breast, brain, spleen or thyroid. More information can be obtained from the International Contrast Ultrasound Society (ICUS), or The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB).

REFERENCES


Further information and clinical guidelines are available from:
- The International Contrast Ultrasound Society (ICUS), www.icus-society.org
- The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), www.ufsmb.org

FDA approval for new ultrasound contrast agent

Lumason (sulfur hexafluoride lipoid-type A microspheres) is now approved in the U.S. for use in adults with suboptimal echocardiograms

Bracco Diagnostics Inc announced last month that the U.S. Food and Drug Administration (FDA) has approved its new ultrasound contrast agent Lumason (sulfur hexafluoride lipoid-type A microspheres, better known internationally in 39 countries as SonoVue) is indicated for use in adults with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

There are an estimated 28 million echocardiograms annually performed in the United States; 10% or more of those exams are reported as suboptimal and, possibly inconclusive. Lumason, has an extensive and established safety profile and has been shown to convert suboptimal images into images of adequate diagnostic quality. The product has been approved for use in adult patients with suboptimal echocardiograms, based on data submitted to the FDA from three multicenter controlled clinical trials that showed significant improvement in image quality compared to unenhanced, native images.

“We’re thrilled with the approval of Lumason as it represents a significant milestone in the company’s history. Today’s approval follows a long-term strategy of delivering the benefits of our Contrast Enhanced Ultrasound agent also in the US. Lumason has a strong reputation and solid track record in many other key markets,” said Fulvio Renoldi Bracco, Head of Global Business Unit Imaging at Bracco Imaging. To learn more about Lumason, visit http://imaging.bracco.com/us-en/lumason