Abstract
Contrast-enhanced ultrasound imaging (CEUS) is a non-invasive imaging modality that permits improved accuracy and reliability in performing ultrasound images of the heart and is safe, cost-effective and avoids ionizing radiation. When used appropriately, CEUS also reduces redundant downstream testing, resulting in a positive impact on patient management. Recently, professional and regulatory societies including governmental advisory boards have promulgated newer standards and recommendations for the appropriate clinical use of CEUS. Based on the proven clinical utility, efficacy, cost-effectiveness, uniform safety profile, and lack of ionizing radiation, CEUS is now poised to assume a prominent role in the diagnosis and management of patients with cardiovascular disease and in the respective fields of radiology and vascular medicine.

Keywords
Contrast ultrasound, echocardiography, Contrast-enhanced ultrasound imaging (CEUS), non-invasive imaging

Contrast-enhanced ultrasound imaging (CEUS) is a non-invasive imaging modality that utilizes air-filled microspheres as blood pool agents, which act as intravascular indicators, resulting in improved accuracy and reliability in performing ultrasound images of the heart. CEUS is increasingly used throughout the US, South America, Australia, the Middle East, Europe, Japan, Canada, and Asia as a diagnosis modality in the fields of cardiology, radiology and vascular medicine disciplines. The added value of CEUS is improvements in accuracy, patient management and cost-effectiveness, and superior sensitivity and specificity.1–4 CEUS also offers the following additional benefits:

- safety;
- cost-effectiveness;2,3
- does not utilize ionizing radiation;3–4
- reduces redundant downstream testing; and5–6
- positively and directly impacts patient management.2

Furthermore, CEUS and non-contrast ultrasound are more accessible than other non-invasive technologies and may be performed in a variety of outpatient and hospital settings to screen patients, monitor therapy, and to diagnose acute coronary artery disease (CAD).

Professional Society Recommendations for Contrast-enhanced Ultrasound Imaging
Recently, several independent accreditation bodies, government advisory boards, and professional societies have published standards, recommendations and consensus statements recognizing the clinical value, enhanced accuracy and related benefits of using CEUS.

In June 2010, the Intersocietal Commission for Accreditation of Echocardiography Laboratories (ICAEL) announced new standards for laboratory accreditation specific to echocardiography testing.9 The new standards recognize, for the first time, that ultrasound contrast agents play an important role in improving the accuracy of echocardiograms and mandate the use of ultrasound contrast agents under specified circumstances consistent with criteria established by the American Society of Echocardiography in 200010 and 2008,11 and by the European Association of Echocardiography in 2009.12 These standards serve as clinical guidelines for the clinical practice of cardiology.

The Ontario (Canada) Health Technology Advisory Committee (OHTAC) of Canada developed recommendations in 2010 following an assessment of the comparative effectiveness of non-invasive imaging tests for the diagnosis of CAD in the Canadian population.13 The recommendations stated that CEUS in stress echocardiography “should be considered in future planning for cardiac diagnostic imaging once approved by Health Canada for this indication.”13 The conclusions from the OHTAC documents also included the following statements:

- Stress echocardiography with contrast has a higher diagnostic accuracy in the detection of CAD than stress echocardiography (without contrast).
by Kurt et al. Based on their study, two recent prospective reviews of the clinical utility of CEUS were published. These patients are particularly well served by using CEUS for left ventricular endocardial detection.

The ultrasound contrast agents are used to enhance echocardiographic resolution and identification of the carotid artery anatomy including those published by the American Society of Echocardiography (ASE) and European Association of Echocardiography in 2009. The position papers from these societies indicated that ultrasound contrast agents should be utilized clinically during indicated rest and stress echocardiograms.

Clinical Utility of Cardiac Ultrasound and Contrast-enhanced Ultrasound Imaging

The accuracy of using echocardiography has been reported and is equally effective in diagnosing coronary artery disease (CAD) among women and men. Similarly, ultrasound exams were equally effective in men and women for non-invasive diagnosis of increased carotid intimal media thickness (c-IMT) and plaque, permitting early detection and outcome prediction of cardiovascular disease in both genders. Furthermore, the use of ultrasound has been called the ‘test of choice’ for acutely ill patients.

It has been shown that echocardiography is highly predictive of long-term outcomes in women and men diagnosed with CAD. In addition, echocardiography provides comparable accuracy and similar sensitivity and specificity to SPECT for men and women.

Ultrasound contrast agents were initially introduced and approved for routine echocardiography at rest by the US Food and Drug Administration (FDA) in 1994. The current commercially available contrast agents approved by the US FDA are indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The ultrasound contrast agents are used to enhance echocardiographic imaging, thus improving the accuracy of echocardiograms, reducing downstream testing, and avoiding exposure to ionizing radiation.

The morbidly obese population now comprises a significant proportion of patients referred for imaging. Not only are these patients imaged quite well with ultrasound contrast agents, but often times, these patients cannot be accommodated by other imaging modalities since they exceed the weight limits for computed tomography (CT), magnetic resonance imaging (MRI), SPECT and positron emission tomography (PET). These patients are particularly well served by using CEUS for left ventricular endocardial detection.

A recent prospective review of the clinical utility of CEUS was published by Kurt et al. Based on their study, the following conclusions were made:

- CEUS decreased uninterpretable studies from 11.7 % to 0.3 %; decreased technically difficult studies from 86.7 % to 9.8 %.
- CEUS changed therapeutic decisions in 10.4 % of patients.
- Additional downstream procedures were avoided and therapy changed in 35.6 % of patients.
- The most effective use of CEUS was observed in the sickest patient base (intensive care units).

Vascular Imaging—Contrast-enhanced Ultrasound Imaging

Recently, several studies established the clinical value of non-invasive ultrasound imaging of carotid arteries for the purpose of detecting increased c-IMT and plaque in men and women. These data suggest that c-IMT imaging may be incorporated into the non-invasive risk assessment of men and women who are considered to be at risk for premature cardiovascular disease. The value of CEUS is that it increases the resolution and identification of the carotid artery anatomy including the lumen, near and far wall c-IMT and the intra-plaque vasa vasorum.

Current Advantages of Contrast-enhanced Ultrasound Imaging

CEUS and non-contrast ultrasound do not expose patients to ionizing radiation, whereas SPECT and CT angiography (CTA) imaging do. Since exposure to ionizing radiation is associated with an increased lifetime risk of developing cancer, serious concerns are emerging relating to medical imaging procedures that utilize ionizing radiation. Evidence suggests that, in the US, the per capita dose of radiation from medical imaging increased almost 600 % from the early 1980s to 2006, primarily due to higher use of CT and nuclear medicine studies. In fact, an estimated 29,000 future cancers could be related to CT scans performed in the US in 2007 alone, and that risk may be growing. Even if a single individual’s risk of developing cancer from a single test may be relatively small when compared to the risk associated with the failure to diagnose CAD, the ‘small’ risk may nevertheless be reduced or avoided altogether to the extent that equivalent (or superior) non-invasive imaging tests are available for the diagnosis of CAD without exposing patients to ionizing radiation.

Consistent with these concerns, the FDA, in February 2010, announced its Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging. In addition, The American Heart Association recently published the following statement: “Physician education should emphasize that cardiac imaging studies that expose patients to ionizing radiation should be ordered only after thoughtful consideration of the potential benefit to the patient and in keeping with established appropriateness criteria.”

Women may have greater long-term exposure to ionizing radiation than men due to mammography screenings routinely performed in women. Consequently, to the extent that equivalent (or superior) diagnostic information may be obtained from non-invasive tests that avoid ionizing radiation, those tests should be preferred, especially for diagnosing CAD in women.

Safety of Contrast-enhanced Ultrasound Imaging

Recent studies demonstrate that CEUS is significantly safer than other diagnostic imaging procedures, and that use of an ultrasound contrast agent improves the accuracy of diagnoses leading to changed treatment in a significant number of patients.
In October of 2007, the FDA issued a label change (‘black box’ warnings) and new contraindications for ultrasound contrast agents based on self-reported adverse events and the failure of a manufacturer to initiate an "important post-marketing clinical study commitment to assess its product’s safety". Subsequently, numerous peer-reviewed safety studies were published, showing that contrast agents were used safely in over 266,000 patients studied. In May of 2008, the FDA reversed all of the new contraindications and most of the new black box warnings. Additional safety data have since been published and experts in the field have written that the new safety data support additional reversals of the black box warnings and the conclusion that CEUS is considerably safer than alternative imaging options.21

CEUS is safe, as evidenced by numerous multi-center studies demonstrating the superior safety profile of CEUS compared to other non-ultrasound based non-invasive tests. Indeed, a 2008 analysis of the comparative mortality of cardiac imaging procedures in a multi-center registry of 4,300,966 patients showed, among other things, that compared with patients not receiving a contrast agent, administration of a contrast agent during echocardiography was associated with a 24 % decreased risk of mortality within 1-day (adjusted odds ratio = 0.76 95 % CI = 0.70–0.82).22

Abdelmoneim et al. recently found that there was no short- or long-term risk of death or myocardial infarction associated with CEUS among male and female patients. The report stated that 10,792 cardiac patients received echo contrast without evidence of increased death or serious cardiac event compared with the 15,982 patients in the non-contrast cohort.23

Dolan et al. recently found no evidence suggesting a causal relationship between commercial ultrasound contrast agents and serious adverse events, based on an examination of work representing combined experiences with more than 60,000 patients.1

Another multi-center retrospective analysis of more than 78,000 contrast doses found that commercially available ultrasound contrast agents have a good safety profile, and severe adverse reactions were no greater than, and were possibly lower than, those reported for contrast agents commonly used in other cardiac imaging tests. Specifically, the study found no deaths related to the ultrasound contrast agents, no serious adverse events in the in-patient setting, and an incidence of 0.01 % of serious adverse events ‘probably’ associated with an ultrasound contrast agent, half of which would have been anaphylactoid reaction.24

Exuzides25 and Main et al.22 found that there is no increase in mortality in critically ill patients undergoing echocardiography with ultrasound contrast agent compared with case–matched control patients.

Safety Conclusions for Contrast-enhanced Ultrasound Imaging
- There have been no safety signals in any patient group, including high-acuity patients.
- There is no increase in mortality in hospitalized patient undergoing contrast echocardiography.
The risk of an anaphylactoid reaction is comparable to non-ultrasound contrast at 1/10,000 events.

Risk of misdiagnosis, and risks of alternative testing procedures, is increased without CEUS.

Clinical Case Example

Figures 1 to 3 illustrate the clinical utility of CEUS as used in the routine clinical practice of cardiology. The clinical details of the case are as follows: an elderly man was referred to the outpatient clinic center for a transthoracic echocardiogram to assess the left ventricular ejection fraction.

In the past, the patient had suffered from a heart attack and subsequently required the insertion of a pacemaker. The initial transthoracic echocardiogram revealed a large left ventricular chamber with poor endocardial visualization as seen in Figure 1 (the pacemaker lead was identified in the right ventricle). In this particular case the use of an ultrasound contrast agent was based on the current ASE/ICAEL guidelines, which recommend the use of contrast when two contiguous segments of the left ventricle are not well visualized.11 Following the peripheral, intravenous injection of 0.5 ml of a commercially available ultrasound contrast agent, the entire left ventricular endocardial surfaces were well visualized. What was not apparent prior to the injection of the ultrasound contrast agent was a large thrombus, which was identified in the apex of the heart (see Figure 2).

In Figure 3, it is apparent that the contrast material provided clarity and allowed one to identify that the thrombus was pedunculated and not sessile. Subsequently, the patient was admitted for full anticoagulant therapy. Serial CEUS will be performed to monitor the therapy and observe the potential resolution of the thrombus.

Summary

Based on the proven clinical utility, efficacy, cost-effectiveness, uniform safety profile, and lack of ionizing radiation, CEUS is now poised to assume a prominent role in the diagnosis and management of patient with cardiovascular disease and in the respective fields of radiology and vascular medicine.

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