

# Clinical Applications of Left Ventricular Opacification

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The significant advances made in ultrasound microbubble technology now permits reliable, reproducible left ventricular opacification, and this review reiterates the evidence that has shown contrast echocardiography to be clinically effective, to reduce downstream costs and to spare patients further, potentially hazardous investigations. Despite the evidence and the advances, there remains ambivalence towards the administration of contrast agents in echocardiography laboratories throughout the world, particularly in the performance of rest studies. Therefore, this review also addresses some of the reasons for the suboptimal uptake of contrast agents and encourages physicians, sonographers, and accreditatory bodies to adopt a different approach towards the difficult-to-image patient. (J Am Coll Cardiol Img 2010;3:188–96)

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Quantitative assessment of left ventricular (LV) volumes and left ventricular ejection fraction (LVEF) frequently mandates the timing and type of therapy offered to patients with cardiovascular disease. Therefore, physicians are increasingly demanding more robust and reliable echocardiography than ever before. However, despite the advent of harmonic imaging, studies are still frequently undermined by unsatisfactory endocardial border resolution and underestimation of both LV volumes and LVEF. The main impediments to confident endocardial border delineation are obesity, chronic lung disease, ventilatory support, and chest wall deformities resulting in decreased diagnostic accuracy and poor reproducibility (1). These shortcomings seem particularly pronounced in patients undergoing stress echocardiography. Near field noise, clutter, and reverberation also hinder the identification of apical abnormalities with unenhanced scans such as LV thrombus, apical hypertrophic cardiomyopathy, and noncompaction. Many of the misgivings concerning the accu-

racy of echocardiography in the assessment of LV function and structure have been largely overcome by the development of ultrasound contrast agents that confer a benefit over harmonic imaging (2).

## Principles of Contrast Imaging

Contrast echocardiography essentially enhances discrimination between myocardial tissue and the blood pool by opacifying the LV cavity and simultaneously making the myocardium appear dark. Effective LV opacification is achieved by the intravenous administration of engineered microbubbles that consist of a gas contained by an outer shell. In general, microbubbles generate echo contrast by increasing backscatter in an ultrasound field. The nature of backscatter is related to the degree of microbubble contraction and expansion (oscillation), which in turn is affected by the acoustic power of the transmitted ultrasound field or the mechanical index (MI). Harmonic imaging was developed primarily as a contrast specific imaging

modality that utilizes the nonlinear scattering properties of ultrasound contrast agents. However, tissue also generates a harmonic signal as ultrasound propagates through it, and a high-quality contrast-enhanced image is one in which the distribution of contrast within the LV cavity is clearly seen without the presence of confounding myocardial tissue signals. Harmonic imaging requires relatively high MI that very quickly bursts contrast agents, but the ongoing bubble destruction and suboptimal differentiation between contrast and tissue, make it an unsuitable imaging modality for continuous or “real-time” contrast imaging. Therefore, contrast-specific imaging modalities are required to optimally enhance the contrast-to-tissue backscatter signal ratio and produce meaningful LV opacification and structure definition.

Real-time imaging is necessary to assess wall thickening during LV opacification but requires more sophisticated, contrast-specific imaging modalities. These technologies utilize the nonlinear oscillations of microbubbles, which produce low-amplitude backscatter that can be distinguished from tissue signals with lower MI imaging. The 2 most important real-time techniques are power pulse inversion imaging and power modulation imaging. As with traditional Doppler, both techniques work by transmitting multiple pulses down each scan line of the image, but transmitted pulses are either of alternating polarity or varying amplitude. Returning signals are processed as being derived from tissue, hence suppressed if the returning scatter is perfectly out of phase or proportionally altered in amplitude. The remaining nonlinear signals are considered to be derived from contrast microbubbles and are displayed. This type of imaging is preferable to high-power imaging for LV endocardial border enhancement as it discriminates effectively between the contrast-enhanced cavity and the myocardium (Figs. 1A and 1B).

### Approved Contrast Agents

The commercially available, Food and Drug Administration (FDA)-approved contrast agents for LV opacification are Optison (GE Healthcare, Princeton, New Jersey) (3) and Definity (Lantheus Medical Imaging, North Billerica, Massachusetts) (4), whereas the European Medicines Agency have also approved SonoVue (Bracco Diagnostics, Milan, Italy). These 3 contrast agents are also referred to as “second-generation” agents, providing successful LV opacification in 90% of cases in which baseline images are suboptimal compared with successful LV opacification in 64% to 81% of cases using Albutex (formerly manufactured by Mallinck-

rodt Medical, Inc., St. Louis, Missouri), the first commercially available ultrasound contrast agent.

For LV opacification, contrast agents should be administered as a slow bolus followed by 10 ml of a slow saline flush. This allows for uniform opacification of the LV cavity and minimizes attenuation artifact in the far field. Ideally, contrast should be administered as a continuous infusion, which offers the advantage of maintaining the same flow rate throughout the study and achieving more uniform LV opacification as compared with bolus injections.

### Clinical Applications of LV Opacification

Both the 2008 American Society of Echocardiography consensus statement and the 2009 European Association of Echocardiography (EAE) recommendations regarding contrast echocardiography provide clear indications as to when contrast agents should be utilized for resting LV opacification (5,6). In difficult-to-image patients requiring rest echocardiography with reduced image quality, contrast enhancement is recommended where  $\geq 2$  contiguous segments are not seen on noncontrast images as well as in patients requiring accurate assessment of LVEF regardless of image quality, with the intention of increasing the confidence of the interpreting physician in assessing LV volumes and systolic function. Contrast enhancement is also recommended in patients requiring confirmation or exclusion of LV structural abnormalities, intracardiac masses, for patients in the intensive care unit, and to enhance Doppler signals.

**LV endocardial delineation and assessment of LV function.** The superiority of second-generation agents in delineating the endocardium compared with first-generation agents has been demonstrated (3,4), and segment visualization by echo has also been shown to be comparable to cardiac magnetic resonance (CMR) after the administration of a contrast agent (7). A natural corollary to the enhanced endocardial delineation conferred by using contrast agents is the ability to quantify LV volumes and ejection fraction more accurately (1,7–12). Unenhanced 2-dimensional echocardiography (2DE) is known to markedly underestimate LV volumes by as much as 30% to 40% and LVEF by 3% to 6% (7–9,13,14) when compared with CMR. The underestimation of LV volumes by

#### ABBREVIATIONS AND ACRONYMS

**2DE** = 2-dimensional echocardiography

**3DE** = 3-dimensional echocardiography

**CAD** = coronary artery disease

**CMR** = cardiac magnetic resonance

**EAE** = European Association of Echocardiography

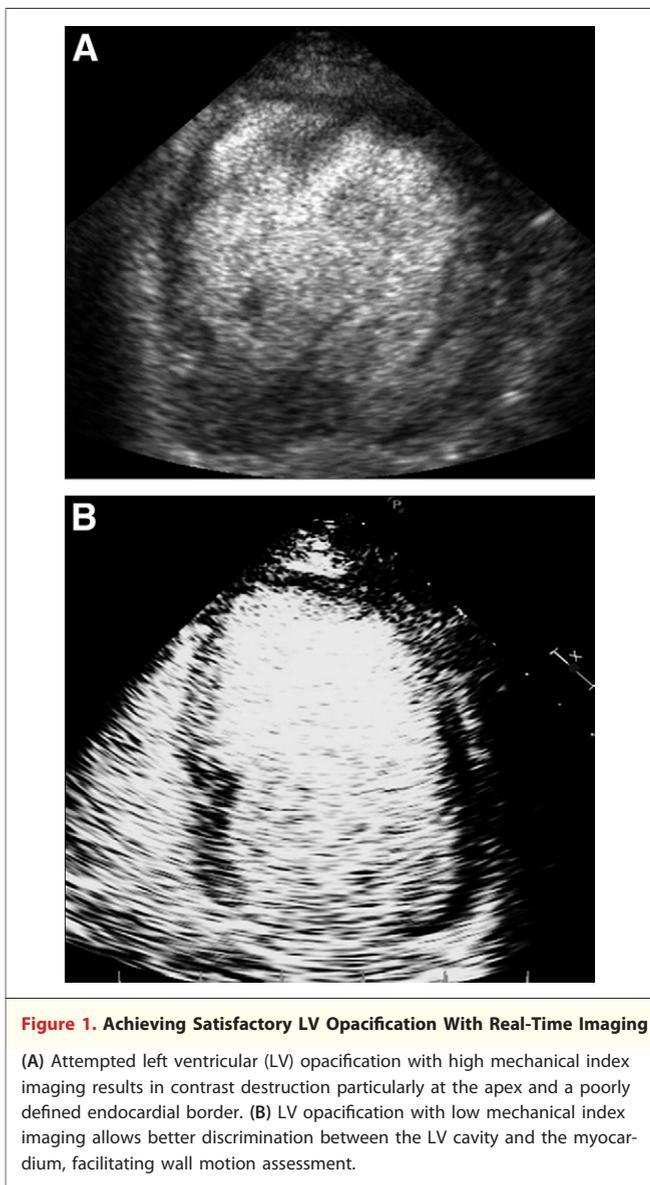
**EF** = ejection fraction

**FDA** = Food and Drug Administration

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**MI** = mechanical index



unenanced 2DE is attributed not only to the poor tracking of the endocardial border with this technique, but also to the adoption of off-axis imaging planes and foreshortening of the LV apex. A recent study of 50 patients after acute myocardial infarction demonstrated that the improvement in accuracy of estimation of LV volume and LVEF with contrast-enhanced 2DE is similar to that obtained by unenhanced 3-dimensional echocardiography (3DE) when compared with CMR (13). In this study, contrast-enhanced 3DE was superior to both techniques and provided LV volumes and LVEF data approximating those obtained with CMR. The efficacy of contrast agents in enhancing quantification of LVEF is also reviewed in detail in both the

American Society of Echocardiography (5) and EAE (6) consensus documents concerning contrast echocardiography.

#### Assessment of cardiac structure with LV opacification.

As mentioned previously, satisfactory imaging of the LV apex is often confounded by near-field artifacts. LV thrombus, usually located in the LV apex, often has to be excluded in patients with low LVEF (Fig. 2), apical aneurysms, or thromboembolic phenomena. In a retrospective study of 409 patients who underwent unenhanced tissue harmonic imaging, 46% of scans were deemed nondiagnostic for this purpose. After an additional study with contrast administration, 90% of these scans provided definitive diagnostic information for establishing or excluding the presence of thrombus (15).

Contrast echocardiography is also recognized as the technique of choice in the investigation of patients with suspected apical hypertrophic cardiomyopathy (16) (Fig. 3), LV noncompaction (17) (Fig. 4), myocardial rupture, and LV pseudoaneurysm (18).

#### Clinical Efficacy of Contrast-Enhanced Stress Echocardiography

Conventional stress echocardiography is well established, with a high sensitivity and specificity for the diagnosis of coronary artery disease (CAD). However, endocardial visualization can be compromised during stress echocardiography by chest wall movement during hyperventilation (with exercise stress) and cardiac translational movement during tachycardia. Poor quality studies have been shown to be less reproducible and to have low interobserver agreement (19). Moreover, quick and reliable acquisition of diagnostic quality images is mandated during stress echocardiography, particularly when exercise stress is undertaken.

The benefit of ultrasonic contrast agents in endocardial delineation during stress studies has been confirmed unequivocally. Second-generation contrast agents have shown improved endocardial resolution, greater concordance in test interpretation, and greater confidence in wall motion analysis even by less experienced readers (20-22).

The improved image quality and endocardial border definition during contrast-enhanced stress echocardiography has translated into improved sensitivity and accuracy of the technique for the detection of CAD (23-26). The routine use of LV opacification, regardless of baseline image quality, in improving the accuracy of diagnosing CAD has also been confirmed (27).

### Can Rest Contrast Imaging Have a “Clinical Impact”?

There have been 2 studies to date that have addressed the clinical impact of contrast echocardiography when assessing LV function. One study demonstrated that contrast echocardiography should be routinely used after acute myocardial infarction for better prediction of hard cardiac end points compared with unenhanced echocardiography (Fig. 5) (28). Until recently, there had also been little evidence for rest contrast echocardiography in conferring a clinical impact upon a patient’s subsequent management, such as alterations in their therapy or avoidance of downstream tests (Fig. 6). A study by Kurt et al. (29) sought to ascertain the day-to-day impact of contrast echocardiography upon the clinical care of 632 consecutive patients who had undergone both unenhanced and contrast-enhanced echocardiograms as part of their routine care. Patients with echocardiography deemed technically difficult had their scans repeated with an appended contrast-enhanced examination, with both sets of images interpreted by independent observers. The primary physician of the patient was then contacted with the results of the unenhanced scan, and the impact it would have on the patient’s subsequent management was recorded. The results of the contrast-enhanced echocardiogram were then revealed to the primary physician, and any alterations to the patient’s management, if any, were documented. *Impact* upon cardiovascular management referred to initiation or discontinuation of medications (inotropes, diuretics, intravenous fluids, vasodilators, anticoagulants) and the need for further diagnostic studies (transesophageal echocardiography, radionuclide imaging, stress testing, coronary angiography). After contrast LV opacification, the proportion of uninterpretable studies decreased from 11.7% to 0.3% and of technically difficult studies decreased from 86.7% to 9.8%. This led to a significant avoidance of further diagnostic procedures in patients, primarily due to improved assessment of LV function. Of the patients who ultimately underwent further testing, 67% of these were based on the findings of the contrast echocardiogram. Medical therapy was altered in ~11% of the patients in this study after interpretation of the contrast study, and combined with the avoidance of further downstream tests, a total of 35.6% patients receiving contrast experienced a significant impact on their clinical care.



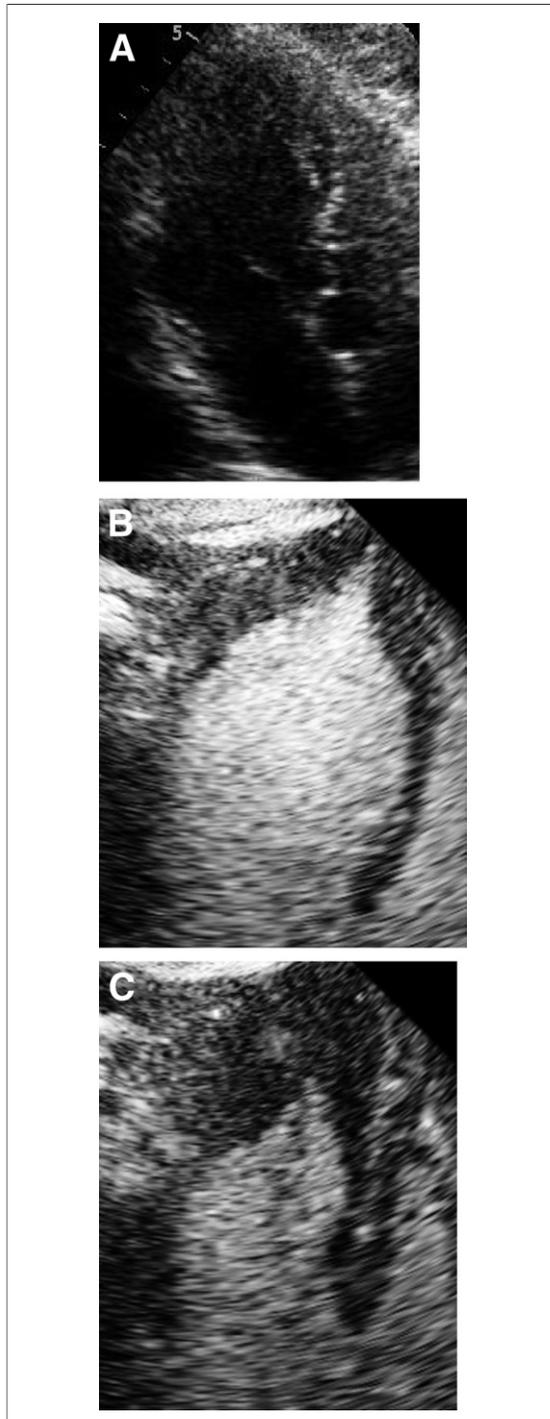
**Figure 2. Apical Thrombus**

A mobile, large thrombus is clearly visualized on administration of ultrasound contrast agent in this patient who suffered an acute myocardial infarction in the left anterior descending artery.

### Cost Efficiency of Contrast Agents

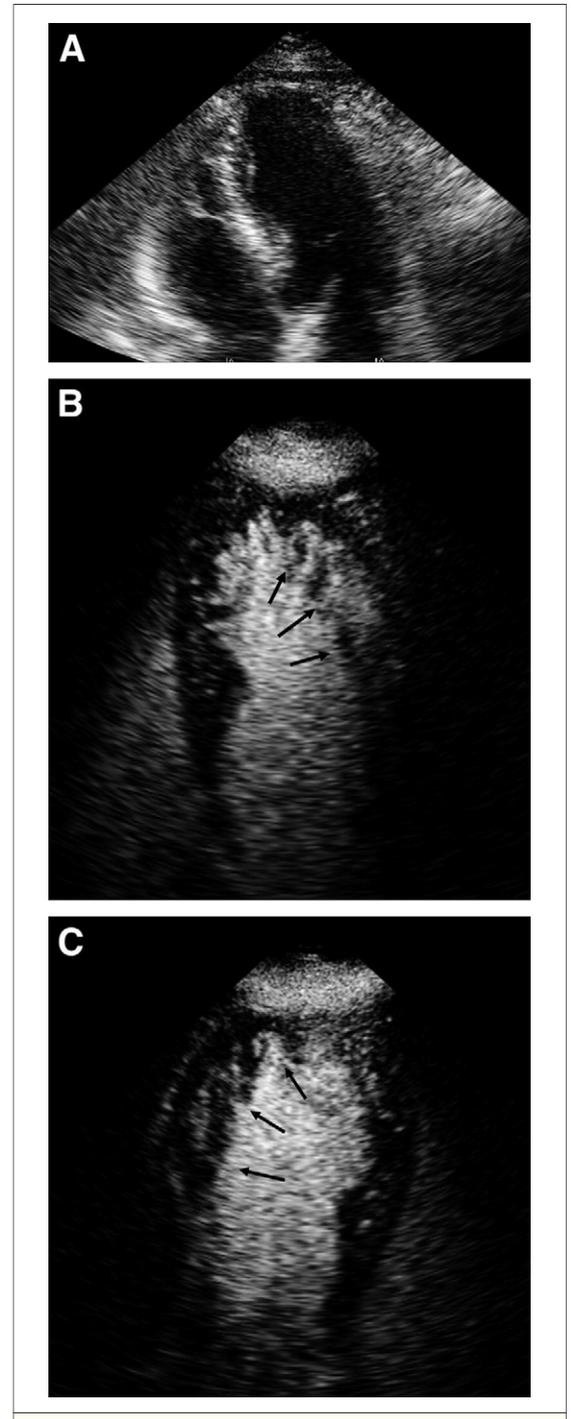
The improved image quality afforded by LV opacification not only improves clinical efficacy, but can also result in a more cost-effective paradigm of care. The most obvious method of cost saving is through the reduction of downstream, additional tests that are incurred as a result of an initially nondiagnostic echocardiographic study. Administration of contrast agents reduces potential downstream testing by ~33%, with an average cost saving of \$122 per patient (29). Improved image quality can also realize cost savings through enhanced diagnostic accuracy and reducing the false positive and false negative rate, although the magnitude of this effect is more difficult to quantify.

The improved diagnostic yield achieved with contrast-enhanced stress echocardiography has been shown to result in only 12% of patients requiring further downstream testing, compared with 42% of patients who received unenhanced stress scans (30). Thanigaraj et al. (31) defined the cost effectiveness of contrast usage in patients with suboptimal image quality during stress echocardiography. During a 3-week period following stress echocardiography, 53% of patients who underwent suboptimal, unenhanced scans required additional testing in the form of nuclear scintigraphy. Administration of contrast in a group with similar quality scans resulted in a saving of \$238 per



**Figure 3. Apical Hypertrophic Cardiomyopathy**

(A) An unenhanced, 3-chamber echocardiogram at rest in a 70-year-old woman referred for stress echocardiography to investigate breathlessness is of poor quality but does not suggest any significant structural disease. Following administration of a contrast agent, the characteristic spade-like left ventricular cavity contour is fully appreciated in both (B) diastole and (C) end-systole, permitting the diagnosis of apical hypertrophic cardiomyopathy to be made.



**Figure 4. LV Noncompaction**

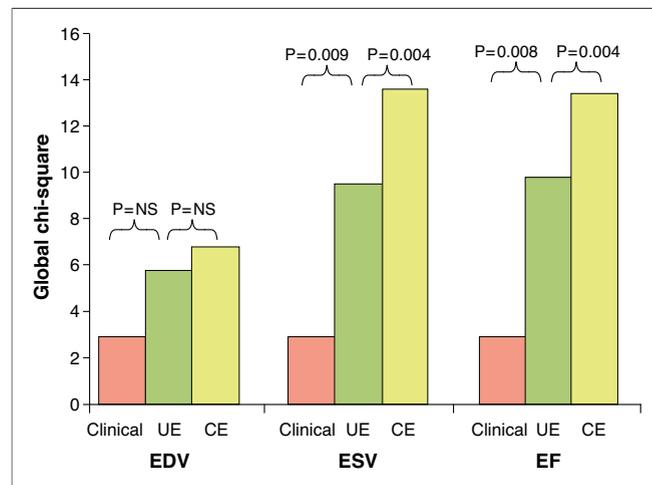
(A) The resting, unenhanced scan in a patient referred for stress echocardiography to investigate chest pain is of poor quality and nondiagnostic. After left ventricular (LV) opacification, multiple deep trabeculations (arrows) of the LV myocardium are seen in (B) the lateral (4-chamber view) and (C) the posterior (3-chamber view) walls involving the apex, typical of LV noncompaction.

patient. Contrast-enhanced stress echocardiography has also been proven to be cost effective in the acute setting. In a United Kingdom study, stress echocardiography with contrast was performed in 15% of patients, and even when extrapolated to 30% of cases, resulted in reduced downstream costs compared with exercise ECG for the detection of CAD in patients presenting with troponin-negative acute chest pain (32).

### The Ambivalence Towards Contrast Agents

Despite the clinical evidence supporting LV opacification in terms of clinical efficacy and cost efficiency, there clearly remains a considerable ambivalence towards using ultrasound contrast agents despite reimbursement being widely available. As mentioned previously, ~11% of unenhanced scans are deemed uninterpretable in a real-world setting with respect to making a reliable assessment of LV function (29). However, during 2008, a total of ~22,236,000 transthoracic rest scans were performed in the U.S., of which ~93,000 (0.4%) were performed with either Definity or Optison administration for the purpose of LV opacification (33). These figures starkly convey the large proportion of echocardiograms that are being performed and interpreted that do not even provide the most basic and important data one would expect from them.

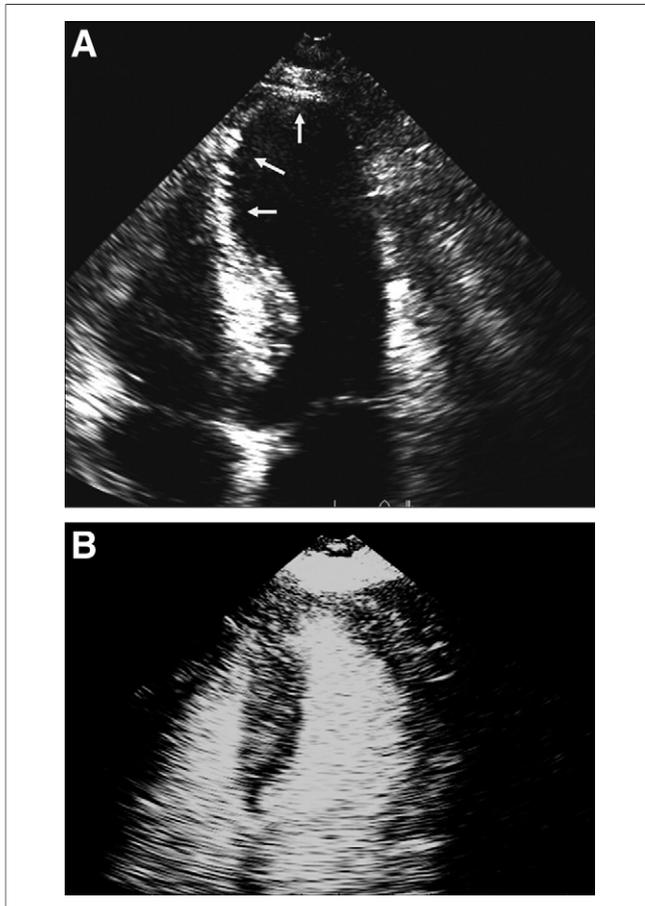
Efforts are required by individuals, departments, and organizations alike to remove impediments perceived to be restricting the uptake of contrast ultrasound agents in the performance of rest echocardiograms. The role of physician leaders in ensuring that good quality scans are being performed in their echocardiography laboratory cannot be underestimated (5). As well as providing training and assistance in the technical aspects of successfully administering contrast, the physician must remove the complacency, which has crept into echocardiography, of accepting poor quality images. This complacency is probably the biggest barrier confronting advocates of contrast echocardiography, and it is here that organizations and accreditory bodies could have an impact. At present, neither the Intersocietal Commission for the Accreditation of Echocardiography Laboratories (ICAEL) nor the EAE Laboratory Accreditation module suggest, let alone mandate, the use of contrast agents when baseline imaging is poor. Both the British Society of Echocardiography and the EAE require submission of a logbook of 250 studies representative of typical pathologies encountered in the echo laboratory to achieve individual transthoracic echocardiography accreditation. However, none of these



**Figure 5. Bar Chart**

Bar chart comparing global chi-square values obtained with clinical variables alone, clinical variables plus unenhanced echocardiography remodeling parameters (UE), and clinical variables plus unenhanced echocardiography remodeling parameters plus contrast echocardiography (CE) for the prediction of cardiac death. CE determined remodeling parameters provide improved prediction of outcome compared with UE echocardiography following acute mechanical index. EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume.

scans are required to demonstrate examples of the diagnostic benefit that can be achieved with contrast enhancement. Echo laboratories seeking national/international accreditation in transthoracic echocardiography should be required to provide the necessary facilities, training, and expertise to perform contrast echocardiography in patients who meet the criteria as defined by societal guidelines. After appropriate training in intravenous cannulation and contrast agent administration, a member of the laboratory personnel, either a sonographer or nurse, should be identified as being capable of performing a contrast-enhanced scan where necessary. A move towards setting obligatory policies by accreditation agencies for contrast use when image quality is poor together with a mandate that sonographers applying for individual accreditation perform at an agreed number of contrast-enhanced scans will help to empower the sonographer to change his/her approach towards the difficult-to-scan patient. There are also concerns that contrast studies are time consuming; however, “sonographer-driven” contrast echocardiography has been shown to reduce the total time required to perform a contrast-enhanced study to less than the time required to perform an unenhanced, technically difficult study (34). An accredited echo laboratory should have a designated sonographer or nurse who has been appropriately trained to perform intravenous cannulation and administer contrast agents, thereby alleviating the



**Figure 6. Avoidance of Further Downstream Tests After LV Opacification**

(A) This unenhanced, 4-chamber image taken at end-systole was reported as showing extensive wall motion abnormalities (arrows) in a patient being investigated for atypical chest pain who was duly referred for coronary angiography. (B) The echocardiogram was repeated with left ventricular (LV) opacification, clearly demonstrating normal wall thickening during systole, obviating the need for invasive coronary angiography as a first-line investigation of this patient's symptoms.

dependency of the laboratory on the availability of a physician to perform the test. If the contrast-enhancement is not felt to be feasible at the time of the initial study, the patient could be invited back to a dedicated LV opacification out-patient clinic, although this would be a less desirable arrangement.

The reluctance to perform contrast studies may also be due to residual fears, or misperceptions, regarding the safety profile of contrast agents. The concerns regarding ultrasound contrast agents arose primarily after a handful of deaths over a 6-year period (esti-

mated at 1 death per 500,000 contrast injections in the U.S.) that occurred in temporal relation to contrast administration in patients with significant underlying, unstable cardiovascular disease. However, it is worth reiterating that after a temporary withdrawal of the approval for Sonovue for use in cardiac applications by the European Medicines Agency in 2004, the committee soon restored its approval for patients not suffering suspected acute coronary syndrome or unstable heart disease. Likewise, the black-box warning issued by the FDA for Definity in 2007 was reviewed, and initially, several new contraindications were imposed on its use (acute myocardial infarction, unstable heart failure, unstable arrhythmias, respiratory failure, mechanical ventilation, pulmonary emboli), which were felt to be unnecessary and expose critically unwell patients to alternative, more invasive diagnostic procedures. Moreover, the potential effect of pseudocomplication confounding the interpretation of safety was raised and later confirmed by large, retrospective analyses that found no difference in complication rate to a matched cohort undergoing unenhanced studies (35,36). The FDA reviewed the new restrictions in May and June 2008, and subsequently lifted the new contraindications, replacing them with warnings instead.

## Conclusions

Contrast echocardiography has been shown to be clinically effective, to reduce down stream costs and to spare the patient further, potentially hazardous investigations. The enhanced diagnostic accuracy conferred by ultrasound contrast agents should make them indispensable in routine as well as in the more advanced echocardiographic examinations, but contrast uptake remains woefully poor. To fully realize the potential of contrast echocardiography, we must remove both the complacency surrounding the acquisition of suboptimal rest studies and the "freedom" of echo laboratories to avoid LV opacification if they choose through the implementation of mandatory policies for the application of contrast agents by existing accreditatory bodies.

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