



A Case for Utilizing Ultrasound Contrast Agents During Echocardiography

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A diagnostic test should be able to provide as much information regarding the organ system being investigated as possible. Echocardiography has evolved into a ubiquitous diagnostic tool in cardiovascular medicine from M-mode to B-mode to 3D imaging, and along the way it has incorporated continuous-wave and pulsed Doppler as well as tissue imaging techniques. At each stage of its evolution it has delivered additional data that has informed clinical decision-making. However, its full potential is not always met, mainly because of a lack of training and extraneous factors.

It is well appreciated that echocardiographic image quality is not uniformly adequate in order to confidently answer critical questions. Ultrasound contrast agents (UCAs) have been shown to significantly enhance image quality, particularly the delineation of left ventricular (LV) endocardial borders. Table 1 lists the commercially available UCAs. Both the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend use of UCAs when the endocardial borders are not adequately visualized.^{1,2} This indication alone accounts for UCA use in at least a third of our patients during a rest echocardiogram and all our patients during stress echocardiography. The improvement in image quality allows for greater confidence in making a call and reduces the need for additional testing.^{1,2}

In many situations, the cost of UCAs can be an impediment to their use. However, when the overall cost of making a diagnosis in a patient is calculated, which frequently includes multiple tests because of incomplete information from the first test, use of UCA during rest echocardiography is very cost-effective.³ Relying on echocardiography as a one-stop shop makes sense because its overall cost is low compared to other diagnostic tests, and the patient is not exposed to radiation. It can be easily performed at the patient's bedside in the inpatient setting, in the emergency department, in the intensive care unit, and in the outpatient clinic.

The better delineation of endocardial borders has led to a increased diagnosis of conditions affecting the LV apex.^{1,2} Because the lateral resolution of ultrasound (which is an order of magnitude worse than the axial resolution) is used to interrogate the apical walls, there is more ambiguity regarding findings pertaining to the apex. This is compounded by reverberation induced artifacts that are present to some extent even with harmonic imaging. Further, the apex is often foreshortened. Use of UCAs can guide the examination to include the true apex. They can allow differentiation of LV

thrombus from ultrasound-induced artifacts as well as apical strings. Suspected apical thrombi are more often ruled out than ruled in by use of UCA. This is important because one can then more confidently prescribe anticoagulants when an actual thrombus is present. UCA can also better define apical aneurysms and differentiate them from pseudoaneurysms. The former requires medical therapy while the latter demands surgery. LV apical non-compaction is now being diagnosed more frequently with use of UCA.⁴ The trabeculae can harbor small thrombi that can embolize, in which case anticoagulation is indicated. More apical hypertrophic cardiomyopathy is also being diagnosed with UCA use, which is frequently missed otherwise.^{1,2}

A very small dose of an UCA can also enhance Doppler signals. Thus, tricuspid and mitral regurgitation jets can be more clearly defined, allowing a more precise estimation of pulmonary artery pressure and LV dP/dt, respectively.⁵ Further, flow signals across the aortic valve are enhanced leading to a more accurate estimation of the severity of aortic valve stenosis.⁶ Because UCAs increase both signal and noise, it is important to reset the baseline so as not to overestimate pressures.

Because coronary artery disease is so common, a comprehensive cardiovascular evaluation should ideally include assessment of myocardial perfusion for which we frequently depend on radionuclide studies, thus exposing patients to radiation. Although it requires additional training and experience, myocardial contrast echocardiography (MCE) can be routinely performed in an echocardiography laboratory.⁷ When performed at rest and during stress (supine exercise or pharmacological) it provides the same if not better information as radionuclide studies.^{8,9} Similar to radionuclide studies, a reversible perfusion defect on MCE indicates the presence of physiologically significant coronary stenosis that exhibits reduced coronary flow reserve.¹⁰ During exercise or pharmacological stress a perfusion mismatch between stenosis supplied myocardium and normal myocardium precedes regional wall thickening abnormality.¹¹ Consequently, stress MCE is more sensitive than wall thickening assessment on routine stress echocardiography for the diagnosis and prognostication of coronary artery disease.¹² It is also more cost effective.¹³ Because the presence of a coronary stenosis results in compensatory distal arteriolar vasodilation, careful measurement of phasic changes in myocardial arteriolar blood volume can be used to detect presence of coronary stenosis at rest without recourse to stress.¹⁴

MCE performed at rest can provide valuable diagnostic information in patients presenting to the emergency department with chest pain and a normal or non-diagnostic electrocardiogram. With use of UCAs both regional function and perfusion can be assessed.¹⁵

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Table 1 - Commercially Available Ultrasound Contrast Agents

Name	Manufacturer	Year Approved	Shell Composition	Gas	Approved Application
Optison	General Electric Healthcare	1986	Denatured albumin	Octafluoropropane	Left ventricular opacification
Definity	Lantheus Medical	2011	Phospholipid	Octafluoropropane	Heart, liver, kidney imaging
SonoVue	Bracco Diagnostics	2011	Phospholipid	Sulphur hexafluoride	Heart, liver, breast

Table 2 - Major Adverse Effects of Common Cardiovascular Tests

Procedure	Adverse Events	Event Rate
Exercise Stress Test	Myocardial infarction/death	1 in 2,500
Dobutamine Stress Test	Myocardial Infarction/ ventricular fibrillation	1 in 2,000
High Osmolality Iodinated Contrast Agents	Potentially life-threatening allergic reactions	1 in 500
High Osmolality Iodinated Contrast Agents	Potentially life-threatening allergic reactions	1 in 5,000
Cardiac Catheterization	Serious arrhythmias, myocardial infarction/death/neurological event, vascular complication, Contrast reaction	1 in 500
Ultrasound contrast agents	Anaphylactoid reaction (pseudo-allergy)	1 in 15,000
Ultrasound contrast agents	Fatal allergic reaction	1 in 500,000

When both are normal the chance of an acute coronary syndrome is very low, and the patient can be safely discharged. Despite the additional cost of UCA, the cost-effectiveness of using this approach in the emergency room has been clearly defined.¹⁶

Resting MCE can also be used to define the vascularity of tumors within cardiac chambers or LV walls. Highly vascular tumors are more likely to be malignant.¹⁷ For instance, myxomas are not very vascular, while primary and secondary cancers located in the heart tend to be very vascular.

UCAs are safe.¹⁸⁻²¹ Table 2 compares the adverse reaction rate of UCAs compared to other tests routinely used for diagnostic imaging (Table 2).²⁰ A relatively common reaction is back pain caused by complement activation, particularly by negatively charged phospholipid encapsulated microbubbles. Pseudo-allergy is far more common than true anaphylactic shock and can be easily managed. The latter is very rare. Egg allergy should be ruled out in patients who receive albumin coated bubbles (Optison). Patients who are uniquely prone to allergic reactions such as those with systemic mastocytosis should not be given UCA.

In summary, a strong case can be made for the use of UCAs for delineating the LV endocardial borders in patients undergoing

echocardiography. They improve diagnostic accuracy of the examination, thus reducing the need for additional tests, as well total cost to the healthcare system. UCAs can also be used for enhancing Doppler signals, thus allowing a better assessment of valvular pathology and pulmonary artery pressure. An additional case can be made for specialists to train in the use and interpretation of MCE during rest and stress, thus bringing to the echocardiography laboratory the ability to diagnose the presence of coronary artery disease in patients with normal regional LV function. Use of UCAs could therefore facilitate a comprehensive one-stop cardiovascular examination without recourse to multiple tests for various pieces of information pertaining to an individual patient. Managers of echocardiography laboratories should make a strong argument for their use.

Conflict of interest

none declared.

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