Cardiovascular Applications of Ultrasound Contrast Agents

Sanjiv Kaul, MD, FACC, FASE, FAHA, FRCP

Distinguished Professor of Cardiology, Professor of Medicine and Radiology, and
Head, Division of Cardiovascular Medicine, Oregon Health and Science University

Abstract
Over the last 40 years, contrast echocardiography (CE) has experienced numerous technical advances, most notably with online signal processing of ultrasound (US) backscatter from insonified microbubbles. It now has a number of clinical applications, including left ventricular cavity opacification and Doppler signal enhancement. However, the most excitement has been generated in the field of myocardial perfusion, where CE may be used to accurately measure perfusion. The future growth of CE is dependent on US Food and Drug Administration (FDA) approval of more US contrast agents, as well as on reimbursement, currently only given for left ventricular (LV) cavity opacification at rest, and not for either interpretation of studies or myocardial perfusion assessment. The potential of CE as an inexpensive tool for acquiring sophisticated information for patients in a variety of clinical scenarios means that overcoming these obstacles will be key to utilising its full potential for the enhancement of patient care.

Keywords
Contrast echocardiography, ultrasound contrast agents, microbubbles, Doppler signal enhancement, myocardial perfusion assessment, left ventricular cavity opacification

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Correspondence: Sanjiv Kaul, MD, Head, Cardiovascular Medicine, Oregon Health & Science University, UHN62, 3181 SW Sam Jackson Park Road, Portland, OR 97239.

E: kauls@ohsu.edu

Contrast echocardiography (CE) was 40 years old in 2008. Gamiak and Shah first described the use of ultrasound (US) contrast in 1968 during the early days of M-mode echocardiography. In that study, US contrast was produced by inadvertently introducing air bubbles into the indocyanine green solution that was injected into the left heart during cardiac catheterization and observing its appearance in the aortic root. The intravenous injection of hand-agitated saline that contains small air bubbles has since been used to detect left-to-right (negative contrast effect in the right atrium) and right-to-left (appearance of contrast in the left atrium and left ventricle) shunts at the inter-atrial level, such as atrial septal defects and patent foramen ovale (see Figure 1). It has also been used to detect pulmonary arterial–venous malformations and other pulmonary vascular shunts.

The bubbles, produced by hand agitation, are relatively large (10–100µm) and are too short-lived to cross capillary beds, so left ventricular (LV) cavity and myocardial opacification had to wait for the development of small (smaller than erythrocytes) and stable microbubbles. Currently, there are many commercially produced US contrast agents (see Table 1) with common salient features. The microbubbles in these agents do not aggregate, are biologically inert and safe, remain entirely within the vascular space, have an intravascular rheology that is similar to that of erythrocytes, respond non-linearly to US, and are eliminated from the body via the reticuloendothelial system with their gas escaping from the lungs. A key technical advance for CE was online signal processing of US backscatter from insonified microbubbles. Prior to this it was not possible to separate bubble signals from myocardial backscatter without off-line image processing. Unlike tissue, microbubbles are compressible and oscillate in a US field. At even low mechanical index (MI), these oscillations become non-linear; that is, during each oscillation the microbubbles expand more than they contract. Using novel signal processing techniques the non-linear signals emanating from these oscillating microbubbles can be amplified and the linear signals can be suppressed, resulting in excellent opacification. Using these approaches, both high MI intermittent imaging (using B-mode and power Doppler) and low MI continuous imaging are currently being employed for CE.

Left Ventricular Cavity Opacification
The only current US Food and Drug Administration (FDA)-approved indication for US contrast agents in the US is LV endocardial border delineation in patients where two or more myocardial segments are not visualized on routine echocardiography at rest. The majority of patients who benefit from the use of these agents for this specific purpose are those in intensive care units, those on respirators, and those who have poor acoustic windows, such as those with obesity or chronic obstructive pulmonary disorder. It has been shown that the use of US
contrast agents in such patients provides information identical to the more invasive transesophageal echocardiography.15

US contrast agents are also very useful in patients in whom quantitative assessment of LV ejection fraction is required. It is much easier to trace the LV boundaries on end-diastolic and end-systolic still frames when there is contrast in the cavity. Figure 2 illustrates four- and two-chamber views with and without contrast in the LV cavity: it is clear that despite 'good' images without contrast, LV boundaries can be accurately traced only when US contrast is present. Using US contrast provides LV ejection fraction measurements that are closer to those provided by magnetic resonance imaging.16 In addition, assessment of LV regional function also becomes much easier, and less experienced observers can make more accurate assessments with greater confidence.17,18

US contrast agents are also very useful in ruling in or ruling out thrombus in the LV cavity.19,20 The apex is not always clearly defined in apical views despite the use of harmonic imaging. It is common to mistake the presence of LV string or acoustic reverberations for the presence of thrombus, especially if apical wall motion abnormality is also suspected. This obviously has therapeutic implications, since the presence of thrombus usually necessitates the use of warfarin, which can have serious side effects. Therefore, accuracy in the definition of thrombus is highly desirable. Figure 3 illustrates the ability of contrast to clearly define the presence of LV thrombus, and CE has become the 'gold standard' for this purpose. In panel A there is the suggestion of an apical thrombus (identified by the arrow) in a non-contrast-enhanced image, while the contrast-enhanced image clearly rules out a thrombus. In panel B, use of US contrast clearly demarcates an apical thrombus (identified by the arrow). CE is also used with transoesophageal echocardiography to differentiate left atrial appendage thrombus from ‘smoke.’21

LV cavity masses need not all be thrombi, and CE has been used to differentiate these masses from thrombi based on their vascularity. Figure 4 is one such example where a mass in the LV cavity (see arrow on panel A) shown not to be a filling defect on contrast echocardiography (CE), but to have a vascularity that is higher than that of the surrounding myocardium when perfusion imaging is performed (arrow on panel B). On angiography (arrow on panel C) and histopathology (panel D), it was confirmed to be a cavernous hemangioma.22 Similar results have been reported for masses in other regions of the heart.23 Another condition where CE has become the gold standard is in the diagnosis of apical
hypertrophic cardiomyopathy, since in many patients with this condition the endocardium is not well visualized. Hypertrophic cardiomyopathy, since in many patients with this condition the endocardium is not well visualized.24 Figure 5 illustrates echocardiographic images before (panel A) and after (panel B) the administration of US contrast in a patient with apical hypertrophic cardiomyopathy. The endocardium was not clearly defined in the non-contrast-enhanced images (A), while after administration of contrast (B) better endocardial definition led to the accurate diagnosis of the condition.

The incidence of non-compaction of the LV has also markedly increased with the use of US contrast agents, since it is much easier to visualize the thinner LV wall and the myocardial indentations and crevices seen in this condition.25 All patients with muscular dystrophy being referred to our laboratory to rule out cardiac involvement receive US contrast to rule out non-compaction or other abnormalities. The endocardium is not clearly seen in many patients with apical aneurysms or pseudo-aneurysms. US contrast can help physicians to make the correct diagnosis and begin an appropriate therapy.26 There also have been reports of the diagnosis of cardiac rupture with the use of US contrast agents.27

One of the biggest clinical applications for CE is stress echocardiography, where visualization of every myocardial segment during stress is crucial to make the diagnosis of coronary artery disease (CAD).28,29 In many cases the endocardium may be visualised during rest and not during stress. Consequently, in our laboratory all patients are required to undergo CE during stress unless there is a specific contraindication or if the patient declines. Our exercise stress

### Table 1: Ultrasound Contrast Agents

| Name         | Manufacturer     | Shell                        | Gas              | Diameter (µm) | Concentration (ml⁻¹) | Comments                                                                 |
|--------------|------------------|------------------------------|------------------|---------------|----------------------|--------------------------------------------------------------------------|
| Levovist     | Schering         | None—stabilised with 0.1% palmitate | Air              | 1.2           | 1.2–2·10⁹ when 2.5g is dissolved in 10ml saline. | Available for cardiological applications in 69 countries but not in the US |
| Albunex      | Molecular Biosystems, Inc. | Denatured human albumin | Air              | 4.3           | 0.5·10⁹               | Approved for LV cavity opacification in the US, but no longer manufactured |
| Imagent      | Alliance Pharmaceuticals/ IMCOR | Surfactant-coated | Perfluorhexane   | 5.0           | 0.5·10⁹               | Approved for LV cavity opacification in the US, but no longer manufactured |
| Optison      | General Electric | Denatured human albumin | Perflutren       | 3.0–4.5       | 5.0–8.0·10⁸           | Approved for LV cavity opacification in the US, Europe, and Latin America |
| Sonazoid     | General Electric | Lipid                        | Perfluorbutane   | 2.4–2.5       | 0.3·10⁹               | Approved in Japan for liver opacification                                |
| Definity     | Lanthus Medical Imaging | Lipid                        | Octafluorpropane | 1.1–3.3       | 1.2·10¹⁰              | Approved for rest echo LV cavity opacification in the US, Europe, Canada, Australia, and some countries in Latin America, Asia, and the Middle East; for radiology applications in Canada, Mexico, and Australia; and for stress echo in the EU and Mexico |
| Sonovue      | Bracco Diagnostics | Lipid                        | Sulphur hexafluoride | 2.5 | 5.0·10⁸ | Available in Europe for LV cavity opacification and radiological applications |
| Cardio-sphere | Point Biomedical, Inc. | Bilayer: inner polymer and outer albumin | Nitrogen         | 3.0 | 2.0–5.0·10⁸ | Development terminated for financial reasons |
| Imagify      | Acusphere, Inc.  | Polymer                      | Decafluorobutane | 2.3 | Gas is 260±25µg·ml⁻¹ of reconstituted product | Under FDA review for myocardial perfusion |

FDA = US Food and Drug Administration

Figure 5: Echocardiographic Images Before and After the Administration of Ultrasound Contrast in a Patient with Apical Hypertrophic Cardiomyopathy

The endocardium was not clearly defined in the non-contrast-enhanced images (A), while after administration of contrast (B) better endocardial definition led to the accurate diagnosis of the condition.
tests are all performed using supine bicycle and our pharmacological stress tests are all performed with dobutamine. In both instances we administer contrast as a slow infusion using a pump and acquire images at rest and recovery and during at least two exercise stages. As the presence of contrast does not often result in ambiguity regarding the occurrence of inducible wall motion abnormalities, we rarely if ever read a test as equivocal. Such an approach has shown to drastically reduce downstream resource utilization.30

Doppler Signal Enhancement
The clinical development of Levovist was initially for Doppler signal enhancement.31 Hand-agitated saline can be used successfully to enhance the signal from the tricuspid regurgitation jet in patients with minimal tricuspid regurgitation so as to make the assessment of pulmonary artery systolic pressure easier. However, the enhancement of left-sided signals requires transpulmonary passage of microbubbles, and US contrast agents have been very helpful, especially in the case of mitral regurgitation,32 prosthetic valves,33 and aortic stenosis.34,35 Figure 6 illustrates how the presence of just a few microbubbles can enhance the pulsed-wave Doppler signals from the pulmonary veins. US contrast-enhanced Doppler signals have been reported to allow better non-invasive hemodynamic assessment of heart failure patients.36 These agents have been used for assessing pulmonary artery diastolic pressure from the pulmonary regurgitant jets that are present in almost all patients.37 Despite the availability of hand-agitated saline, US contrast agents have also become popular for enhancing the tricuspid regurgitant Doppler velocity signals in order to measure pulmonary artery systolic pressure.38

Myocardial Perfusion Assessment
By far the most research and greatest excitement has been generated in the field of myocardial perfusion, and the reader is directed to in-depth reviews elsewhere.39–43 CE can be used to measure myocardial perfusion quite precisely.44 Microbubbles are administered as a constant infusion, and approximately two to three minutes later steady state is achieved when their concentration in any blood pool (LV cavity, myocardium, etc.) becomes constant and proportional to...
the blood volume fraction of that pool. For example, during normal conditions, for every 100 microbubbles within a sample volume in the LV cavity, there will be eight microbubbles within a similar-sized sample volume in the myocardium. When normalized to that from the LV cavity, the acoustic intensity measured from the myocardium after background subtraction (to eliminate native backscatter from myocardial tissue) provides a measure of myocardial blood volume fraction (since LV cavity is 100% blood). As in end-systole, 90% of the myocardial blood volume fraction is composed of capillary blood, and a single end-systolic CE image provides an assessment of capillary density in the different myocardial regions.

At steady state, the microbubbles within the myocardium are destroyed with high-energy ultrasound pulse(s) so that microbubbles are no longer seen in the myocardium. Imaging is then performed to measure the rate of microbubble reappearance, which reflects erythrocyte velocity (see top panel of Figure 7). Time versus acoustic intensity (AI) curves can be generated from different myocardial regions (see bottom panel of Figure 7) and fitted to an exponential function: $y = A(1-e^{-bt})$, where $y$ is AI at a pulsing interval $t$, $A$ is the plateau AI $b$ representing myocardial blood volume, and $b$ is the rate constant that represents the rate of rise of AI (and thus mean microbubble velocity). Since blood flow is a volume of blood moving at a mean velocity, the product of $A$ and $b$ reflects tissue blood flow.44

This approach can be used at rest and during stress. At rest it is usually used to assess risk area for the diagnosis of acute myocardial infarction (AMI) and other acute coronary syndromes, define the extent of collateral blood flow, determine the infarct size after reperfusion, and assess myocardial viability. During stress it is used to make the diagnosis of CAD. Non-stress detection of CAD has also been reported using CE where the technique utilizes the increase in arteriolar blood volume to detect coronary stenosis. Several studies have reported on the use of CE for the diagnosis of AMI in the emergency department. In these studies, adding regional function assessment by CE increased the prognostic information of the clinical variables significantly. When myocardial perfusion assessment is added, further additional information is obtained. Patients with normal perfusion and function have excellent outcome, while those in whom both are abnormal have the worst outcome. Intermediate outcome is noted in those with normal perfusion despite abnormal function. These patients include those with spontaneous reperfusion (about one-sixth of the AMI patients) and those with non-ischemic cardiomyopathies.

Figure 8 illustrates a large perfusion defect that helped make the diagnosis of AMI in a patient with chest pain and normal electrocardiogram (ECG) (see left panel). This patient had total occlusion of a dominant left circumflex coronary artery that was opened successfully. A repeat study showed excellent myocardial reperfusion except in a small apical region that showed no reflow (see right panel). A month later there was normal wall motion in all myocardial segments except the apex, which continued to show akinesia. Figure 9 illustrates a case of Tako-Tsobu syndrome where apical ballooning (indicated by the arrows) is seen in the B-mode end-systolic image (see panel A), but myocardial perfusion is normal (see panel B). Based on this study in the emergency department, the patient was not taken to the catheterization laboratory and the regional dysfunction resolved spontaneously. In the absence of prior infarction, the detection of CAD on myocardial perfusion imaging is based on the occurrence of reversible perfusion defects during pharmacological or exercise stress. CE can be used to detect coronary stenosis and to quantify the degree of MBF mismatch during pharmacological stress. Figure 10 demonstrates normal perfusion. At rest, microbubble replenishment should occur in four to five seconds if blood flow is normal (see Figure 7). Therefore, the rest image (see left panel) is captured at the fourth heartbeat after bubble destruction. If blood flow reserve is normal, the myocardium should replenish within one second at stress, hence the stress image (right panel) is captured at the first heartbeat after bubble destruction. In the normal setting, these two images (rest and stress) should look similar. If there is a significant stenosis in the absence of prior infarction, the rest image should look normal (see left panel in Figure 11), while the stress image should show a defect (indicated by the arrow in Figure 11).
In the presence of infarction where myocardial blood volume is markedly reduced due to capillary loss, a fixed defect (present at both rest and stress) should be noted (indicated by the arrow in Figure 12). Similar results are also obtained when dobutamine is used as a stressor. Using this approach, CE had significant incremental value over clinical factors, resting ejection fraction, and wall motion responses in predicting events. One of the earliest experimental and clinical applications for CE was the detection of myocardial viability based on microcirculatory integrity after attempted reperfusion in AMI. Another aspect was the maintenance of myocardial viability in AMI based on adequate collateral flow.

More recently attention has shifted to the assessment of viability in chronic CAD. CE was compared with 201Tl imaging and low-dose dobutamine stress in patients with CAD and dysfunctional myocardium undergoing coronary bypass surgery.92 It was found that the sensitivity of CE for recovery of function after bypass was similar to that of 201Tl imaging and dobutamine echocardiography. However, its specificity was higher and the microvascular density on biopsy correlated very well with CE parameters.93

CE has been found to be very effective in defining the septal perforator arteries that supply the thickened muscle, which contributes to outflow tract obstruction in hypertrophic cardiomyopathy. Thus, selective intra-coronary injections of microbubbles can be used to define the vessel through which alcohol needs to administered to create localized necrosis and reduction in the outflow tract gradient.94 This has also been attempted for visualization of the right ventricular myocardium95 and to demonstrate improved perfusion after stem cell therapy.96

**Conclusion**

The growth of CE is dependent on FDA approval of more US contrast agents, particularly for myocardial perfusion. It also depends on reimbursement. Currently, reimbursement is given only for the cost of the US contrast agent and for LV cavity opacification at rest, and not for the interpretation of the studies or for myocardial perfusion assessment. Reimbursement for LV cavity opacification during stress is imminent. These are important hurdles for clinical adoption and investment in CE, which is rather unfortunate because, for a relatively inexpensive tool, myocardial CE can provide rather sophisticated information in individual patients in various clinical scenarios. Its greater clinical adoption can only enhance patient care.

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Sanjiv Kaul, MD, FACC, FASE, FAHA, FRCP, is a Distinguished Professor of Cardiology, a Professor of Medicine and Radiology, and Head of the Division of Cardiovascular Medicine at the Oregon Health & Science University. His major clinical and research interest is coronary artery disease. Dr. Kaul has published over 250 papers in the most prestigious cardiovascular journals, and has been funded continuously by the National Institutes of Health (NIH) since 1986. He is a member of the Editorial Board of the top cardiovascular journals in the world. He is Vice President of the American Society of Echocardiography (ASE). Dr. Kaul received his medical degree from Delhi University and completed his residency in internal medicine at the University of Vermont. He completed a two-year clinical cardiology fellowship at the Oregon Health & Science University and a clinical and research fellowship at the Massachusetts General Hospital, Harvard Medical School.