Clinical applications of contrast echocardiography

Natesa G. Pandian*

Tufts-New England Medical Center, Boston, MA, USA

Abstract Advances in the engineering of transpulmonary ultrasound contrast agents have greatly enriched contemporary two-dimensional (2D) echocardiography, a technique that has become the most commonly employed imaging tool in cardiology. The currently approved application of contrast echocardiography is for left ventricular opacification (LVO) and enhanced endocardial border delineation (EBD) in patients with sub-optimal echocardiograms. In addition, the use of contrast echocardiography in clinical practice allows blood-flow assessment, identification of geometric distortions (such as an aneurysm or a pseudoaneurysm), and differentiation of various mass formations (such as thrombus, tumor, or simple trabeculation). Ongoing scientific work points to the potential of contrast echocardiography in assessing myocardial perfusion and in using contrast agents in therapeutic maneuvers. The use of modern contrast agents in echocardiography can shorten examination time, improve diagnostic accuracy, eliminate unnecessary tests, and lower medical costs. In fact, qualitative or quantitative assessment of cardiac function is difficult to achieve without the improved visualization provided by contrast enhancement.

© 2004 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Echocardiographic examination has been the cornerstone of cardiac diagnosis in a variety of cardiovascular disorders for over two decades. Two-dimensional and Doppler echocardiographic modalities provide valuable information on cardiac structures, chamber function and hemodynamic derangements. While considerable strides have been made in refining the resolution and quality of ultrasound images, poor acoustic windows encountered in patients with obesity, lung disease or unfavorable chest geometry pose a major challenge in acquiring diagnostic-quality images in a sizable portion of patients. While two-dimensional images have unsatisfactory resolution, Doppler signals are of weak caliber in the setting of high acoustic impedance. Transesophageal echocardiography can aid in a certain number of patients but cannot be applied widely because of its invasive nature. The development of ultrasound contrast agents that traverse the pulmonary circulation and opacify left heart chambers has allowed us to overcome the difficulties in obtaining diagnostic data in patients with technically sub-optimal acoustic windows.

These agents are smaller than 6 microns and thus are able to pass through the pulmonary capillary bed. Many contain high-molecular-weight gases such as perfluorocarbon or sulfur hexafluoride. Optison® is an agent that consists of perfluoropropane-filled albumin microspheres with a mean size of less than 4 microns. Definity® is a liposome-coated bubble containing perfluorocarbon gas that has been shown to have a similar use. SonoVue® is a phospholipid-coated, sulphur-hexafluoride-containing agent that can be used for cavity opacification as well as perfusion assessment. Imagent® is an agent that contains nitrogen and perfluorocarbon gases. Other agents under
investigation include Al-700 and Bisphere. All these agents can be used for cavity opacification, and some have a strong prospect for myocardial perfusion assessment. While the initial impetus in engineering transpulmonary contrast agents was the desire to develop a technique to assess myocardial perfusion, the widely applied indication today is opacification of left-sided cardiac chambers. Evolving advances point to the strong potential of myocardial contrast echocardiography in the evaluation of perfusion abnormalities in various coronary syndromes. In this article we will review the current application of contrast echocardiography and its future potential.

Application in the assessment of global and regional left ventricular function

Successful evaluation of global and regional left ventricular (LV) function requires optimal visualization of endocardial borders. Correct detection of wall-motion abnormalities is important in patients with suspected or established coronary artery disease for diagnostic purposes. It allows identification of coronary artery disease in patients with chest pain. Accurate delineation of the extent of contractile abnormalities in patients with myocardial infarction has prognostic implications. The key sign of coronary artery disease during stress echocardiography is inducible wall-motion abnormality. If interpretation of echocardiographic images is attempted when the chamber borders are ill defined, both false positive and false negative errors can frequently occur. Fig. 1 shows the best possible two-dimensional images during systole from the apical window (left-hand panel) in a patient with chest pain. The LV cavity borders are not seen in most parts of the chamber. LV opacification with contrast brings out the borders clearly, aiding in correct interpretation (right-hand panel). Shown in Fig. 2 are images from two patients with apparent apical dyskinesia (left-hand panel). Contrast-enhanced images (right-hand panel) allow one to establish not only that the apex is not dyskinetic, but that in fact it is hyperdynamic. In addition, the apical myocardium has increased wall thickness, providing the diagnosis of apical hypertrophic cardiomyopathy. The difficulty in assessing regional wall motion is compounded by increased heart rate and breathing artifacts during stress echocardiography. In an obese patient with poor acoustic windows, contrast administration allowed better visualization of LV borders and aided in correct interpretation (Fig. 3). Ultrasound contrast is used in more than 50% of patients undergoing stress echocardiography in many laboratories.

Indices of global LV function have diagnostic, prognostic and therapeutic implications. Without optimal border visualization, it is difficult to
Clinical applications of contrast echocardiography

Applications in the assessment of LV geometry and intracardiac pathology

If echocardiographic images are of sub-optimal quality, alterations in LV geometry, presence or absence of LV aneurysms, and presence or absence of intracardiac masses such as clots and tumors can be missed or misdiagnosed. Fig. 5 displays an LV image from an apical orientation in a young patient with ventricular tachycardia and an history of syncope. The apex was poorly defined in the pre-contrast image. The contrast-enhanced study unmasked a small, well-defined apical diverticulum, an entity associated with life-threatening ventricular arrhythmias. This diagnosis could have been missed if contrast echocardiography had not been performed in this subject. More frequently raised questions however are whether a patient has an LV aneurysm and whether a patient has intracardiac clots. The presence or absence of thrombi in the LV has implications with regard to the use of anticoagulant therapy. It is hard to detect or exclude an apical thrombus if the apex is not well defined, as in the two-dimensional echocardiographic image seen at left in Fig. 6. A contrast-enhanced recording (right-hand image) in the same patient led to the correct interpretation that there was no apical thrombus present. The left-hand panel of Fig. 7 shows two other examples of how difficult it can be to confirm or exclude the presence of a thrombus. On the contrary, the contrast images in the right-hand panel clearly expose intracardiac clots in both cases.

Detailed investigation of any pathology associated with the heart is aided by contrast echocardiography. Fig. 8 shows images from a patient who had inferior wall ischemic changes on the electrocardiogram. In real-time imaging, the inferior wall was hypokinetic, and there was an area that resembled a possible pseudoaneurysm (top panel of Fig. 8). Contrast-enhanced imaging

Application in the assessment of LV function and quantitation

evaluate LV function properly. The challenge is compounded if quantitative estimates of LV volumes and percentage ejection fraction (%EF) are to be derived. In contemporary cardiology, LV ejection fraction (LVEF) has become the single most important index in clinical decision making. Whether LVEF is 50% or less could be the marker in giving a diagnosis of LV dysfunction or cardiomyopathy in a given patient. Whether the LVEF is less or more than 40% has implications regarding the use of pharmacologic agents such as angiotensin-converting-enzyme inhibitors. Whether the LVEF is 35%, or 30%, or less, could influence the decision with regard to intracardiac defibrillator placement. Unless the LV endocardial borders are crisp, quantitative assessment of LV volumes and EF cannot be performed. Diastolic and systolic images of the LV from a patient with ischemic heart disease are shown in the upper panel of Fig. 4. The information needed for this patient was LVEF. It is obvious that border tracing for quantitation would be impossible in images of such poor quality. Administration of ultrasound contrast opacified the LV chamber, allowing the operator to perform accurate quantitative analysis. The LVEF in this study was 27%, and this information had implications in terms of pharmacologic and electrical therapy in this patient. Administration of ultrasound contrast agent has thus greatly increased our ability to correctly assess regional and global LV function, and has decreased the number of errors made in such assessments.1-4.
Fig. 6. Left: non-contrast image from a patient with acute myocardial infarction; the presence or absence of an aneurysm or thrombus can not be verified with certainty. Right: chamber opacification with contrast defines the left ventricular apex better and allows exclusion of an apical thrombus.

Fig. 7. Left: non-contrast images from two patients do not display the apex with clarity. Right: contrast enhancement allows recognition of apical dysfunction and thrombi.

excluded a pseudoaneurysm, and successfully characterized the abnormality as a mass adjacent to the inferior wall, infiltrating into the myocardium, with lack of perfusion in that region. Further investigations documented that it was a lymphoma (bottom panel of Fig. 8).

Ultrasound contrast agents are also useful in transesophageal echocardiography (TEE) examinations. TEE is frequently performed to verify the presence or absence of thrombi in the left atrial appendage (LAA). With its high-resolution images, TEE generally can answer that question. However, thick sludge in the LAA can masquerade as a thrombus in some patients. Contrast administration can aid in differentiating between true organized clot and simply a thick sludge. Two examples are portrayed in Fig. 9. In the top panel, a circular echo density raised the question of a thrombus (top left, Fig. 9). When contrast was administered (top right), it filled the whole LAA, delineating the LAA borders and demonstrating that the echo density noted was an extracardiac
structure and that the LAA was free of thrombus. In the bottom example the pre-contrast image raised the suspicion of an LAA clot (bottom left); the contrast-enhanced image displayed a definite filling defect and confirmed the presence of a clot.

Application in the assessment of Doppler recordings

Doppler echocardiography provides important hemodynamic data in the study of valvular disorders, congenital heart defects and ventricular function. In patients with sub-optimal acoustic windows, the Doppler signals can be weak despite proper techniques. In such a setting, contrast agents can be used to enhance the strength of the Doppler signals. In color flow imaging, contrast is useful in augmenting coronary artery flow and carotid artery flow. A more frequent application, however, is in spectral Doppler imaging. In patients with abnormalities such as aortic stenosis, in whom accurate delineation of velocity profile is desired to determine pressure gradients, contrast-enhanced Doppler examination can bring out the velocity profile as illustrated in Fig. 10. Tricuspid regurgitation velocity is an important datum in the determination of pulmonary artery systolic pressure. While agitated saline can be employed to visualize the right heart chambers, this method is not consistently useful in delineating tricuspid regurgitation velocity because of spiky signals due to uncontrolled bubble size and distribution (Fig. 11). The new-generation contrast agents allow more robust signal enhancement. Pulmonary vein flow velocity recording is of value in the assessment of diastolic LV function and filling pressures. Pulmonary vein flow can be difficult to record in a certain proportion of patients because of the resolution compromise in the far field when examined from apical imaging windows. Contrast imaging augments flow signals at any depth and is thus useful in the determination of LV diastolic function.

Fig. 10. Left: non-contrast Doppler recording of aortic flow in a patient suspected of aortic stenosis portraying weak signals. Right: contrast enhancement brings out the flow profile crisply.

Application in the assessment of myocardial perfusion

Currently available non-invasive methods such as nuclear imaging and stress echocardiography have limitations. Ischemic syndromes are often complex with frequent admixtures of reversible ischemia, acute or old infarction, myocardial stunning, and myocardial hibernation, and these often express themselves as stable or unstable syndromes. There is thus a need for a method that can be used in all clinical circumstances to identify coronary syndromes even before contractile abnormalities evolve, and that can easily be performed at the bedside. Myocardial perfusion imaging utilizing contrast echocardiography has the potential to fulfill this need. Optimal assessment of the perfusion status requires appropriate imaging modes and examination protocols in various ischemic syndromes. Intentional destruction of the microbubbles with high-power ultrasound and evaluation of the rate of replenishment is an important element in the assessment of myocardial perfusion (Fig. 12). In the setting of a myocardial infarction, as in a patient with an old or new coronary occlusion, perfusion imaging at rest demonstrates a lack of contrast enhancement in the area devoid of myocardial blood flow while normal regions exhibit increased brightness due to contrast enhancement. While imaging at rest is sufficient in most patients, the use of a vasodilator can further aid in defining normal and abnormal perfusion.

Myocardial contrast echocardiography can be extremely useful for assessing the status of the
Fig. 12. Myocardial perfusion imaging with transpulmonary contrast. Left: contrast enhancement of the myocardium. Middle: following a high power ultrasound, immediate destruction of myocardial signals is noted. Right: replenishment of myocardial blood is demonstrated by normal contrast distribution in the myocardium.

Fig. 13. Left: a large dyskinetic zone is seen in this systolic apical image of the left ventricle in a patient with myocardial infarction following reperfusion therapy. Right: myocardial contrast echocardiography exhibits normal contrast enhancement in most of the dyskinetic region except for a small residual area of necrosis.

Fig. 14. Left: a large dyskinetic zone is seen in this systolic apical image of the left ventricle in a patient with myocardial infarction following reperfusion therapy. Right: myocardial contrast echocardiography exhibits lack of contrast enhancement in the dyskinetic zone, indicating a lack of reperfusion at the microcirculation level.

Fig. 15. Left: perfusion image at rest in a patient undergoing stress echocardiography reveals normal perfusion. Right: image at peak stress displays a large zone of lack of myocardial contrast signals, indicating ischemia.

microvasculature and myocardial viability after thrombolytic therapy or coronary angioplasty. Normal or near-normal myocardial contrast enhancement in the risk territory implies restored microvascular integrity and salvaged myocardium, or a small residual infarct (Fig. 13). This would be so even if the myocardial region exhibits contractile abnormalities due to stunning. On the other hand, a lack of contrast enhancement or a markedly decreased perfusion implies tissue necrosis in most circumstances or depressed microvascular function (Fig. 14). The use of myocardial contrast echocardiography in patients undergoing recanalization therapy has clearly demonstrated that recanalization and restoration of flow in an epicardial coronary artery does not equal myocardial reperfusion. Myocardial malperfusion can be the result of a number of mechanisms operating during the perirecanalization period. Showers of microemboli, formation of microthrombi, microvascular spasm, and reperfusion injury caused by oxygen free radicals, neutrophil plugging of capillaries, and tissue edema could individually or in combination lead to myocardial malperfusion. Serial myocardial contrast echocardiography yields valuable physiologic insights into the integrity and behavior of the microvasculature in the risk area and yields prognostic data. This information could be useful in formulating optimal therapy and in exploring means of improving myocardial malperfusion.

The detection of functionally significant coronary stenoses requires some form of stress that challenges coronary vascular reserve. Both exercise stress and pharmacologic stress can be employed. Among pharmacologic approaches, dipyridamole and adenosine are commonly employed vasodilators, and dobutamine is a widely used inotropic agent. Dipyridamole and dobutamine are administered as infusions while adenosine is used both as an infusion and in boluses. Some contrast agents are given in boluses, and some as infusions. Perfusion imaging during pharmacologic or exercise stress unmasks the coronary reserve and can aid in the recognition of coronary disease and the regions at risk (Fig. 15). Dipyridamole perfusion imaging yields a diagnostic accuracy of >80% in the detection of reversible
ischemia. The use of adenosine bolus or infusion yields a diagnostic accuracy of 80-95%, depending on the experience of the investigators. Exercise and dobutamine stress procedures have also proven to be reliable. Performing myocardial contrast echocardiography following physical exercise is somewhat of a challenge because of the short ischemic time available for acquiring the images. Infusion of the contrast agent, rather than a bolus administration, makes the exercise more practical. Perfusion imaging can be easily performed during dobutamine stress. A multitude of clinical investigations employing various forms of stress during echocardiography have demonstrated that myocardial contrast echocardiography carries a high diagnostic accuracy in the evaluation of functionally significant CAD.

Intracoronary contrast administration aids in the identification of the appropriate target site in the interventricular septum in patients with hypertrophic obstructive cardiomyopathy undergoing septal ablation with ethanol. During the ablation procedure, contrast agent is administered onto the catheter cannulating the septal perforator artery. The region supplied by this vessel exhibits contrast enhancement. If this is not the portion of the septum that needs to be ablated, a different septal perforator vessel is chosen. In addition, the necrosis produced by ethanol can be recognized by perfusion imaging (Fig. 16).

Contrast echocardiography is also combined with other innovations in cardiovascular ultrasound. Three-dimensional echocardiography has become a clinical tool, but it suffers from the same resolution problems as two-dimensional ultrasound in patients with poor acoustic windows. In these settings, contrast agents improve resolution of chamber borders and aid in three-dimensional quantitation of cardiac chamber volume and function (Fig. 17).

Conclusion
Contrast echocardiography using the new generation of ultrasound contrast agents has become an important technique in the evaluation of regional and global LV function, intracardiac pathology, and hemodynamics. Its potential in providing information on myocardial perfusion is highly promising. Possible applications in local drug and gene delivery are being actively explored. The optimal practice of echocardiography today is not possible without the use of ultrasound contrast agents.

References
1. Kasprzak JD, Ten Cate FJ. New ultrasound contrast agents
for left ventricular and myocardial opacification. Herz 1998; 23:474-82.