Clinical Utility of Contrast-Enhanced Echocardiography

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Summary: Over the past three decades, echocardiography has become a major diagnostic tool in the arsenal of clinical cardiology for real-time imaging of cardiac dynamics. More and more, cardiologists' decisions are based on images created from ultrasound wave reflections. From the time ultrasound imaging technology provided the first insight into a human heart, our diagnostic capabilities have increased exponentially as a result of our growing knowledge and developing technologies. One of the most intriguing developments that brought about a decade-long combination of expectations and disappointments was the introduction of echocardiographic contrast agents. Despite repeated waves of controversy regarding the readiness of this technology for clinical use, it has overcome multiple hurdles and currently provides useful clinical information that helps cardiologists to diagnose heart disease accurately. Since the initial reports on the use of ultrasound contrast media such as agitated saline or renografin, the major advances in the field of contrast echocardiography have included (1) the development of stable perfluorocarbon-filled microbubbles, frequently referred to as second-generation contrast agents; and (2) the development of contrast-targeted nonlinear imaging modes, such as harmonic imaging, pulse inversion, and power modulation, which allow consistent real-time visualization of these agents. These contrast agents in conjunction with the new imaging technology constitute powerful tools that improve our ability to evaluate left ventricular function and myocardial perfusion, and allow differential diagnosis of thrombi and intravascular masses. In this manuscript, we briefly review some of the literature that has provided the scientific basis for the use of echocardiographic contrast agents in the context of these important variables.

Key words: contrast, microbubbles, endocardial borders, stress echocardiography, thrombus, 3-dimensional imaging

Efficacy and Safety of Echocardiographic Contrast

The concept of ultrasound contrast enhancement is based on the use of microscopic particles comprised of gas-filled aqueous shells. When injected into the bloodstream, these particles remain intravascular, and the gas–fluid interface of each particle causes ultrasound reflections that are orders of magnitude stronger than those generated by the native components of the cardiovascular system. It is essential for these microbubbles to be stable enough to traverse the lungs in sufficiently high concentration to enhance the blood–tissue contrast in the heart. This was achieved with the second-generation agents by the use of perfluorocarbon gases with high molecular weight, which diffuse through the shell relatively slowly and are thus capable of transpulmonary passage resulting in contrast enhancement in the left ventricle after intravenous injection. On the other hand, it is crucial that none of the microbubble components have toxic effects on any organ that may be affected or involved in its eventual metabolism. To achieve this goal, microbubble shells are made of indigenous materials, such as human albumin or lipids, which are naturally metabolized by the human body. In addition, the safety of the gas component of these agents has been thoroughly tested in a variety of animal models. Several contrast agents have been approved over the past decade for clinical use by the U.S. Food and Drug Administration and the equivalent authorities in Europe. These agents have been safely used in large numbers of human subjects, as shown in several human studies aimed at studying the safety issue,^{1–3} as well as in many other published reports. Based on this literature, the incidence of adverse effects of these contrast agents is very low, and the effects reported are usually minor and nonpersistent. Accordingly, it is generally agreed that, when indicated by clinical needs, the approved contrast agents are well tolerated and can be safely used in general populations.⁴

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Delivery Mode: Bolus or Infusion?

Echocardiographic contrast agents are typically administered via an antecubital vein. Two methods are commonly

used to deliver contrast agents into the intravenous line: manual bolus and continuous infusion. Each of these two techniques has its own advantages and disadvantages. The manual bolus is delivered by injecting a small amount of agent, which is followed by a slow flush of saline solution. This technique is simple and effective and therefore has practical appeal for daily use. However, the life time of the microbubbles in the imaging field is relatively short, which requires rapid, immediate image acquisition and makes the optimization of image settings more difficult to achieve. The bolus method is generally recommended for sonographers with significant experience in the acquisition of contrast-enhanced images. In comparison, the infusion technique is based on a steady-state delivery of the contrast agent over a longer period of time. This can be achieved with the use of an infusion pump or saline drip. The advantage of this approach is that it allows titration of the contrast effects to provide a constant level of contrast, which is extremely helpful for image optimization and acquisition, especially for less experienced personnel. The drawback of this approach, however, is that it is more involved in terms of the initial setup, which requires a longer time for setup and expertise in the use of infusion equipment.

Contrast Enhancement and the Assessment of Ventricular Function

Effects of Contrast Enhancement on Endocardial Delineation

Echocardiographic evaluation of left ventricular (LV) function is mostly based on subjective visual interpretation of gray-scale two-dimensional (2-D) images, or it relies on manual tracing of the endocardial boundaries. Adequate endocardial visualization is essential for reproducible assessment of LV ejection fraction (EF), which is crucial for correct identification of patients who may benefit from an automatic implantable cardioverter/defibrillator (AICD) and biventricular pacing therapy. It is also essential for accurate interpretation of regional endocardial motion and wall thickening, which constitute the diagnostic hallmarks of coronary artery disease. Multiple studies have estimated the number of patients with suboptimal endocardial delineation to be approximately 30%. These studies highlighted the problem of suboptimal acoustic windows as one of the major limitations of transthoracic echocardiography, since failure to visualize adequately more than two contiguous segments either at rest or during stress compromises the ability of the interpreting physician to identify areas of regional ischemia.

In such patients, echocardiographic contrast agents capable of producing LV cavity opacification from a venous injection were shown to be useful for delineating endocardial borders (Fig. 1).⁵ In a multicenter trial, bolus injections of sonicated albumin microbubbles (Albunex® Mallinkrodt, Inc., St. Louis, MO) were found to improve endocardial definition in 83% of patients enrolled on the basis of incomplete echocardiographic endocardial visualization.⁶ Of the remaining patients, a sec-

ond, higher-dose contrast injection resulted in an improved endocardial definition in 64%,⁶ indicating an improvement in 94% of the patients enrolled in the study. Other investigators have since confirmed the effectiveness of echocardiographic contrast enhancement for improved endocardial visualization. Cohen *et al.* compared side-by-side the effects of Albunex and a second-generation agent based on perfluoropropane-filled albumin microbubbles (Optison™ GE Healthcare, Princeton, NJ) in a large group of patients. They found that Optison was more effective in every measure of contrast enhancement.⁷ Of importance is the fact that contrast allowed conversion of nondiagnostic to diagnostic echocardiograms in 74% of patients with the optimal dose of Optison. Also, in a subset of patients with potentially poor transpulmonary transit of contrast due to chronic lung disease or dilated cardiomyopathy, the effects of Optison were similar to those noted in the rest of the study population.⁷

Effects of Harmonic Imaging

Several other studies have compared the effects of contrast enhancement using fundamental imaging and second harmonic imaging, which uses the nonlinear components of the reflected waves generated by resonating microbubbles for image formation.⁸⁻¹¹ The addition of harmonic imaging in patients with poor acoustic windows has been reported to result in significant improvement of the rates of successful LV cavity opacification (Fig. 2), leading to the recommendation for routine use of this imaging mode in conjunction with contrast enhancement.⁸ Other investigators later reported that the use of harmonic imaging even without contrast resulted in improvement in endocardial visualization of all myocardial

FIG. 1 Apical four-chamber view of the left ventricle obtained in a patient with poorly visualized endocardium (A). Same view obtained during contrast enhancement with intravenous injection of Optison (B). Note the improvement in endocardial definition with contrast enhancement. Modified with permission. Copyright© 2000 Blackwell Publishing. All rights reserved.⁵

FIG. 2 Example of improvement in contrast enhancement by use of harmonic imaging: images obtained in the fundamental (A) and harmonic (B) modes in the same subject during steady-state infusion of Definity contrast agent. Courtesy of Drs. Roberto M. Lang and Victor Mor-Avi.

segments in apical views, which was optimal in the apical segments.⁹ Nevertheless, this improvement was less significant in the basal segments because of signal attenuation. Another study sought to determine the additive diagnostic value of contrast to both fundamental and harmonic imaging for endocardial border definition in patients undergoing echocardiographic stress testing.¹⁰ The results of this study confirmed that the use of harmonic imaging with contrast significantly improved endocardial visualization when compared with the combination of fundamental imaging with contrast, but importantly also showed that the use of contrast harmonic imaging increased the interobserver agreement in the interpretation of endocardial motion from 83 to 95% of segments. Later, a detailed study aimed at determining the relative benefits of contrast enhancement and harmonic imaging on a segment-by-segment basis confirmed that in many segments the use of harmonic mode alone may allow optimal endocardial visualization.¹¹

Improvement in Accuracy and Confidence of Interpretation

Several studies subsequently demonstrated that this improvement in endocardial delineation resulted in improved accuracy and increased confidence in the interpretation of both global^{12–14} and regional LV function^{15–17} in a variety of clinical settings. Kornbluth *et al.* reported that, in mechanically ventilated patients, contrast enhancement with harmonic imaging was superior (improvement in 85% of patients) compared with harmonic imaging alone, which resulted in only modest improvement (15% of patients) in the assessment of LV function.¹² Another group reported that the use of contrast significantly improved the confidence of the interpretation of regional LV wall motion in patients in the intensive care unit (ICU)¹⁶ and suggested that this methodology should be used in these patients with suboptimal transthoracic echocardiograms, in agreement with the findings and recommendations of Kornbluth *et al.*¹²

The potential of contrast enhancement not only to aid in the visual assessment of LV function but also to improve the accuracy of quantitative measurements was subsequently explored by a number of investigators. The improvement caused by contrast enhancement in both accuracy and reproducibility of echocardiographic measurements of LV volume and EF was confirmed in a large group of consecutive patients by comparisons with magnetic resonance values and repeated measurements.¹⁴ Hundley *et al.* also used magnetic resonance to validate the effects of contrast enhancement, but focused their investigation on regional wall motion rather than on global LV function.¹⁵

Furthermore, other investigators studied the feasibility of using automated techniques for quantitative evaluation of LV function using acoustic quantification in conjunction with contrast enhancement.^{13, 18} The results of these studies showed that contrast enhancement improved the accuracy of the automated quantification of LV volumes and EF using automated border detection compared with manually traced endocardial boundaries that served as a reference. This approach was also used to quantify regional wall motion (Fig. 3) and it allowed automated interpretation of wall motion in patients with poor acoustic windows.¹⁹

Most recently, Hoffmann *et al.* compared the ability of cine-ventriculography, cardiac magnetic resonance imaging, and nonenhanced and contrast-enhanced echocardiography to detect LV wall motion abnormalities that were validated against a “standard of truth” defined by a panel of experts based on other clinical information in a large group of patients enrolled in a multicenter trial.¹⁷ It was interesting that the results of this study showed that contrast-enhanced echocardiographic assessment of wall motion was the most accurate and reproducible among the four techniques studied. This finding may be surprising to many as far as the superiority of contrast echocardiographic data over magnetic resonance values in view of the superior spatial and contrast resolution of the latter technique, which is commonly used as a standard of reference for

FIG. 3 Example of apical two-chamber images obtained in a normal subject (A and C) and a patient with apical hypokinesis (B and D): non-enhanced (A and B) and contrast-enhanced color-encoded images (C and D). In the normal subject, the color-encoded images revealed color bands of relatively uniform thickness, reflective of normal wall motion; however, in the patient with apical hypokinesis, the color bands appeared thinned in the apical area. Histograms of regional fractional area change (RFAC) were averaged in a group of normal subjects (E) and used for automated detection of wall motion abnormalities (F); line represents the lower limit of the normal range. REDA = regional end-diastolic area. Modified with permission. Copyright© 2004 Elsevier Publishing. All rights reserved.¹⁹

global and regional LV function. On the other hand, if confirmed in larger groups of patients, these findings may serve as a basis for future use of contrast-enhanced harmonic echocardiography as an alternative standard reference technique in the context of global and regional LV function.

Contrast-Enhanced Stress Echocardiography

Since the early report on the applicability of contrast enhancement in the context of functional stress testing,²⁰ several studies have concluded that the use of contrast to improve endocardial delineation during either exercise or dobutamine stress testing is safe.²¹ Other studies sought to determine the effects of contrast enhancement on the diagnostic accuracy of echocardiographic stress testing,²² as well as confidence in the interpretation of regional LV wall motion during contrast-enhanced dobutamine stress testing.^{23, 24} The prognostic value of this methodology was demonstrated by a 2-year follow-up study, in which a positive contrast stress test was the strongest predictor of cardiac events while a negative test was found to be associated with a good prognosis.²⁵ Overall, multiple investigators endorsed contrast-enhanced stress testing for routine clinical use on the basis of its safety, diagnostic accuracy, improvement in confidence of interpretation, and prognostic value.^{21–23, 25–28}

Cost Effectiveness of Left Ventricular Opacification

Several investigators focused their efforts on establishing the cost effectiveness of echocardiographic contrast enhancement for improved functional assessment of the left ventricle at rest^{29, 30} as well as under conditions of stress testing.^{27, 28, 31} The results of these studies and others led to the endorsement of this methodology for routine clinical use by the American Society of Echocardiography³² and its equivalent authorities in other countries.

Assessment of Myocardial Perfusion

While 2-D echocardiographic imaging has been playing a pivotal role in the clinical assessment of cardiac function for several decades, its ability to assess myocardial perfusion is not as well established. Since the early reports of successful visualization of myocardial perfusion in the mid 1980s,^{33–37} a large number of research studies and scientific publications have been dedicated to this cause. A quick literature search on this subject today will result in over a thousand published papers. These studies have been instigated by multiple technologic breakthroughs in both the development of improved contrast agents and imaging technologies, such as the develop-

ment of contrast-targeted modes specifically “tailored” to improve the contrast-enhancing effects of these agents.

Among these techniques, the most widely used are pulse inversion and power modulation, both currently available in commercial scanners. These techniques were designed to enhance microbubble-generated reflections selectively, while simultaneously suppressing reflections originating from cardiac structures and tissues. The basic assumption underlying these imaging modes is that the reflective properties of cardiac structures and tissues are mostly linear, while those originating from the microbubbles are nonlinear. Pulse inversion and power modulation techniques utilize this assumption by transmitting repeated pulses of different intensities in the same direction and manipulating the intensities of the reflections in real time in order to isolate the nonlinear components. Using these nonlinear components for image formation increases contrast enhancement and thus results in better visualization of intramyocardial contrast.

For over two decades, the evaluation of myocardial perfusion has been frequently referred to as the “holy grail” of contrast echocardiography. This term, commonly used in the context of the Crusades, reflects the difficulties encountered by the investigators who have dedicated their efforts to pursuing this elusive goal. The different aspects of this “crusade” have been previously discussed by others in over a hundred review papers in the English language alone.^{38–52} Thus, it is difficult to present a brief review of the published work on myocardial contrast echocardiography without unjustly omitting many important studies. Generally speaking, published papers ranged from attempts simply to visualize intramyocardial contrast and thus detect perfusion defects (Fig. 4) using different imaging techniques^{32, 34, 53–62} to methodologically more complex approaches aimed at quantification of myocardial tissue blood flow.^{63–75}

With the steady improvements in stability and uniformity of contrast agents as well as the development of more robust

imaging techniques, the qualitative perfusion imaging studies showed incremental improvements in the ability to visualize myocardial contrast and thus demonstrated a steady increase in the confidence of the interpretation of echocardiographic perfusion images. While many of these studies reached high levels of diagnostic accuracy, these levels remained only modest in most multicenter trials. It is likely that this hurdle mostly reflects the subjective nature of the interpretation and its reliance on significant experience of the reader required to differentiate accurately between true perfusion abnormalities and attenuation-related artifacts that are more severe in the presence of highly echogenic contrast materials.

The quantitative perfusion techniques rely on measuring induced beat-by-beat changes in myocardial contrast, such as contrast inflow or washout following bolus injection,^{64, 66–69, 71} or alternatively, its replenishment after destructive high-energy ultrasound pulses delivered during contrast infusion.^{46, 72, 76–78} Although it is well understood that these changes are essential for the assessment of tissue blood flow dynamics, each specific maneuver has its advantages and disadvantages in terms of ease of use and the reliability of the information yielded.^{76, 79, 80} As a result, there is no general agreement on the specific technique that would be preferable for routine clinical use. Also, quantification offers little if anything in terms of dealing with image artifacts and cardiac translation, which may affect quantitative techniques even more than intelligent visual interpretation capable of immediately recognizing these issues.

Nevertheless, myocardial contrast echocardiography, with or without quantification, has been shown useful in multiple clinical scenarios. Beyond the obvious detection of resting perfusion defects^{33, 35, 53–62} and evaluation of severity and extent of perfusion deficit,^{56, 62, 81–85} it was found useful in detecting stress-induced myocardial ischemia,^{86–91} diagnosing acute coronary events in patients presenting with atypical chest pain in the emergency department,^{92–94} and in the assessment of reperfusion after coronary revascularization.^{87, 95–98}

In summary, despite the vast body of literature endorsing myocardial contrast echocardiographic perfusion imaging, the number of clinical laboratories that routinely employ this methodology remains relatively low, probably because of the limited reproducibility and various image artifacts that hinder confident interpretation of perfusion in consecutive patients. Additional technologic leaps are still necessary in order to overcome these limitations. Undoubtedly, the debate over the readiness of contrast echocardiography for clinical evaluation of myocardial perfusion is far from over.

FIG. 4 Example of contrast-enhanced images from a patient with distal left anterior descending (LAD) stenosis obtained at rest (A) and during infusion of adenosine (B). The dark area in the apical myocardium reflects a stress-induced perfusion defect. Courtesy of Drs. Roberto M. Lang and Victor Mor-Avi.

Assessment of Thrombi and Intravascular Masses

Another area where contrast enhancement can provide clinically useful information is in the assessment of intracardiac thrombi and intravascular masses. Initially, Takeuchi *et al.* demonstrated the ability of contrast echocardiography to aid in detecting intracardiac thrombi in experimental animals,⁹⁹ based on the fact that a thrombus retains its low echogenicity during chamber opacification. This concept was further ex-

plored in a retrospective human study that involved over 400 patients with suspected LV thrombi.¹⁰⁰ In this study, contrast injection allowed definitive diagnosis in 43 of 48 patients, whose nonenhanced images were interpreted as nondiagnostic, representing a 90% success rate; similar findings were subsequently described by other investigators.¹⁰¹ More recently, contrast-enhanced transesophageal echocardiography (TEE) was used to diagnose left atrial thrombus in patients with atrial fibrillation prior to cardioversion.¹⁰² In this study, left atrial thrombi were definitively excluded in 25 of 41 patients with inconclusive nonenhanced TEE findings, who subsequently safely underwent cardioversion.

Furthermore, contrast echocardiography has been shown to be useful in differentiating between different types of cardiac masses, including thrombi and benign or malignant tumors. While such differentiation has important prognostic and therapeutic implications, accurate differentiation is difficult and erroneous diagnosis is known to lead to unnecessary surgery or inappropriate anticoagulation. It is known that most malignancies have abnormal neovascularization that supplies rapidly growing tumor cells, while stromal tumors, such as myxomas, have a poor blood supply and thrombi are generally avascular.

Accordingly, contrast echocardiographic differentiation between thrombi from intracardiac masses is based on their unequal ability to enhance (Fig. 5).^{103, 104} This methodology was validated by pathologic analysis or findings of mass resolution after anticoagulant therapy.¹⁰⁴

Contrast-Enhanced Three-Dimensional Imaging

The ability of conventional contrast-enhanced echocardiographic imaging to provide accurate information on the extent and severity of either wall motion or perfusion abnormalities is limited by its 2-D nature. Despite the obvious appeal of three-dimensional (3-D) imaging in this context, this methodology has not been possible until recently. This is because it has relied on off-line reconstruction from multiple planes, significantly complicating volumetric assessment of LV function and essentially precluding the possibility of perfusion quantification that would require repeating contrast maneuvers for each plane. The recently developed real-time 3-D echocardiographic (RT3DE) imaging technology offers an opportunity for online volumetric imaging of the entire heart during a sin-

FIG. 5 Examples of a right atrial mass (A) and a left ventricular apical mass (B) in two different patients. The atrial mass enhanced with contrast (C), indicating neovascularity, was confirmed by the biopsy specimen diagnosis of follicular thyroid carcinoma (D). The apical ventricular mass showed no enhancement consistent with thrombus (E), which was confirmed by analysis of a surgical specimen that showed no staining with CD31 antibody and minimal cellularity consistent with thrombus (F). Modified with permission. Copyright © 2004 Elsevier Publishing. All rights reserved.¹⁰⁴

FIG. 6 Example of a cut-plane of the left ventricle extracted from a contrast-enhanced real-time three-dimensional echocardiographic (RT3DE) end-diastolic data set obtained with dual triggering (A). The set of points defined during manual initialization of the endocardial surface is superimposed. Left ventricular (LV) endocardial surface detected from this data set using a level-set approach (B). Time curves obtained in one patient from RT3DE (solid dots) and magnetic resonance (MRI) data (open dots): global LV volume (C) and regional wall motion measured in one endocardial surface segment [mid anteroseptal (D)]. Modified with permission. Copyright © 2005 Lippincott, Williams and Wilkins. All rights reserved.¹⁰⁷

gle contrast enhancement maneuver. Accordingly, our group has recently used contrast-enhanced RT3DE imaging during dobutamine stress testing to test the hypothesis that this approach could potentially improve the detection of regional wall motion abnormalities, since it allows visualization of multiple segments from simultaneous acquisition.¹⁰⁵ Furthermore, we have recently developed and tested new techniques for volumetric imaging and quantitative analysis of both LV function^{106, 107} and myocardial perfusion¹⁰⁸ from contrast-enhanced RT3DE data sets.

The RT3DE quantification of LV function is based on semi-automated detection of the endocardial surface in the 3-D space, followed by dynamic volumetric analysis that does not involve geometric modeling, another known limitation of 2-D evaluation of LV volume and function. This technique was validated in a group of patients against magnetic resonance measurements of global and regional LV function (Fig. 6) and tested as a basis for automated interpretation of regional wall motion in patients with good images.^{106, 107} Subsequently, we

applied this methodology to contrast-enhanced RT3DE data sets obtained in patients with suboptimal image quality and found that, when used with selective dual triggering at end systole and end diastole, it allows quantification of global¹⁰⁹ as well as regional¹¹⁰ LV function. Since a similar approach was recently incorporated into a commercial imaging system, it is rapidly gaining widespread clinical use due to its high speed and ease of use¹¹¹ and is poised to become part of the mainstream quantification of LV function.

The RT3DE quantification of myocardial perfusion was based on measuring contrast levels over time and calculating peak contrast inflow rate in 3-D myocardial regions of interest. After this approach was shown to follow accurately the global changes in myocardial perfusion in isolated rabbit hearts, its ability to detect regional perfusion variations in vivo was tested in a pig model of acute ischemia (Fig. 7) and in human subjects during adenosine stress.¹⁰⁸ This approach can potentially allow more accurate assessment of the extent of perfusion defects than 2-D myocardial contrast echocardiography.

FIG. 7 Real-time three-dimensional echocardiographic data set that contains the mid portion of the left ventricle, obtained in a pig [(A) anteroseptal region (ASP) of interest shown]. Regional myocardial videointensity curves obtained in this region of interest during contrast inflow: baseline and partial left anterior descending artery occlusion. Note the differences in peak contrast inflow rates (PCIR) (B). a.u. = arbitrary units. Modified with permission. Copyright© 2006 Elsevier Publishing. All rights reserved.¹⁰⁸

Conclusion

The major clinical application of echocardiographic contrast remains chamber opacification, which currently provides valuable information on both global and regional LV function in patients with poor acoustic windows. They are commonly encountered in patients suffering from obesity, congestive heart failure, and chronic obstructive pulmonary disease, as well as in patients who have had cardiovascular surgery and other conditions that adversely affect echocardiographic imaging. In many of these patients, the addition of contrast allows confident interpretation of images that are otherwise uninterpretable. The safety, efficacy, and cost effectiveness of contrast enhancement in these patients are well established, and this methodology is currently used routinely in multiple laboratories worldwide. Other applications, such as imaging and quan-

tification of myocardial perfusion, which has been the focus of enormous research efforts for over two decades, as well as combined assessment of perfusion and function,^{112–114} may also materialize in the near future, pending further technological developments.

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