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The Value of Contrast Echocardiography

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Purpose	There is much evidence-based research proving the effectiveness of contrast echocardiography, but there are still questions and concerns about its specific uses. This study tested the effectiveness of contrast echocardiography in defining the left ventricular endocardial border.
Methods	From 30 patients, a total of 60 echocardiograms — 30 with and 30 without use of contrast — were retrospectively reviewed by four blinded cardiologists with advanced training in echocardiography. No single cardiologist reviewed contrast and noncontrast images of the same patient. Each set of 30 echocardiograms was then studied for wall-motion scoring. Visualization of left ventricular wall segments and a global visualization confidence level of interpretation were recorded.
Results	Of all wall segments (N=510), 91% were visualized in echocardiograms with use of contrast, whereas 75% of the walls were visualized in echocardiograms without contrast ($P<0.001$). Of 30 examinations, 17 contrast echocardiograms were read with high confidence compared to 6 without contrast use ($P=0.004$). The number of walls visualized with contrast was increased in 18 patients (60%), whereas noncontrast echocardiograms yielded more visualized walls in 6 patients (20%, $P=0.002$).
Conclusions	This study demonstrates that contrast is valuable to echocardiographic imaging. Its use should be supported throughout echocardiography clinics and encouraged in certain patients for whom resting and stress echocardiography results without contrast often prove uninterpretable. (<i>J Patient-Centered Res Rev.</i> 2016;3:40-47.)
Keywords	contrast echocardiography; left ventricular delineation; contrast administration; safety; misuse; examination time; cost-effectiveness

Echocardiography is the test most performed for evaluation of cardiac function. In patients for whom obtaining clear ultrasound images of the heart is considered technically difficult, such as those with obesity or lung disease,¹ contrast echocardiography improves visualization.² Contrast agents improve image quality and endocardial border definition, which is important in assessing heart function (particularly when identifying abnormalities³). Currently the most common applications of contrast echocardiography are: 1) to opacify the left ventricle (LV), and 2) to enhance endocardial border delineation.⁴ LV opacification is the approved indication for contrast agents⁵ because accurate measurements of LV function provide valuable diagnostic and prognostic information.⁶

Accurately delineating endocardial borders leads to reduced variability and increases accuracy in LV volume and ejection fraction measurements.¹

Despite the proven diagnostic benefits of contrast echocardiography, use of contrast agents is not a common practice in clinical laboratories.^{7,8} Many labs and hospitals are reluctant to use contrast due to perceived issues of cost, effect on examination time, misuse and, more recently, questions concerning its safety.^{7,9} The purpose of this report is twofold. First, we present our study of the effectiveness of contrast echocardiography in defining the LV endocardial border as further evidence that contrast should be used routinely on technically difficult patients in whom noncontrast echocardiography produces inadequate image quality and therefore insufficient information to make an accurate diagnosis. Second, we discuss the added value and the controversies regarding the use of contrast in echocardiography.

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METHODS

Research Participants

This study was approved by the local institutional review board. The research subject population included a sampling of adult patients for whom use of a contrast agent was clinically indicated. Contrast is clinically indicated for endocardial border detection and LV opacification when at least 2 out of 17 wall segments of the LV are not well visualized. It is also indicated for Doppler enhancement, thrombus detection and patients who have suboptimal stress echocardiographic images as determined by the institution's contrast policy.¹

Our institution's cardiologists created a standing order that use of contrast would be at the sonographer's discretion, with or without physician approval, during the time of examination. Echocardiograms and contrast administration were performed by a single American Registry for Diagnostic Medical Sonography (ARDMS)-credentialed sonographer to eliminate variability in the use of contrast as well

as limit the differences in contrast administration technique and machine parameters used. Of all 30 patients included in this investigation, no side effects from use of contrast were documented.

Sampling Method

Thirty clinically indicated contrast echocardiograms from May 2011 to July 2011 were randomly selected for review. Gender and age were not indications for study inclusion or exclusion. LV images with and without use of contrast were obtained from each patient's echocardiogram. Parasternal images of the LV from the long and short axes with and without use of contrast (Figures 1 and 2; Online Videos 1–4) as well as apical images of the four- and two-chamber views with and without use of contrast (Figures 3 and 4; Online Videos 5–8) were obtained from each patient. Contrast and noncontrast images of each patient were separated to create 60 examinations (30 noncontrast, 30 contrast), each consisting of four images (long-axis, short-axis, two-chamber and four-chamber views).

Figure 1. Echocardiography in the parasternal long-axis view without (A) and with (B) contrast in a sample patient.

Figure 2. Echocardiography in the parasternal short-axis view without (A) and with (B) contrast in the same patient as Figure 1.

Figure 3. Echocardiography in the apical four-chamber view without (A) and with (B) contrast in the same patient as Figure 1.

Figure 4. Echocardiography in the apical two-chamber view without (A) and with (B) contrast in the same patient as Figure 1.

Four cardiologists who had Level III training in echocardiography, the highest level per the Core Cardiology Training Symposium training guidelines,¹⁰ were asked to define the LV segments in each image. LV segmental visualization was the main variable measured. All patient identifiers were deleted from the images to generate a blinded study for the reading cardiologists. To further reduce potential for bias, no cardiologist read both the contrast and noncontrast images of the same patient.

Instruments used to obtain this study sample beyond physician and sonographer contrast protocols and procedures were ProSolv[®] software (ProSolv Cardiovascular, Indianapolis, IN), contrast agent Definity[®] (Lantheus Medical Imaging, North Billerica, MA), Vialmix[™] shaker (Bristol-Myers Squibb Medical Imaging, North Billerica, MA), three different brands of echocardiography machines (Vivid E9[™], GE Healthcare, Waukesha, WI; iE33 xMATRIX[™], Philips Healthcare, Best, The Netherlands; and Artida[™], Toshiba Medical Systems, Tochigi, Japan), and MAC Numbers spreadsheet program (Apple Inc., Cupertino,

CA) for data analysis. All three echocardiography machines carry updated and advanced contrast package software that includes adequate settings for obtaining optimal contrast images.

Definity is a nonblood-based ultrasound contrast approved by the U.S. Food and Drug Administration (FDA). The Definity product contains components that, upon activation, yield perflutren lipid microspheres, a diagnostic drug that is intended to be used for contrast enhancement during indicated echocardiographic procedures. The suspension of activated Definity is administered by intravenous injection. After activation and injection, the physical acoustic properties of activated Definity provide contrast enhancement of the endocardial borders during echocardiography (2011 package insert, Bristol-Myers Squibb Medical Imaging). The dilution method was used to administer contrast in our sample echocardiograms.

Statistical Analysis

All data was analyzed with a two-proportion Z-test. Physician scores of the 17 LV wall segments (per

American Society of Echocardiography's 17-segment model) were collected. Degree of physician confidence in the overall global visualization of the 17 segments, including ability to interpret wall motion throughout the endocardial border, was recorded for each examination. Adequacy of overall global visualization was graded by each physician as: No confidence in overall visualization; Low confidence in overall visualization; or High confidence in overall visualization. High confidence was interpreted as the best possible examination accuracy. While these grades were subjectively determined by each physician, and therefore open to bias, making a judgment on the overall strength of the examination reflects standard clinical decision-making and provides a real-world setting to compare results from contrast and noncontrast images.

RESULTS

Endocardial Border Visualization

Of the 510 total wall segments in all 30 patients, 462 (91%) were visualized with use of contrast and 383 (75%) visualized without use of contrast (Figure 5). A two-proportion Z-test comparing endocardial border visualization with and without contrast revealed a statistically significant improvement in endocardial border visualization after contrast administration ($Z=6.56$, $P<0.001$).

Wall-motion visualization results are provided in Figure 6. Six patients (20%) had no change in visualization with contrast. The number of wall segments visualized with contrast increased in 18 patients (60%), whereas noncontrast echocardiograms yielded more visualized walls in 6 patients (20%, $P=0.002$). Figures 1–4 and Online Videos 1–8 demonstrate a benefit of contrast

Figure 5. Pie charts depicting percentage of total wall segments ($n=510$) for which endocardial border was visualized versus not visualized without and with the use of contrast in patient echocardiograms.

Figure 6. Bar graph of endocardial border visualization with and without use of contrast in 30 patients. Each pair of bars represents a patient with both their contrast image readings and noncontrast image readings provided.

in a sample patient for whom all segments were visualized with contrast compared to 8 segments without contrast. A decrease in the number of wall segments visualized with contrast was found in 6 patients (20%). Total visualization of all 17 segments with contrast was seen in 18 patients (60%), whereas total visualization without contrast occurred in 10 patients (33%).

Confidence Level

Of 30 contrast examinations, 17 were read at a High confidence level. Figures 1–4 and Online Videos 1–8 provide an example in a sample patient. Of the 30 noncontrast examinations, 6 were read at a High confidence level. Two-proportion Z-test comparing High confidence readings with contrast to High confidence readings without contrast administration revealed a statistically significant improvement in these readings ($Z=2.92$, $P<0.001$). A No confidence level was recorded in 6 noncontrast studies, whereas a No confidence level was not recorded in any contrast study.

Wall Segments

Of the 17 wall segments, those in the LV apex (wall segments 14–17) were found to have the largest increase in visualization with administration of contrast. Contrast did not drastically change visualization of the mid- and basal portions of the LV (wall segments 1–12). Figure 7 breaks down individual wall segments to show how frequently each could be adequately visualized on the 60 echocardiograms.

Figure 7. Line graph of 17 wall segments visualized with and without use of contrast in patient echocardiograms.

DISCUSSION

This research study explored the value of contrast echocardiography in a high-volume echocardiography laboratory. Significant improvement in endocardial border definition as well as confidence of interpretation was shown with the use of contrast, ultimately increasing accuracy of the final echocardiography report. The difference between contrast and noncontrast images in defining endocardial borders was especially profound, with an extreme Z score of 6.56. Our results reflect previously published studies^{1,4,6,7,11-13} that concluded contrast echocardiography contributes significant value to the accuracy of diagnostic studies. We found that using contrast significantly improved endocardial definition over echocardiograms obtained without contrast and provided quality diagnostic images in echocardiography studies once considered suboptimal.

Interpretation of Endocardial Border and Confidence Level Results

The American Society of Echocardiography's consensus statement on the clinical applications of contrast agents notes that the accuracy of contrast echocardiography in assessing LV function and volumes has been validated and should be considered in patients in whom precise information is clinically required, such as those undergoing serial assessment of LV function and those being evaluated for intracardiac device placement.¹ Valuable diagnostic and prognostic information can be obtained with total visualization of LV function.⁶ If echocardiograms are unable to fully diagnose heart conditions, patients often require more

invasive and costly examinations. Some patients' heart issues may be misdiagnosed.

Our findings provide additional evidence that contrast increases visualization in a way that significantly boosts even experienced cardiologists' confidence when interpreting echocardiographic tests. Our physicians' confidence levels for their readings of endocardial border definition were shown to significantly improve with contrast use. A No confidence level was not found in any of the 30 contrast studies, whereas 20% of examinations without contrast were read at a No confidence level. A No confidence level may indicate an uninterpretable study.

Implications to the Field of Echocardiography

Many laboratories and hospitals are reluctant to use contrast.⁷ This study demonstrates that use of contrast echocardiography is important despite the potential issues of cost, time, safety and misuse. Contrast agents add extra cost to the echocardiogram and, because of this, sonographers and physicians may be reluctant to use it on all patients with suboptimal images, even though studies have shown that the use of contrast is cost-effective.^{6,8} Castello et al. determined that cost savings can be achieved if use of contrast saved 10 minutes in echocardiography examination time for patients in whom visualization without contrast was difficult,⁷ and a cost-benefit analysis by Kurt et al. found significant savings (\$122/patient) from using contrast in technically difficult patients.¹¹ Moreover, physicians may not need to order another costly examination if crucial patient information is found on an initial echocardiogram with contrast. A study demonstrating the cost-effectiveness of contrast noted that 42% of noncontrast echocardiograms indicated follow-up testing compared to 12% of contrast echocardiograms.⁶ Critical and costly management decisions are based on quantification of LV volumes and ejection fraction.² Our study indicates that contrast can improve the accuracy of these important quantifications and could lessen the need for more costly examinations. Echocardiography is a noninvasive study that has the ability to provide physicians with important and critical patient information. When contrast is not used properly or when clinically indicated, patients may not receive the most efficient and accurate diagnosis.

There is a perception that contrast echocardiography use takes more time to complete and therefore is impractical in a high-volume laboratory. However, Castello et al. and Lester et al. provided evidence that contrast eliminates “struggle time” for sonographers.^{7,8} Our study was performed in a laboratory where the sonographer did not have to delay the examination by requesting physician approval to administer contrast. Although data on contrast administration time were not available for our retrospective study, our clinical experience suggests it typically adds less than 15 minutes to total examination time. Contrast protocols with a standing order for contrast use when clinically indicated are important in reducing examination time.¹⁴

In 2007, the FDA issued a black box warning for two perflutren-based microbubble contrast agents following the deaths of four patients who were administered both agents.¹⁵ This warning was issued even though there was no significant evidence that their deaths were related to either contrast agent,¹ and despite the possibility the deaths were caused by an existing condition, i.e. a pseudocomplication.¹³ Nonetheless, this warning sparked much disagreement regarding contrast use in echocardiography laboratories across the country. Because of this official warning, contraindications for use of contrast agents were recommended for patients with unstable cardiopulmonary status, including patients with unstable angina, acute myocardial infarction, respiratory failure or recent worsening congestive heart failure. Bhatia et al. suggested that the balance of risk to benefit needs to be considered with each patient and that the benefits obtained with use of contrast may outweigh the risks.⁶

Since the warning was issued, concern over the contraindications among cardiologists led to the FDA revising the labeling for contrast agents. The FDA’s current prescribing information for Definity was approved in May 2008, and includes a revised review of the four patient deaths that supports causation by possible pseudocomplication.¹³ Research has not shown enough evidence to define any bioeffects from the maximum-approved clinical injection dose of contrast agents.¹ Contrast is now only discouraged in patients with known right-to-left shunts or a hypersensitivity to perflutren.⁹ Although these contraindications have been changed, some concern remains regarding

contrast’s safety. While none of the patients in our study experienced any safety issues or side effects with use of contrast, the most common complaint in our clinical experience is back pain that lasts a few minutes and resolves once the agent has fully dissipated. Other reported side effects for Definity — including but not limited to headache, nausea and prolonged Q-T interval — occur infrequently.¹⁶

Proper administration of contrast also is an issue of debate. Contrast incorrectly administered by sonographers and physicians may actually impede examination quality to a level lower than that of noncontrast examinations. In a test performed on an 80-year-old patient, the misuse of contrast displayed a large atrial mass that was actually not there.¹⁷ Subsequent transesophageal echocardiography allowed for the correct diagnosis. Artifacts induced by contrast agents are caused by poor administration and/or poor ultrasound machine mechanics, and can severely degrade image quality.¹⁸ Attenuation occurs when a higher concentration of contrast agents are injected. The injection produces intense ultrasonic backscatter, which precludes adequate interpretation of the echocardiogram.¹⁹ This attenuation compromises LV assessment by creating an acoustic shadowing affect.¹⁸ Ultrasound technology has improved to help correct these problems, but sonographers must use the machine and contrast appropriately to avoid artifacts.

Every echocardiographic laboratory should have a detailed written protocol for physicians, fellows and sonographers to follow to administer contrast correctly and to know when it is clinically indicated. With continual advances in echocardiography, some sonographers may be inadequately trained in the use of contrast, possibly leading to nondiagnostic studies.²⁰ The need for proper training and written protocols in echocardiography laboratories is imperative.

Recommendations for Future Study

Our study produced tangential outcomes that could be further studied. One such finding was that contrast echocardiography proved most beneficial in particular wall-segment locations. Visualization of the apical LV segments significantly increased with use of contrast, whereas the mid- and basal segments were not. Hamilton-Craig et al. found similar results in

their contrast study,²¹ which resulted in incomplete endocardial definition for 11% of patients due to the reduced definition of the basal myocardial segments. This is a recognized phenomenon known as “basal attenuation,” in which shadowing of basal segments is seen due to a high concentration of contrast in the apical blood pool near the ultrasound transducer,²¹ and may explain why several noncontrast images of our patients received superior grades to their contrast counterparts. Future studies on why this is happening and what can be done to aid visualization of the basal segments would be beneficial to the field of echocardiography. Until then, sonographers need to be aware of the complications that may occur during contrast administration. We recommend sonographers visualize basal segments as clearly as possible prior to administration of contrast. The combined effect may result in all segments visualized in views with and without contrast, thereby improving physician confidence level.

An unexpected finding was the differential results observed among machine-contrast packages. Unfortunately, our sample size was not large enough to truly signify which machine-contrast package increased visualization and confidence the most, but this could be a subject for future studies. Not only would determining this aid in laboratories’ investment plans, but it would also contribute information to manufacturers about their products’ disadvantages and advantages with contrast use.

Study Limitations

This study is limited by the respective availability of microbubble contrast packages by four manufacturers. Confidence level interpretation is subjective data and open to bias, which may limit the accuracy of these findings. However, the four reading physicians all had Level III echocardiography training and clinical experience in reading echocardiograms, which could serve to minimize interobserver subjectivity.

CONCLUSIONS

This study further demonstrates the superiority of contrast echocardiography for defining the left ventricular endocardial border compared to examinations without contrast. Yet, there are clinics and hospitals in the United States and other countries that are either not using contrast consistently or at all.

It is beneficial for laboratories to establish a consistent written protocol for the administration of contrast echocardiography that includes proper technique, explanation of machine mechanics and thorough definition of indications for contrast use. Sonographers should be trained in these skills and equipment. Contrast agents are significantly valuable to the field of echocardiography and their proper use should be supported in inpatient and outpatient laboratories.

Patient-Friendly Recap

- Echocardiography, also known as ultrasound imaging of the heart, is a diagnostic test that reveals the heart’s structure and motion.
- Adding an intravenous contrast agent to improve visual clarity is optional in many cases.
- The authors found that use of contrast significantly helped highly trained echo readers confidently interpret images.
- Echo laboratories should establish a written protocol for the consistent use of contrast that defines proper administration technique, machine settings and indications.

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Conflicts of Interest

None.

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