

CONTRAST ECHOCARDIOGRAPHY FOR EVALUATING TREATMENT OF LEFT VENTRICULAR DYSFUNCTION

Leo HB Baur, MD, PhD

Address for Correspondence:

Department of Cardiology

Atrium Medical Centre

Henri Dunantstraat 5

6401 CX Heerlen

The Netherlands

Phone: + 31 45 5766129

Fax: + 31 45 5766133

E-mail: lhbaur@yahoo.com

ABSTRACT

Assessment of left ventricular volume and wall-motion endocardial border definition is essential in patients with heart failure. Conventional two-dimensional imaging has limited reliability in the assessment of the left ventricular cavity. Contrast agents used in combination with harmonic imaging or power Doppler imaging are able to improve endocardial border definition, reproducibility of left ventricular volume measurements, and pharmacologic stress echocardiographic results.

INTRODUCTION

Echocardiography has become a first-line technique for the detection of left ventricular dysfunction, the identification of viable myocardium, risk assessment of patients after myocardial infarction, the prediction of functional recovery after revascularization, and evaluation of pharmacologic treatment.^{1,2} Although image quality has improved during the last few years through the development of second harmonic imaging,³ subop-

timal images are frequent. This can be due to obesity, chest deformity, emphysema, and tissue factors. Limited endocardial border delineation can result in problems with estimation of left ventricular ejection fraction and left ventricular volumes; these problems can impede wall-motion abnormalities during pharmacologic stress echocardiography.⁴

Myocardial contrast agents that are able to cross the pulmonary circulation may improve endocardial definition and increase accuracy of the measurement of left ventricular function and volume.^{5,6} This paper provides a stepwise description of methods, indications, and results of contrast echocardiography for left ventricular opacification.

CONTRAST AGENTS FOR LEFT VENTRICULAR OPACIFICATION

It has been known for more than 30 years that an agitated saline solution or another fluid, containing gas bubbles, injected in an antecubital vein is able to produce strong echoes or contrast on an echocardiogram.⁷ Injection of such fluids produces ultrasound contrast by increased backscatter from inclusion of micro bubbles within the injectant.⁸ These micro bubbles dissolve rapidly in blood and lose their echogenicity. Therefore, these contrast agents are used primarily to detect cardiac shunts and examine right atrial and ventricular structures. A major aspect resulting in backscatter from sonicated micro bubbles at nonresonating frequencies is their size. Even a small decrease in micro bubble size can result in a significant attenuation of backscatter intensity. Earlier contrast agents were associated with features that contributed to decreases in micro sphere size, such as low molecular weight and the diffusibility and solubility of the gases (primarily nitrogen and oxygen) contained in the micro bubbles. The size of the micro bubble declines as the gases leak out of the micro bubbles to dissolve in the surrounding blood. This process decreases their contrast intensity.⁹ Recently, new ultrasonic contrast agents have been developed that are characterized by smaller mean size of the micro bubbles and prolonged persistence attributable to the substitution of octafluoropropane gas for air in the micro bubble.

Conflicting forces influence the optimal size of a

venous contrast agent's micro bubble. Although the micro bubbles must be large enough to produce high-contrast intensity, they must also be small enough to reduce hemodynamic effects for successful imaging of the left heart structures. Microtubules larger than the pulmonary capillary vessels can potentially cause blockage of the pulmonary microcirculation, thereby failing to reach the left ventricle. This blockage results in decreases in both contrast intensity and duration of contrast. An overview of the most frequently used contrast agents-both old and new-is presented in Table 1. The new contrast agents are able to visualize both the right and left ventricular chamber after intravenous injection.⁸

Table 1. Characteristics of Echocardiographic Contrast

| Name | Shell Composition | Gas |
|------------------------------------------------------------|---------------------|----------|
| Human albumin | Albumin | Air |
| Albumin micro spheres | Albumin | PFP* |
| Perfluorocarbon-Exposed sonicated dextrose albumin (PESDA) | Albumin | Air/PFC* |
| Sulphur [hexafluoride] | Surfactant/ powder | SF6* |
| Galactose-based micro bubble (not approved in the US) | Galactose/palmitate | Air |
| Dodecafluoropentane | Surfactant | PFC |

*PFP= Perfluoropropane; PFC= Perfluorocarbon; SF6= Sulphurhexafluoride

MACHINE SETTINGS FOR CONTRAST ECHOCARDIOGRAPHY

Bubbles undergo radial oscillation in the ultrasound field and have a natural frequency of oscillation at which they will absorb and scatter ultrasound with a high efficiency: The bubble behaves as an active source of sound¹⁰ (Figure 1). If the ultrasound field drives bubbles at sufficiently high acoustic pressures, the oscillatory excursions of the bubble reach a point where its alternate expansions and contractions are not equal. The consequence of such nonlinear motion is that the sound emitted by the bubble and detected by the transducer contains harmonics.¹¹ Newer echocardiography equipment is able to transmit ultrasound at between 1.5 and 4 MHz and receive at the second harmonic between 3 and 8 MHz. This is called *harmonic imaging*.¹² In harmonic images, the echo from tissue is reduced but not eliminated, reversing the contrast between the agent and its surroundings (Figure 2). Harmonic imaging can specifically detect the characteristic signature of micro bubbles in contrast agents. This technology provides selective enhancement of the echoes

from ultrasound contrast relative to the surrounding tissue, allowing improved visualization of blood flow as well as direct imaging of the contrast agent in the left ventricle. Harmonic imaging offers increased sensitivity to the ultrasound contrast signal and provides valuable information that cannot always be obtained using conventional two-dimensional (2-D) echocardiography.

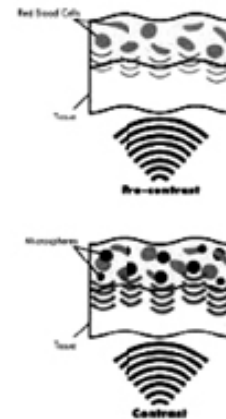


FIGURE 1. Contrast improves ultrasound wave reflection.

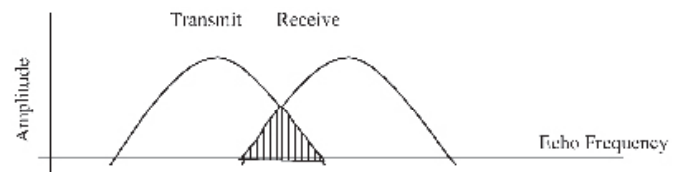


FIGURE 2. System frequency response in harmonic mode showing an area of overlap between the transmitted and received frequencies that results in residual tissue imaging (adapted).¹⁰

An acoustic wave has high and low pressures. If an acoustic wave reaches the micobubble, this results in compression of the bubble with a positive pressure. The following expansion has a negative pressure. This expansion is more than that of the surrounding tissue. If the intensity (ie, power) of the ultrasound beam increases, the intensity of the compression increases and the bubble explodes. Therefore, the acoustic pressure (ie, power) should not be too high. Generally, the mechanical index is set between 0.6 and 0.8 for left ventricular opacification.

FACTORS INVOLVED IN THE USE OF CONTRAST AGENTS

Echocardiographic diagnosis of ischemic heart disease is primarily made by detection of regional wall motion and regional wall-thickening abnormalities.¹³ This means that endocardial border definition is critical for a correct diagnosis. In approximately 30% of patients, endocardial

border definition is sub-optimal and causes difficulty in the assessment of left ventricular ejection fraction and left ventricular volume.^{14,15} Therefore, reliability of left ventricular volume measurements is low.¹⁶ However, studies with contrast agents have consistently shown improvement of endocardial border visualization¹⁷⁻¹⁹ compared with baseline imaging. One drawback with some contrast agents is that the distribution of the contrast is not uniform and that ultrasound energy destroys bubbles in the near field.²⁰

CONTRAST AGENTS IN PHARMACOLOGIC STRESS ECHOCARDIOGRAPHY

In the next decade, pharmacologic stress echocardiography will become more and more important in detecting ischemia and performing follow-up study of coronary artery disease. Because the number of elderly people will increase, more and more patients will not be able to perform maximal exercise, some because of orthopedic problems, some due to vascular abnormalities and some because of cerebral disease.²¹ Some studies have shown that 30% to 40% of patients either cannot exercise at all or are unable to reach maximal exercise levels.²² Therefore, pharmacologic stress echocardiography will be indicated in several situations where exercise cannot yield the diag-

nosis. Some examples are:

- Diagnosis of viable myocardium in post-myocardial infarction patients and patients with left ventricular dysfunction²³⁻²⁶
- Evaluation of patients with chest pain in an emergency room scenario²⁷
- Diagnosis of patients with coronary spasm by ergonovine stress testing²⁸

Interpretation of pharmacologic stress echocardiograms is *qualitative* because multiple factors may produce sub-optimal image quality and decreased endocardial border definition, leading to diminished diagnostic accuracy. Nondiagnostic images due to chest deformity, pulmonary disease, and excessive cardiac motion due to hyperventilation and tachycardia can be present in up to 30% of images.²⁹

Contrast echocardiography may provide up to 80% to 95% improvement in endocardial border definition and increased accuracy of pharmacologic stress echocardiograms.³⁰ Harmonic imaging of second-generation contrast results in homogeneous and persistent left ventricular opacification and improved image quality, as can be observed in Figure 3.

Use of contrast results in improvement of diagnostic

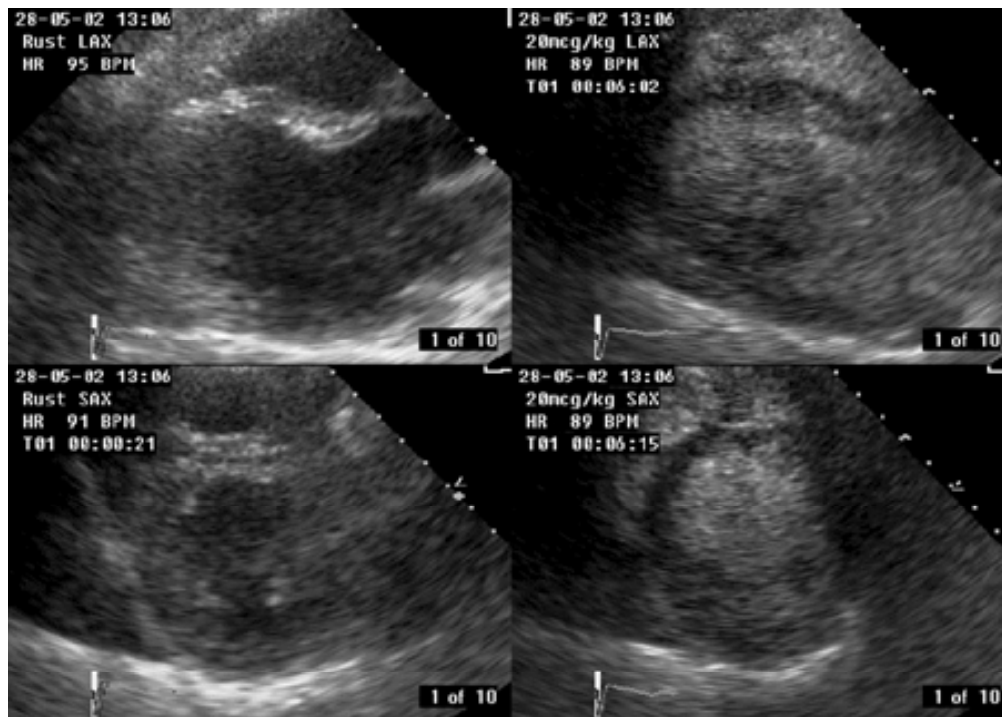


FIGURE 3. Top Left: Parasternal long axis view using second-generation harmonic imaging. There is a poor border definition of the apex and posterior wall. Top Right: Parasternal long axis view after injection of a sulfur hexafluoride contrast agent. The left ventricular cavity now appears white, and the myocardium appears black. Now the endocardium is well visualized. Bottom Left: Short axis view using second-generation harmonic imaging. The lateral wall has a poor border definition. Bottom Right: Short axis view of the same patient after injection of a sulfur hexafluoride contrast agent. Now all endocardial borders are clearly visualized.

accuracy.³¹ Use of echocardiographic contrast may contribute to a more cost-effective pattern of care by a reduced rate of false-positive and false-negative echocardiograms and increased laboratory efficiency in evaluation of the difficult-to-image patient.³²

Guidelines for the use of contrast during pharmacologic stress echocardiography have been provided by the American Society Task Force assigned to evaluate standards and guidelines for the use of ultrasonic contrast in echocardiography (Table 2).⁸

CONTRAST-ENHANCED HARMONIC COLOR-DOPPLER IMAGING

A new method to improve contrast-enhanced images is contrast-enhanced harmonic color Doppler.³³ This method is basically a combination of multiplane 2-D harmonic imaging, echocardiographic contrast, color Doppler ultrasonography, and digital image processing. Color Doppler without contrast is sometimes able to create cavity-only images. In practice, this is difficult in most patients because

- The amplitude of the blood-pool signal is near the clutter level of the Doppler motion detector (especially in patients that are technically difficult to image)
- The velocity of intracavitary blood is relatively low at the moment of end-diastole and end-systole.³⁴

Echocardiographic contrast overcomes both limitations because it increases the backscatter of the blood pool by 20 to 40 dB.³⁵ In addition, image quality is improved by an odd characteristic of color Doppler imaging.³⁴ Bubble movement caused by acoustic radial force or bubble destruction results in color-flow signals, even in the absence of true blood flow.^{36,37} The multiple transmit pulses required to create a Doppler image (usually four or more pulses per scan line compared with 2-D imaging) creates a more homogeneous image compared with 2-D imaging.³⁴ The cavity is further enhanced when harmonic imaging is used because the myocardial echoes are relatively depressed.³⁸ One can use conventional contrast-enhanced color Doppler imaging, in which the image displays velocity, and contrast-enhanced power Doppler imaging, in which the image displays amplitude.³⁹ Because power Doppler imaging is able to detect very low bubble concentrations, this technique is more sensitive to display the left ventricular cavity in contrast studies than conventional contrast imaging and conventional contrast-enhanced color Doppler imaging.⁴⁰ The entire left ventricular cavity is opacified, especially the apex and lateral area. A typical image is seen in Figure 4.

TABLE 2. Technical Guidelines for Left Ventricular Opacification in Harmonic Contrast Studies⁸

| Ultrasound Machine Settings | |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Set mechanical index (MI): 0.4-0.6 Select harmonic imaging Optimize transmit focus location (usually far-field; may be apical) Optimize Time gain controls and gain Minimize near-field gain Use and modify contrast presets supplied by specific vendors |
| Intravenous Contrast Injection | |
| Rest Study | Bolus injection of contrast Slow NaCl flush (2-3 mL over 3-5 sec) |
| Stress Study | Imaging as described for rest study Low-dose and peak-dose dobutamine Contrast as a bolus in dobutamine line Dobutamine infusion acts as flush If clinical reasons require termination of dobutamine infusion Use NaCl flush (2-3 mL over 3-5 sec) |
| Peak Exercise | While on treadmill, inject 30 seconds before exercise termination If bicycle exercise is used, inject at peak stress stage (at the beginning if 2-minute stage is used; at 1 minute if 3-minute stage is used) Inject optimal resting dose of contrast with NaCl flush Transfer to imaging bed Add additional contrast |
| Image Acquisition: Practical Guidelines | |
| | Start at apical window; use bed with cut-out To improve image quality and decrease shadowing Use inspiration and expiration Move transducer position If shadowing cannot be eliminated Attempt to direct shadow through center of the ventricle If apex is under filled with contrast Reduce mechanical index Inject more contrast Use larger and more rapid saline flush If attenuation exists Wait; increase mechanical index |

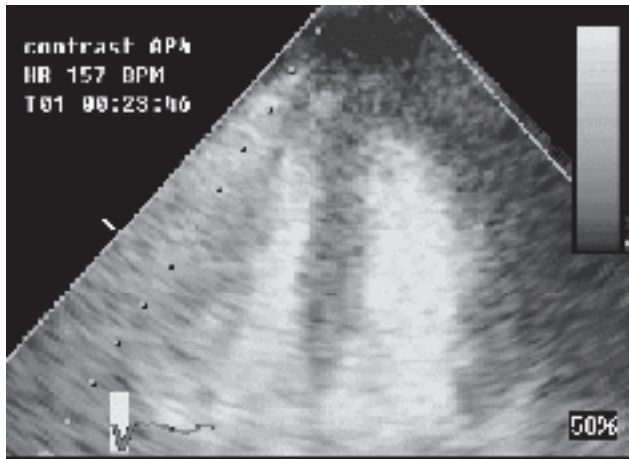


FIGURE 4. Contrast-enhanced power Doppler image in four-chamber view clearly shows all endocardial borders.

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CONTRAST ECHO FOR EVAL TREATMENT OF LV DYSFUNCTION POST TEST

Expires: July 15, 2009 Approved for 1 ARRT Category A Credit.

1. **Echocardiography has been proved helpful for which of the following?**
 1. Detection of left ventricular dysfunction
 2. Identification of viable myocardium
 3. Risk assessment of patients after myocardial infarction
 4. Evaluation of pharmacologic treatment
 - a. 1 only
 - b. 2 only
 - c. 2 and 3
 - d. 1, 2, 3, and 4
2. **Which is a TRUE statement regarding echocardiography?**
 - a. Image quality has remained approximately the same over the past 20 years.
 - b. The development of second harmonic imaging has not had a substantial effect on image quality.
 - c. Suboptimal images can be due to obesity, chest deformity, emphysema, and tissue factors.
 - d. Because of recent technological advances, suboptimal images are rare.
3. **Inadequate delineation of the endocardial border can result in problems with all of the following EXCEPT:**
 - a. the determination of valvular stenosis.
 - b. estimation of the left ventricular ejection fraction.
 - c. estimation of left ventricular volumes.
 - d. impedance of wall-motion abnormalities during pharmacological stress.
4. **The limitation of the agitated saline solutions that have been used for many years in echocardiography is**
 - a. the high risk of adverse reactions following injection.
 - b. the highly unstable nature of these solutions that makes them dangerous to store.
 - c. the great expense of these solutions.
 - d. the fact that micro bubbles in the solution dissolve rapidly in blood.
5. **What inherent characteristic make the micro bubbles in contrast agents useful in echocardiography?**
 - a. High atomic number that scatters ultrasound
 - b. Low viscosity that absorbs radiation
 - c. A natural frequency of oscillation at which they will absorb and scatter sound
 - d. Gas bubbles that readily dissolve into the surrounding blood
6. **Newer ultrasonic contrast agents are characterized by**
 - a. their ability to rapidly dissolve in blood.
 - b. their rapid loss of echogenicity.
 - c. their limited use—primarily just to detect cardiac shunts and examine right heart structures.
 - d. smaller mean size and prolonged persistence.
7. **Harmonic imaging is done at what frequencies?**
 - a. Transmit between 0.5 and 2 MHz; receive between 1 and 3 MHz
 - b. Transmit between 1.5 and 4 MHz; receive between 3 and 8 MHz
 - c. Transmit between 4 and 4.5 MHz; receive between 7 and 9 MHz
 - d. Transmit between 5 and 7 MHz; receive between 8 and 10 MHz
8. **Which is a TRUE statement concerning harmonic imaging?**
 - a. In harmonic imaging, the contrast is reversed between the agent and its surroundings.
 - b. In harmonic imaging, the echo from tissue mimicking material can be entirely eliminated.
 - c. Harmonic imaging requires a transmission frequency of 5 MHz.
 - d. At present, harmonic imaging is dramatically limited because it is impossible to reduce the echo from tissue mimicking material.
9. **An acoustic wave has**
 - a. homogeneous pressure.
 - b. high and low pressures.
 - c. positive pressure.
 - d. negative pressure.
10. **When concerned with left ventricular opacification, the mechanical index for acoustic pressure is set between**
 - a. 0.2 and 0.4.
 - b. 0.4 and 0.6.
 - c. 0.6 and 0.8.
 - d. 0.8 and 1.0.
11. **Echocardiographic diagnosis of ischemic heart disease is primarily made by**
 - a. documenting that there is no aortic flow during the pre-ejection period in early systole.
 - b. detection of regional wall motion and regional wall-thickening abnormalities.
 - c. documenting that peak forward flow velocities across cardiac valves are less than or equal to approximately 1.0 m/sec.
 - d. a post-exercise echocardiogram that demonstrates a slight decrease of left ventricular size with hyperdynamic wall motion and an increase of left ventricular ejection fraction.
12. **Approximately what percentage of examinations result in suboptimal endocardial border definition?**
 - a. 10
 - b. 20
 - c. 30
 - d. 40
13. **Why might pharmacologic stress echocardiography play a greater role in the future?**
 - a. Increasing numbers of elderly people will mean that many patients may be unable to reach maximal exercise levels.

- b. Post-exercise echocardiograms are not diagnostic for ischemia.
- c. Post-exercise echocardiogram are very expensive.
- d. Heart disease is expected to increase dramatically in the future.
- 14. Which of the following are situations in which pharmacologic stress echocardiography may be indicated?**
1. Diagnosis of viable myocardium after myocardial infarction
 2. Evaluation of patients with chest pain
 3. Diagnosis of coronary spasm by ergonovine stress testing.
 - a. 1 only
 - b. 2 only
 - c. 1 and 2
 - d. 1, 2, and 3
- 15. Which of the following are advantages of the use of contrast in echocardiography?**
1. Improved diagnostic accuracy
 2. Reduced rate of false-positive echocardiograms
 3. Cost efficient
 - a. 1 only
 - b. 2 only
 - c. 1 and 2
 - d. 1, 2, and 3
- 16. Interpretation of pharmacologic stress echocardiograms is**
- a. quantitative.
 - b. qualitative.
 - c. highly accurate in nearly all cases.
 - d. not dependent on endocardial border definition.
- 17. Harmonic imaging of second-generation contrast results in**
- a. homogeneous and persistent left ventricular opacification.
 - b. shortened examination time.
 - c. artifact elimination.
 - d. ultrasound energy causes the multiplication of bubbles in the near field.
- 18. Which of the following strategies may improve image quality and decrease shadowing?**
1. Use respiratory movements
 2. Move transducer position
 3. Decrease volume and flow rate of saline flush
 - a. 1 only
 - b. 2 only
 - c. 1 and 2
 - d. 1, 2 and 3
- 19. Increasing the backscatter of the blood pool by 20 to 40 dB can be**
- a. dangerous for the patient.
 - b. accomplished by altering the patient's position.
 - c. accomplished by increasing the MI.
 - d. accomplished by using a contrast agent.
- 20. In a contrasted study, why is power Doppler more sensitive in displaying the left ventricular cavity than either conventional contrast imaging or conventional contrast-enhanced color Doppler?**
- a. Power Doppler imaging is able to detect very low bubble concentrations.
 - b. Conventional methods destroy most of the micro bubbles.
 - c. Power Doppler imaging increases the backscatter of the blood pool.
 - d. Conventional methods are unable to display velocity or amplitude.

