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How Do I Do It?

Clinical application and laboratory protocols for performing contrast echocardiography

*Adrian Chong, Brian Haluska, Sudhir Wahi**

Department of Cardiology, Princess Alexandra Hospital, School of Medicine, University of Queensland, 199 Ipswich Road, Woolloongabba, Brisbane 4102, Australia

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ABSTRACT

Technically difficult echocardiographic studies with suboptimal images remain a significant challenge in clinical practice despite advances in imaging technologies over the past decades. Use of microbubble ultrasound contrast for left ventricular opacification and enhancement of endocardial border detection during rest or stress echocardiography has become an essential component of the operation of the modern echocardiography laboratory. Contrast echocardiography has been demonstrated to improve diagnostic accuracy and confidence across a range of indications including quantitative assessment of left ventricular systolic function, wall motion analysis, and left ventricular structural abnormalities. Enhancement of Doppler signals and myocardial contrast echocardiography for perfusion remain off-label uses. Implementation of a contrast protocol is feasible for most laboratories and both physicians and sonographers will require training in contrast specific imaging techniques for optimal use. Previous concerns regarding the safety of contrast agents have since been addressed by more recent data supporting its excellent safety profile and overall cost-effectiveness.

1. Introduction

Transthoracic echocardiography (TTE) remains a versatile and globally the most common cardiac diagnostic imaging modality. Numerous developments in ultrasound technology, including harmonic imaging and improvement in imaging frame rates up to 120 frames per sec, have greatly enhanced the diagnostic capabilities of the technique. However, there is still a need to improve image resolution when the acoustic windows are limited and endocardial definition suboptimal. This may result in potentially missed or incorrect diagnoses and consequential adverse outcomes or further inappropriate downstream investigations with both temporal and financial implications.[1]

Microbubble ultrasound contrast is now regarded as an essential tool in the day-to-day practice of the clinical echocardiography laboratory to overcome some of these limitations. The contemporary approved and appropriate indications for the use of ultrasound contrast agents include left ventricular opacification (LVO) and improvement of endocardial border detection (EBD), when ≥2 contiguous segments are not well-visualized without contrast enhancement.[2–4] Some research and off-label use of contrast agents include augmentation of the spectral Doppler signal and assessment of myocardial perfusion. While the latter showed enormous potential in animal research studies, it has not translated into everyday clinical practice.

* *Corresponding author.*
E-mail address: s.wahi@uq.edu.au (S. Wahi).

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The commonly available second-generation echocardiographic contrast agents are **Sonovue** (Bracco Imaging), **Optison** (GE Healthcare) and **Definity** (Lantheus Medical Imaging) that is also marketed under the label of **Luminity** in Europe. While they are essentially similar in the way they enhance TTE image quality, each of these microbubble contrast agents have their own characteristics, which will be discussed later. Delivered intravenously, these microbubbles are sufficiently small (<10 μm; red blood cells are ~6–8 μm for reference) to allow transpulmonary passage and therefore provide real-time imaging of blood flow through the left-heart. These microbubbles use high-molecular weight gases with low-solubility and the high elasticity shell to reduce acoustic destruction and thereby maintain the microbubble integrity (stability), prolong circulating time (persistence) or contrast effect, and maximize the non-linear contrast backscatter.[5,6]

The injected microbubbles provide multiple gas–liquid interfaces within the blood pool and thereby significantly increasing the backscatter of ultrasound waves from the insonating beam.[2,7] These microbubbles undergo asymmetric oscillation (alternating compression and expansion with inverse changes in radius and stiffness) within the applied ultrasound field and essentially behave as non-linear scatterers. Real-time assessment with ultrasound contrast for LVO and improvement of EBD is conventionally performed with low-MI (usually <0.2) harmonic imaging. This reduces microbubble disruption, enhances the intracavitary contrast intensity, allows subtraction or filtering of linear tissue backscatter and minimizes tissue harmonics.[8] The end result is enhancement of the endocardium that forms the border between the darker myocardium and bright intracavitary contrast.

2. Clinical utility and indications

The current consensus indications for contrast LVO in resting transthoracic echocardiography include (Table 1):

Table 1 – Current approved[a] indications for contrast echocardiography.

LV opacification during resting transthoracic echocardiography in difficult-to-image patients for:
- Improvement of LV endocardial border definition (when ≥2 contiguous segment are not well-visualized)
- Improved accuracy and reproducibility of quantitative LVEF
- Definitive diagnosis of LV structural abnormalities including apical thrombi, apical HCM, LV non-compaction, and complications of myocardial infarction (i.e. LV aneurysms and pseudoaneurysms)

LV opacification during stress echocardiography (when ≥2 contiguous segment are not well-visualized) to improve sensitivity and accuracy of wall motion analysis for detection of myocardial ischemia

a Doppler signal enhancement, myocardial perfusion, and use of contrast echocardiography during interventional procedures are currently regarded as off-label uses for echocardiographic contrast agents.

1) Improvement of left ventricular (LV) EBD,
2) Increased accuracy and reproducibility of ventricular volumetric assessments,
3) Quantitative assessment of ejection fraction,
4) Enhanced diagnostic confidence for LV structural abnormalities (including but not limited to apical thrombus, non-compaction and hypertrophic cardiomyopathy where near-field clutter and artifacts are problematic),
5) Microbubble contrast is also clinically indicated in stress echocardiography when ≥2 contiguous segments are not well-visualized with the intent of improving interpretation of wall motion abnormalities and diagnostic accuracy,[9]
6) Off-label use of microbubble contrast agents for MCE in perfusion imaging and Doppler signal enhancement will also be discussed briefly in this review.

2.1. *Left ventricular structure and function*

2.1.1. *Quantification of left ventricular systolic function*

Quantitative evaluation of LV systolic function in the form of the LV ejection fraction (LVEF) is one cornerstone for the initial diagnosis of heart failure and remains a significant prognosticator of survival. Many currently used chemotherapeutic agents have an increased risk of early or delayed cardiovascular toxicities and regular surveillance of LVEF is a critical part of continuing care.[10] It has been repeatedly demonstrated that contrast-enhanced echocardiography for LVO improves LVEF correlation with radionuclide ventriculography and cardiac magnetic resonance imaging (cMRI), and decreases the overall intra- and interobserver variability.[1,11–16]

2.1.2. *Endocardial border definition and wall motion assessment (resting and stress echocardiography)*

Up to 20% of routine transthoracic echocardiograms may have poor EBD and could be regarded as non-diagnostic.[1,17,18] Patient factors contributing to these difficult images include co-existent chronic obstructive airways disease, chest wall-deformities, and body habitus (obesity). Studies performed in the emergency department or on mechanically ventilated patients in the intensive care setting also pose significant challenges from the perspective of image quality. Multiple studies have demonstrated that microbubble contrast combined with harmonic imaging for LVO improves the diagnostic accuracy, confidence and interobserver agreement in assessment of regional systolic function or myocardial thickening in these technically difficult-to-image patients.[19–22] Kitzman et al demonstrated that contrast-enhanced images resulted in the conversion of 48% of non-diagnostic examinations (defined as ≥4 of 6 non-evaluable segments in a single apical view) into “salvaged” studies (where ≤1 poorly visualized segment remained on the same comparative view) following LVO.[23] These salvage rates have been reported to be higher in intensive care unit (ICU) patients who were mechanically ventilated.[24–26]

The assessment of regional wall motion (segmental myocardial thickening) that forms the basis of interpretation of stress echocardiography is subjective and highly dependent on optimal endocardial definition. The same patient factors contributing to less than ideal images are often further exaggerated during stress. Technically suboptimal studies have