FEATURE ARTICLE

Contrast-enhanced echocardiography: usage, benefits and future directions

Authors: Brennan Ballantyne (Meds 2014), Josh Rosenblat (Meds 2014)
Faculty Reviewer: Bryan Dias MD FRCPC (Department of Medicine, Cardiology)

INTRODUCTION

Contrast-enhanced echocardiography (CEE) is a method of echocardiography that utilizes the echogenicity of specific contrast media to greatly increase the contrast obtained between blood and tissue. The concept, while over four decades old, has recently had increased attention in the clinical and preclinical realms of cardiovascular research due to advances in technology that increase its utility.

EXPLANATION OF FUNCTION

Ultrasound functions by detecting the different densities of tissues in the body based on their different responses to sound energy. CEE derives its superior resolution from the use of contrast agents carried in the circulation that respond uniquely to sound energy. It was first realized by Gramiak and Shah in 1968 that gas suspended in the blood stream alone has advantages for imaging because the density differential between gas and liquid phase provides optimal echo feedback patterns. However, early contrast agents were too large to navigate through the capillary network of the lungs to the systemic circulation, and would prematurely diffuse into tissues. Hence, newer agents were developed to be both smaller and more stable. The so called “second generation” contrast agents were composed of microbubbles of high density gas (usually fluorocarbons), encapsulated with a lipid or albumin coat. These microbubbles undergo volumetric oscillations under the pressure changes induced by the ultrasound transmitter. This vibration produces energy that can be picked up by the transducer and converted into an image.

Microbubbles are very small, similar to the size of red blood cells, and are able to navigate through capillary systems without becoming lodged. They are strong enough to withstand “inertial cavitation,” that is, large oscillations in energy from the ultrasound that can destroy the bubbles. Older contrast agents could only enable CEE to image the right side of the heart, limiting their role to the investigation of intracardiac or intrapulmonary shunts. The second generation agents opened a door for a new role of CEE.

With advances in contrast agents, the ultrasound hardware technology had to adapt as well. Current CEE uses harmonic imaging that was developed as a way for contrast-specific imaging modalities to use lower transmission power than that used for non-contrast imaging. This is required because high transmission power causes destruction of the microbubbles and impairment of tissue signals of the myocardium. Detection methods now preferentially detect the harmonic signals given off from the microbubble oscillations, minimize the signals from tissues, and provide a very high signal-to-noise ratio.

ADVANTAGES AND DISADVANTAGES

The primary advantage of CEE technology lies in its superior image quality when compared to native echocardiography, leading to more accurate measurements of ventricular volumes, better detection of thrombi or hypertrophy, and improved wall motion assessment. For example, it has been found that native echocardiography consistently underestimates left ventricle (LV) volumes when compared to magnetic resonance imaging (MRI) studies because it does not have the capacity to image the trabeculation of the ventricular endocardium when measuring volume. CEE results have been found to be equivalent with MRI due to the ability of contrast agents to include the fine details of cardiac anatomy. The superior imaging capabilities of CEE are also demonstrated in patients with poor baseline quality native echocardiograms, a number that can range from 10-15% of those scanned. To our knowledge, all studies conducted have found better results after CEE in these patients.

Another advantage of CEE is reproducibility of results. Native echocardiography has been criticized for high variability of measurements. This has led to a shift in patients being referred for expensive and time-consuming tests like Multi Gated Acquisition Scans (MUGA) and MRI studies. CEE has reproducibility on par with MRI, and is much less expensive. Even for technically difficult studies, such as stress echocardiography where inter-observer agreement can range from 43-100%, CEE significantly improves the confidence of the interpretation, and therefore, the reproducibility.

The main limitation to CEE technology has been concerns regarding adverse events with the use of contrast agents. In 2007, the FDA issued Black Box warnings to CEE contrast agents after reports of fatalities from cardiopulmonary reactions in at least 18 patients during procedures. These safety concerns slowed adoption of the technology, and posed questions about the future of CEE in the echocardiography community. However, it should be noted that the risks of adverse events are very low. Comparisons of the mortality rates of various cardiac procedures shows that mortality from CEE is (1:145,000) excessively small compared to coronary angiography (1:1000) or even exercise electrocardiography (1:2500). The FDA currently recommends close monitoring of vitals and ECG for at least 30 minutes after administration of contrast agents. This monitoring time may be difficult for busy echo labs at tertiary care centres, negating many of the time-saving benefits of echocardiography as an imaging modality.

INDICATIONS OF USE

As discussed above, CEE provides greater contrast between blood and tissue. Therefore, organ border delineation may be determined with greater resolution and accuracy. This is often applied to endocardial border delineation, which allows for a better determination of wall thickening or other wall abnormalities.

Contrast enhanced ultrasound may also be used to determine the perfusion of tissue. As well, it may be used to estimate the volume of blood in a given organ or section of tissue through the quantification of bubbles present and the extrapolation
tion to a representative volume of blood. 16

With these concepts in mind and evaluation of the current clinical evidence of usage, the American Society of Echocardiography (ASE) published a consensus statement outlining in detail the evidence-based application of CEE. 17 The ASE recommended that CEE should be considered in the following clinical scenarios:

- assessing left ventricular systolic function when quantitative volumes are required and during stress echocardiography
- evaluating the left ventricular apex
- evaluating mechanical complications of a myocardial infarction
- evaluating a potential cardiac mass
- evaluating perfusion (i.e. enhancing Doppler in the systemic circulation).

It should be noted that the above clinical scenarios are where CEE may be considered, however, CEE should not be used routinely in these scenarios. Rather, CEE should be used when non-CEE is not viable. More specifically, CEE should be used if two contiguous left ventricular segments are not seen on non-contrast images. 17 Also of note, since the publication of the consensus statement in 2008, the efficacy of the recommendations has been evaluated and found to be highly beneficial and safe in practice. 21 CEE may be particularly beneficial with obese patients as image quality is usually poorer with non-CEE. 17

FUTURE DIRECTIONS

New Applications in Assessing Myocardial Flow

CEE is currently being used to assess myocardial perfusion, but novel applications to its use are being considered. The first is bedside CEE that could be used in emergency departments to aid in the workup of patients presenting with chest pain. Not only could this identify higher risk patients and provide expedited treatment with the most appropriate modality, but it could obviate the need for other expensive or invasive testing. 7 CEE could also be used in patients with recognized ST elevation myocardial infarctions to gather valuable wall motion information for prognostic purposes. 18 Finally, the power of CEE for assessing perfusion has been recently used in new diagnostic situations to evaluate patients with ischemic symptoms caused by vasoregulatory mechanisms, as opposed to total obstruction of epicardial vessels. This is especially useful for gaining prognostic information in patients that suffer from diabetes, hypertension, or dilated cardiomyopathy, and guiding therapy. 19

Peripheral Vascular Imaging

The ability of CEE to accurately delineate ventricular borders has been further applied to the identification of vascular borders. Recently, CEE has been used to assess vascular disease due to its ability to evaluate the vasa vasorum, the system of vessels that penetrate and supply blood to the walls of large vessels of the body. In atherosclerotic disease, expansion of the vaso vasorum has been shown to be integral in the development of plaques, macrophage accumulation and plaque rupture. 20 CEE may play a future role in monitoring the development of the atherosclerosis, and stratifying patients for new therapies designed to slow the later stages of the disease. 5

Targeted Microbubbles for Specific Imaging

Many novel applications derive from the molecular targeting of microbubbles. Targeting molecules, such as ligands or monoclonal antibodies, may be conjugated to the surface of microbubbles. 22 These targeting moieties may then bind to their target, localizing more microbubbles to the area of interest (where the receptor of interest is located) and enable the non-invasive ultrasonic imaging of this location. For example, inflammatory markers/receptors may be targeted to illuminate the precise location. 23 In preclinical models, microbubbles have been targeted to inflammatory regions, atherosclerosis and cancer. 24,25 Furthermore, this presents the potential to use microbubbles to specifically target cells expressing certain receptors, allowing the delivery of drugs or other materials to these specific cells. 26

Ultrasound-Mediated Gene and Drug Delivery

Using targeted or non-targeted microbubbles, drugs or genes may be delivered to cells of interest. 27 Microbubbles are loaded with the drug or gene of interest and upon imaging, high frequency ultrasound is delivered to the area of interest to burst these bubbles and transiently create pores in the surrounding cells allowing for the intracellular delivery of the microbubbles’ contents. 27 This technique is especially suited for delivery to endothelial cells as they are most easily accessible from the blood stream where microbubbles predominate. Therefore, they can be used to either destroy the endothelial cells (eg. eliminating the blood supply to cancer cells) or promote angiogenesis in the case of vascular disease (eg. promoting the growth of new blood vessels will increase the perfusion of under perfused tissue due to occlusion). 28,29

Centres are increasingly adopting CEE technology for the advantages it offers, especially as the safety of the procedure becomes realized. Clinical and research settings alike can benefit from the current applications of CEE, and the many more promising avenues for its use on the very near horizon.

REFERENCES


FEATURE ARTICLE
FEATURE ARTICLE