Published in final edited form as:

J Cardimetab Syndr. 2008 ; 3(3): . doi:10.1111/j.1559-4572.2008.00010.x.

The Controversy Regarding Contrast Echocardiography and How It Affects Patients With the Cardiometabolic Syndrome

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Case History

T T is a 59-year-old man with ischemic cardiomyopathy who was admitted with sudden onset of left arm and leg weakness as well as facial numbness. His symptoms were transient, resolving within a few hours. The patient had a history of cardiometabolic syndrome (hypertension, impaired fasting glucose, and abdominal adiposity with a body mass index of 31) and coronary artery disease requiring coronary artery bypass surgery. Head computed tomography and brain magnetic resonance imaging did not show evidence of acute stroke. Transthoracic echocardiography was performed for assessment of a cardiac source of embolism.

Initial images failed to show an intra-ventricular abnormality (Figure 1A), but contrast-enhanced images demonstrated an apical mural thrombus (Figure 1B and Figure 1C). The patient was subsequently anticoagulated, and repeat echocardiography performed 10 months later with contrast showed a left ventricle free of thrombi (not shown).

Contrast Echocardiography

The field of echocardiography has undergone significant improvements over the last decade with regard to image quality and data acquisition, thus strengthening its role in serial noninvasive assessment of cardiac structure and function. The advancements have been multifold, including direct digital output,¹ software development, tissue harmonic imaging,² and intravenous contrast enhancement.³

Contrast enhancement of the heart and blood vessels has a long history, beginning initially in the early 1970s with the use of saline agitation to identify intracardiac shunts and right-sided structures particularly in patients with congenital heart disease.⁴ The inability of saline contrast to traverse the pulmonary circulation to enhance left-sided cardiac structures led to investigation in the 1980s of sonicated human serum albumin with air and most recently the use of perfluorocarbon gas to enhance the persistence of microbubbles in circulation. This higher-density gas is contained within a lipid or protein microbubble membrane to reduce gaseous diffusion and increase microbubble stability. The microbubbles produced are approximately the size of red blood cells (6–8 μ m in diameter) and can pass through the pulmonary capillary bed to the left heart. Ultrasonographic waves interact with these microbubbles, causing them to vibrate and generate sound waves at multiple frequencies that are detected by the ultrasound machine, and they are represented as an echogenic area on the generated echocardiographic image.

Perfluorocarbon gas microbubbles satisfy many of the criteria for an ideal contrast agent.⁵ They do not undergo cellular uptake for effect. They are biologically inert, insoluble in blood, do not readily cross the microbubble membrane, and are excreted by the lungs within minutes of initial injection. As detailed above, they have similar physical properties to red blood cells, are neutrally charged to allow passage through the microcirculation, and are relatively stable, dependent on the properties of the incident ultrasound beam. These agents are also easy to administer through a peripheral intravenous catheter and obtain optimal enhanced images.

The two major uses for intravenous contrast in echocardiography are to aid in left ventricular opacification and in myocardial perfusion assessment. This latter application has been confined to research protocols, and no contrast agents have been approved for this indication at present. The two contrast agents currently approved for left ventricular opacification using perfluorocarbon microbubbles are Optison (GE Healthcare, Buckinghamshire, United Kingdom) and Definity (Bristol-Myers Squibb Medical Imaging, Billerica, MA). Optison was voluntarily withdrawn in 2005 because of concerns regarding manufacturing practices but is set to return to the market in the near future.

Product Safety Concerns

On October 10, 2007, the US Food and Drug Administration (FDA) issued an alert for perfluorocarbon contrast agents based upon “reports of death and serious cardiopulmonary reactions following the administration of ultrasound microbubble contrast agents used in echocardiography.”⁶ Ten deaths after the administration of Definity and 1 death after the administration of Optison were cited. Death in the majority of these patients was thought to be secondary to an underlying serious medical condition. Four cases in which death occurred within 30 minutes of intravenous contrast administration have been highlighted and form the basis for the FDA recommendations that are now listed as a black box warning in package inserts by both companies (Figure 2). These 4 cases include a 67-year-old man with ischemic cardiomyopathy who died 1 minute after initiation of an exercise stress test; an elderly man admitted to the intensive care unit with recent myocardial infarction and cardiomyopathy; a 70-year-old man with history of congestive heart failure and deep vein thrombosis who died from a massive pulmonary embolism; and a 34-year-old morbidly obese woman with history of postpartum cardiomyopathy admitted with multilobar pneumonia who was found to have multiple pulmonary emboli and right ventricular thrombi on autopsy.⁷

It remains unclear whether intravenous contrast administration may have played a causative role in these deaths, especially considering the serious underlying conditions that prompted admission or were part of the patient’s medical history. There has been no purported mechanism defining a toxic adverse effect of these agents in humans. Animal models and limited data in humans describe possible bioeffects such as increased vascular permeability and localized cell destruction due to high localized shear forces generated with microbubble destruction. These studies, however, utilized ultrasound settings different from usual clinical situations.⁸ What these patients certainly represent are the typical cases in which intravenous contrast-enhanced echocardiography has been relied upon to provide diagnostic information important in providing optimal care. These 4 deaths were reported over a 6-year post-marketing surveillance period in which more than 2 million doses were administered, underscoring the vast and safe utilization of these agents in a variety of clinical settings. To place this in perspective and assuming intravenous contrast does represent a possible cause of death in these cases, the calculated mortality event rate would be approximately 1 in 500,000. This is an order of magnitude lower than the mortality risk of a standard treadmill exercise stress test, which has been estimated at 1 in 2,500 cases, and underscores the need

for better attempts to characterize the safety of drugs or diagnostic agents once approved for use.

Prior to the current alert, postmarketing surveillance monitoring for all ultrasound contrast agents had revealed adverse reactions such as nausea, flushing, paresthesia, abdominal pain (<1%–2%) and rare idiosyncratic hypersensitivity/allergic reaction. In some of these rare cases, bradycardia and hypotension prompted myocardial ischemia and infarction; however, no clear, direct evidence of cardiotoxicity was identified.⁹ Ultrasound agents used for cardiac indications do have a higher reported rate of adverse events. Definity, for example, in a manufacturer's pre-marketing surveillance trial of 1716 patients, carried an adverse event rate of 8.4%, with headache, dizziness, flushing, nausea, and back pain being the predominate symptoms. Eight deaths also had been noted in this survey; however, these occurred days after administration and were thought to be secondary to progression of underlying disease.¹⁰

The concerns regarding intravenous contrast agents fall under the mandate of the FDA "in protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products ...," with an especially reduced tolerance for agents that are diagnostic rather than therapeutic in use.¹¹ While these reported deaths should engender caution and review of the use of contrast in unstable patients, a recent article also noted that this focus on product safety does not take into account the important issue of how patient safety may be compromised by a reduction in diagnostic accuracy as a result of FDA actions.¹²

Relevance to the Cardiometabolic Syndrome

The cardiometabolic syndrome is a constellation of common disorders (insulin resistance, visceral adiposity, hypertension, and dyslipidemia) that increase a patient's likelihood for ischemic heart disease.^{13,14} The progression of this syndrome results in increased weight gain and metabolic derangement, leading to an increased burden of disease. Diagnostic imaging tests crucial for guiding therapy are more difficult to perform and may be less accurate in overweight and obese patients. Cardiac ultrasonography, in particular, which relies on image quality for accurate diagnosis, has utilized the advantages of contrast-enhanced endocardial definition for ejection fraction assessment, evaluation for apical thrombi, and stress test imaging.

Left Ventricular Thrombi

As shown in our case, contrast echocardiography can provide valuable information in the evaluation of patients with low ejection fractions or in the identification of complications post-myocardial infarction. Left ventricular thrombi must be excluded in these patients, and the current standard diagnostic test is transthoracic echocardiography. Unfortunately, near-field artifact, trabeculation, and poor endocardial definition can obscure apical thrombi in noncontrast echocardiography.¹⁵ Agents such as Optison and Definity improve the sensitivity and specificity of transthoracic echocardiography for detecting these abnormalities.¹⁶ In addition, contrast may help to detect complications from myocardial infarction, such as left ventricular aneurysm or rupture.¹⁷

Stress Testing

In patients with suspected coronary artery disease, stress echocardiography is an important diagnostic tool. Hemodynamic parameters alone (eg, heart rate and blood pressure responses) provide prognostic information. These data supplement the ischemic changes on electrocardiography and echocardiography discovered through stress. Echocardiographic detection of ischemia is currently a subjective assessment of wall motion that relies on the

quality of images obtained.¹⁸ Increased cardiac motion, increased respiratory rate, and interference from pulmonary structures can dramatically increase the difficulty of stress image interpretation. This is especially important in patients who are obese, in whom up to 30% of stress images may be nondiagnostic.¹⁹ Contrast echocardiography has been invaluable in improving the accuracy of this test. This is supported by a study conducted by Rainbird and associates²⁰ in which the percentage of wall segments visualized, the overall image quality, and the confidence of interpretation were better with contrast compared with noncontrast imaging at rest and at peak stress. In patients with obesity, in particular, the diagnostic accuracy of stress echocardiography has been shown to be increased with the addition of contrast enhancement.²¹ This reduces the need for additional testing and leads to improved patient care.²²

Heart Failure

Left ventricular ejection fraction is an important prognostic factor and also serves as an indicator of effectiveness of therapy in patients with heart failure.²³ Indication for cardiac resynchronization or defibrillator therapy is also determined primarily by ejection fraction.²⁴ Reproducible and accurate ejection fraction measurements are therefore vital to heart failure management. Noncontrast echocardiography often underestimates left ventricular volumes because the borders of the cavity are trabeculated and cannot be clearly visualized. Conversely, contrast delineates the true border and provides a clear tracing of the lumen, thus providing more accurate quantification of ejection fraction. Studies have shown that contrast-enhanced echocardiography is significantly superior to unenhanced imaging, especially in patients with poor acoustic windows.²⁵

Discussion

Contrast echocardiography represents a powerful tool for diagnosis of structural left ventricular abnormalities and determination of myocardial perfusion. The FDA has recently recommended a black box warning for newer perfluorocarbon contrast agents in response to 4 deaths temporally associated with contrast administration. The warning particularly pertains to use in unstable cardiac patients and recommends monitoring for at least 30 minutes after contrast administration. No clear evidence of a causative role for contrast agents in toxicity has been established, and risk for adverse events remains low.

The new black box warning and the recommendation for 30 minutes of monitoring after contrast administration have had a clear impact on contrast use in many patient groups, including those with the cardiometabolic syndrome. Cardiac imaging in this patient population remains challenging secondary to body habitus; however, echocardiography remains the most widely utilized imaging technology to help guide management of patients with the cardiometabolic syndrome. The use of contrast has been widespread, particularly where acoustic windows are poor, to optimize images acquired and improve diagnostic accuracy. Monitoring patients for 30 minutes after contrast administration has increased the difficulty for performance of echocardiography in many laboratories. Excluding patients with unstable cardiac disease has also limited the use of an important diagnostic modality.

Alternatives to 2-dimensional echocardiography for guidance in management of patients with the cardiometabolic syndrome are limited. Recent advances in ultrasonographic imaging, such as 3-dimensional echocardiography, are reliant on good acoustic windows for optimal image definition. Other modalities that have improved resolution, such as computed tomography and magnetic resonance imaging, are less available, subject the patient to ionizing radiation (in the case of computed tomography), and are not suitable for patients with unstable cardiac disease or patients who are morbidly obese. Discussions regarding the future use of contrast in diagnostic ultrasonography are ongoing. Diagnostic options and

optimal management for patients with the cardiometabolic syndrome are dependent on accurate assessment of left ventricular function, ischemia, thrombi, and other masses. Echocardiographic assessment of these are optimized by intravenous contrast use; however, this is now limited by the recent warning from the FDA. Continued evaluation of the risks and benefits of contrast enhancement is important for optimizing echocardiography-guided care of patients with the cardiometabolic syndrome.

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Figure 1.
(A) Initial apical image of the left ventricle without contrast and subsequent images (B and C) with contrast, detailing a protuberant thrombus attached to the distal septal segment near apex (arrows).

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Figure 2.
Black box warning from Definity package insert.