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iNEWS

NEWS AND VIEWS

Contrast Echocardiography: Past, Present, and...Future?

THE FOOD AND DRUG ADMINISTRATION (FDA) has recently changed labelling requirements for ultrasound contrast agents, to include a 'Black Box' warning and the recommendation to monitor vital signs, electrocardiography, and pO_2 saturation for 30 min following administration. The warning was a result of an investigation of serious cardiopulmonary reactions, including fatalities, associated with ultrasound contrast administration.

The history of contrast echocardiography dates back to 1968, when Gramiak and Shah first noted the echocardiographic appearance of bubbles in green dye injections. Commercial contrast agents became available in Europe in 1991 (Echovist, Berlex, Lachine, Quebec City, Canada) and in the U.S. in 1994 (Albunex, Mallinckrodt, St. Louis, Missouri), followed by second generation contrast agents (Optison [GE, Waukesha, Wisconsin], 1997, and Definity [BMS, Billerica, Massachusetts], 2001). Early adopting clinicians celebrated the use of contrast echocardiography in enhancing left ventricular borders in suboptimal studies, whereas scientists investigated their potential to quantify myocardial blood flow. An imaging technique that could simultaneously detect wall motion and measure perfusion was indeed the holy grail of coronary artery disease diagnostic testing. With growing use of these agents in academic and community echocardiography labs and a 2000 American Society of Echocardiography guideline touting that "the use of contrast enables acquisition of ultrasound images of improved quality. The technique is especially useful in…approximately 10% to 20% of routine echocardiographic examinations" (1), the future seemed close at hand indeed.

Unfortunately, echocardiography contrast agents have met several challenges. In November 2005, General Electric (GE) voluntarily recalled its agent, Optison, after a Food and Drug Administration (FDA) inspection raised concerns about manufacturing practices. In a consumer letter dated September 6, 2007, GE expressed "great pleasure" in announcing its return to the market in "September/October" (2), although the drug has yet to make its reappearance. In the meantime, the FDA has been investigating deaths associated with the use of Definity and issued a Black Box warning on October 12, 2007 (3). This labeling change states that "serious cardiopulmonary reactions, including fatalities have occurred during or within 30 min following Definity administration." The warning goes on to recommend monitoring of vital signs, electrocardiography, and in some patients phosphorus dioxide saturation, during and for 30 min after administration (4). A similar Black Box warning is required by the FDA when Optison returns to the market.

Although there is no doubt that the use of contrast enables acquisition of ultrasound images of improved quality, these setbacks in contrast agent safety are not the only problem. Over the years, adoption has been slower than expected, whether owing to initial low reimbursement or the "hassle factor" of an intravenous medication, and no agent has yet been approved for myocardial perfusion. No doubt, the recommendation for 30 min of monitoring could be difficult for busy echo labs to comply with, especially given recent cuts in reimbursement. However, adding it all up….is this simply a temporary setback for a clinically proven and widely valued technique, or is this the straw that will break the camel's back of contrast echocardiography?

What is the future for bubbles? We do realize that there will be a significant delay by the

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time this issue of *JACC: Cardiovascular Imaging* reaches you. We have therefore invited expert comments on this recommendation. What do they have to say? Would you share your opinion with us? We encourage you to visit *iJACC-iNEWS* in Cardiosource and tell us what you feel. The opinions presented below are entirely of the authors and do not reflect or express the position of the American College of Cardiology, *JACC: Cardiovascular Imaging*, or the editors.

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Will Contrast Survive?

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IN A RECENT RELEASE, the FDA reported 11 deaths after the administration of ultrasound microbubble contrast agent Definity (3). Four of the 11 deaths occurred within 30 min of injection: 1 patient died during a stress test, 2 patients had severe congestive heart failure, and the fourth was undergoing mechanical ventilation for respiratory failure. Although all complications are important, even this small number of cardiac deaths is particularly troubling. The mechanism by which the microbubbles might have caused these deaths is unclear. Microbubbles can potentially affect the heart by mechanical obstruction of the coronary vessels or cause direct cell damage when destroyed in high-intensity sound fields. Mechanical obstruction can occur when bubbles larger than capillary diameter are injected into the coronary circulation. In the case of Definity, however, the bubbles are generally smaller than the capillaries and should flow freely through the coronary circulation. Although a limited number of larger bubbles can be present in the overall distribution or injectate, they should be filtered out by the lungs. It is also possible that the contrast-containing microbubbles can dilute out the available red cells in areas of critically reduced perfusion, but the volume injected is small and further diluted by the flowing blood as it passes through the right heart, lungs, and left ventricle. The direct biological effects of contrast agents seem to be due to the destruction (inertial cavitation) of the microbubbles in high-intensity sound fields. Bubble destruction produces high-velocity fluid microjets that can penetrate adjacent membranes, leading to pore formation (sonoporation), secondary shock waves, transient high temperatures, and sheer stress. All of these effects are local, affecting only the area immediately surrounding the bubble. Although the specific combinations of contrast dose, ultrasound pressure, delivery mode, and duration of ultrasound exposure that produce bioeffects have been extensively studied in rodent models and rabbits, there are limited data in large animals or humans. Recently, Miller et al. (5) reported increased vascular permeability and cell death in open-chest canine experiments, but only after long exposure (10 min) to high mechanical index (relatively high intensity) scanning with a fixed plane. In a clinical study, Vancraeynest et al. (6) observed that combined exposure to an ultrasound contrast agent (PESDA) and prolonged high mechanical index ultrasound imaging resulted in a slight increase in cardiac biomarkers (troponin I measured in the coronary sinus at 3 and 15 min and creatine kinase-MB at 15 min), indicating microdamage to cardiomyocytes. In both of these studies, the acoustic power and duration of imaging were far beyond what would occur in a typical clinical scenario. Furthermore, these studies have generally been carried out in subjects with normal underlying circulation, and thus the effects in the setting of ischemia or significant left ventricular dysfunction remain to be defined. In addition, contrast agents can increase pulmonary artery pressure that might have accounted for the fatality in the patient with respiratory failure. Even without a specific mechanism, the fatal adverse events in unstable patients suggest that increased caution is appropriate.

What then will be the effect of the new product warning on clinical practice? First, it is important to remember that the actual risk associated with contrast is very small. These 4 deaths occurred on a background of approximately 2 million injections. Three deaths (patients with advanced coronary disease) have also been reported with another agent (SonoVue, Bracco, Italy) but none with Optison. Serious side effects occur more frequently (with the exact rate unclear for Definity but reported at 0.014% for SonoVue and ≤0.002% for Optison) (7). Second, whereas the current focus is on specific commercial products (such as Optison and Definity), many more contrast echo studies use simple agitated saline to detect right to left shunts in patients with stroke, transient ischemic attacks, hypoxia, or suspected pulmonary arteriovenous malformation. In our laboratory, for example, roughly 15% of all studies involve contrast; however, more than 80% of these studies use agitated saline contrast. Although we have been using this agent for more than 30 years and have never had a cardiac or other serious permanent complication, saline contrast will, on occasion, trigger a migraine headache, produce dizziness, or—rarely—cause a transient neurologic deficit. Thus, caution should be employed with all contrast injections, and it should be clear before doing the study that the result, if positive, would motivate some change in the therapeutic response. Finally, the new list of contraindications for Definity (and presumably all encapsulated microbubble contrast

Even without a specific mechanism the fatal adverse events in unstable patients suggests that increased caution is appropriate.

agents), including worsening or unstable heart failure, acute coronary syndrome, serious ventricular arrhythmias, respiratory failure, and severe pulmonary disease, and would preclude most applications in the intensive care unit/critical care unit. Likewise the recommendation that patients be monitored for 0.5 h after injection will limit use in portable studies on nonmonitored hospitalized patients and, in many laboratories will complicate outpatient studies. The use of contrast during stress studies would be easier, because patients are monitored during the study; this would only require extension of the post-procedure monitoring. These new warnings also raise the issue of informed consent. If this is deemed necessary it will further complicate many studies, because the need for contrast enhancement is only obvious after initial images are obtained, and it would then be necessary to find a physician to obtain the consent, again delaying the process. In the end, these new warnings do not preclude the use of contrast, particularly in situations where the information is important and is either not available in any other way or could only be obtained with tests that have their own inherent complications. They do, however, raise the level of awareness of potential complications and will likely further limit or delay the use of contrast in echocardiographic studies.

Action or Over-Reaction?

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ALTHOUGH "PRIMUM NON NOCERE" or "First, do no harm" is a basic tenet of the practice of medicine and reminds clinicians to do all to avoid unnecessary risks to patients, there are few drugs or medical procedures that are without risk. Even routine noninvasive diagnostic tests used in the daily practice of cardiovascular medicine or the contrast agents employed during cardiac imaging are associated with risk for major adverse effects (Table 1) (8–12). Still these tests are frequently performed, because in an individual patient, the potential benefit of the information they provide outweighs the risk of not knowing.

What ratio of risk-to-benefit for a diagnostic test is favorable enough to be considered acceptable by the medical community and society in general? Although difficult to answer, this question is important for the future of ultrasound contrast agents approved for use by the U.S. FDA (Definity and Optison). It was recently reported that the FDA had issued a "black box warning" for the use of 1 of these agents. Yet, insufficient information was provided by the agency to allow us, the clinicians who rely on the use of microbubble agents, to make reasonable decisions regarding their relative risk in the circumstances in which they might be used. Information has now been made available upon request from the manufacturer of Definity for us to judge (4).

This action against ultrasound contrast agents is not based on science and appears to be a result of political expediency by an agency that is keen to demonstrate it's willingness to get 'tough' with pharmaceutical companies.

Post-marketing surveillance after approximately 2 million administered doses of Definity indicates that the risk for serious adverse cardiopulmonary effects is approximately 1 in 10,000 cases. Most of these events are probably from non-immunoglobulin E–mediated or anaphylactoid reactions from local complement activation (13). It must be noted that this risk (0.01%) pales in comparison to approved liposomal drug formulations such as Doxil and amphotericin, which require higher lipid doses and are associated with up to 7% risk. (14,15). It is also much lower than the 1 in 500 risk for anaphylactoid reaction with ionic radiographic contrast agents (10).

Post-marketing surveys also detected 4 cardiopulmonary deaths (risk approximately 1 in 500,000) within 30 min of Definity administration. In 2 cases, the report claimed that death was likely unrelated to contrast administration. Both involved critically ill patients with heart failure who were in the intensive care unit, owing to decompensated condition. One of the 2 patients was on mechanical ventilation for bilateral pneumonia, was on multiple pressors, and had a large right ventricular thrombus. Autopsy demonstrated multiple pulmonary emboli. A third patient who also had severe ischemic heart failure and multiple comorbidities was also thought to have died from massive pulmonary embolism. The sole outpatient case was in a patient with ischemic cardiomyopathy, diabetes, and heart failure. Thirty minutes after contrast administration, an exercise stress protocol was initiated without contrast, and the patient suffered an arrhythmic arrest soon thereafter.

What lessons do we learn from this vital information? First and foremost, there was no causation established between injection of Definity and death. However, the FDA considers the 30-min interval to be important in separating potential causation from other reasons. In most of the 4 reported deaths there were alternative and much more likely explanations for cause of death according to the treating physician and/or post-mortem examination. Second, the risk of adverse cardiopulmonary effects reported with Definity is much lower than that for tests we routinely use in cardiology and deem to have an acceptable risk profile. For example, the various risk profiles depicted in Table 1 indicate that the outpatient death described in the previous paragraph was far more likely to be attributable to exercise stress rather than a contrast reaction.

So why are we permitted to continue exercise or dobutamine stress testing?

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Table 1. Major Adverse Events Associated with Common Cardiovascular Diagnostic Tests or Contrast Agents

Procedure	Adverse Event(s)	Risk
Exercise stress testing (8)	MI and death	1/2,500
Dobutamine stress testing (9)	MI or ventricular fibrillation	1/2,000
Iodinated radiographic contrast agents (10)	Potentially or immediately life-threatening reactions (cardiopulmonary and neurologic)	LOCM 2/1,000 HOCM 2/10,000
Transesophageal echocardiography (11)	Hypotension, cardiac arrest, pulmonary edema, laryngospasm	1/2,000
Diagnostic cardiac catheterization (12)	Death, MI, serious arrhythmia, neurologic event, vascular complication, contrast reaction	1/500

HOCM = high-osmolarity contrast media; LOCM = low-osmolarity contrast media; MI = myocardial infarction.

Why is there no outcry against the astounding growth of cardiac computed tomography when, according to the data from the American College of Radiology (16), the risk for serious, potentially life-threatening reaction with the high-osmolar contrast agents is 10 times higher than that for Definity? In all likelihood, the seemingly capricious action of the FDA against low-risk ultrasound contrast agents was the reaction of an agency that is "once bitten, twice shy." Recent high-profile post-marketing problems with drugs such as Vioxx (Whitehouse Station, New Jersey) and Avandia (GSK, Morrisville, North Carolina) have altered the FDA's tolerance for real or perceived risk. Ultrasound contrast agents are relatively new and not entrenched in clinical practice and thus vulnerable to FDA action. This action against ultrasound contrast agents is not based on science and seems to be a result of political expediency by an agency that is keen to demonstrate its willingness to get "tough" with pharmaceutical companies.

Let us return to the idea of risk versus benefit, with the focus on the latter. It is now indisputable that contrast agents have made a very positive impact on clinical care. However, these agents are now contraindicated in patients who benefit the most from having accurate assessment of regional ventricular function, such as those with worsening heart failure. Another contraindication is suspected acute coronary syndrome, a situation where these agents have been shown to provide critical diagnostic and prognostic information, particularly when the electrocardiogram is nondiagnostic and the initial troponin is negative (17). Now, these patients might be exposed to either the higher risk associated with immediate diagnostic cardiac catheterization or a delay in diagnosis until further serologic studies return.

In summary, the action by the FDA against ultrasound contrast agents has been based on post-marketing reports that, in reality, indicate a safety profile that is quite favorable compared with other alternative diagnostic tests. A balance must be reached by our regulatory agency. Warning and educating health care providers about previously unrecognized risks is an important and laudable goal. In this case, however, this stern and inappropriate overreaction has eliminated our ability to make reasonable decisions regarding appropriate use of ultrasound contrast agents, even on a case-by-case basis.

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