Thinking Outside the “Box”—
The Ultrasound Contrast Controversy

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On October 10, 2007, the U.S. Food and Drug Administration (FDA) announced a new “black box” warning for the perflutren-containing ultrasound contrast agents, contraindicating their use in patients with acute coronary syndromes, acute myocardial infarction, and worsening or clinically unstable heart failure. These warnings ignore the proven efficacy of ultrasound contrast agents, the previously established safety of these compounds, the potential risks of alternative procedures, and the likely confounding effect of pseudocomplication. We suggest that the FDA Medical Imaging Division convene a panel of cardiologists experienced in a variety of imaging modalities to fully assess the adverse events that have been attributed to these agents and that any future FDA warnings acknowledge the possible influence of pseudocomplication, the proven efficacy of the modality in question for early and accurate diagnosis of cardiovascular disease, and the known and theoretical risks of alternative testing that may be necessary. (J Am Coll Cardiol 2007;50:2434–7) © 2007 by the American College of Cardiology Foundation

On October 10, 2007, the U.S. Food and Drug Administration (FDA) announced a new “black box” warning for the perflutren-containing ultrasound contrast agents, contraindicating their use in patients with acute coronary syndromes, acute myocardial infarction, and worsening or clinically unstable heart failure (1). These warnings followed post-marketing reports of 4 patient deaths, which were temporally related, but not clearly causally attributable to, contrast injection. Although appearing prudent at face value, especially in light of the recent intense focus on patient safety, these strident warnings ignore the proven efficacy of ultrasound contrast agents, the previously established safety of these compounds, the potential risks of alternative procedures, and the likely confounding effect of pseudocomplication. To fully appreciate all this, some background is necessary.

Despite significant advances in ultrasound transducer design and signal processing technology (2), as many as 20% of echocardiographic examinations remain technically difficult, largely because of patient factors such as the existence of lung disease and obesity (3). In an effort to circumvent this problem, researchers developed ultrasound contrast agents (“microbubbles”) that were capable of transpulmonary passage after intravenous injection. In 1994, the first ultrasound contrast agent (Albunex® [MBI, San Diego, California], air-filled sonicated albumin microbubbles) was approved for human use in the U.S. (4–6). More recently, “second-generation” fluorocarbon-based agents Optison™ (GE Healthcare, Buckinghamshire, United Kingdom) (7) and Definity® (Bristol-Myers Squibb Medical Imaging, Billerica, Massachusetts) (8) were approved by the FDA after demonstrating superiority to Albunex® and placebo, respectively. Although Optison™ has not been marketed since 2005, Definity® is in widespread clinical use today, with $65 million in sales in 2006, and approximately 2 million patients dosed since product approval in 2001.

Significant safety data exist for these compounds. Dose-ranging studies have shown no changes in systemic or pulmonary hemodynamics, myocardial contractility, gas exchange, or regional myocardial blood flow even after 30 injections over the course of 10 min at doses capable of providing myocardial opacification (9). Large-scale Phase III studies of more than 1,700 patients leading to product approval revealed no safety concerns (7,8). Additionally, there is no defined mechanism for a toxic relationship. These agents act as true red blood cell flow tracers in the systemic circulation after intravenous injection (10) and, unlike the nuclear isotopes used in scintigraphic studies, do not require (or undergo) cellular uptake or mitochondrial metabolism; the fluorocarbon gas is excreted by the lungs within minutes. Additional characteristics contribute to their utility as echocardiographic contrast agents and...
limit the potential for bioeffects. Because of their high molecular weight, the fluorocarbon gases are insoluble in blood and do not readily diffuse across microbubble membranes (11,12). Additionally, because carbon-fluorine bonds are the tightest covalent bonds found in nature, perfluorocarbons are biologically inert.

The efficacy of echocardiographic contrast agents is not in question—multiple studies have established their utility in improving accuracy of stress echocardiography for the diagnosis of obstructive coronary artery disease (13–15) and in reducing health care costs by eliminating the need for additional testing (16). Contrast agents may be even more useful in nonstress studies. With candidacy for drug and medical device therapy in patients with acute myocardial infarction and heart failure now increasingly determined by physicians with the use of left ventricular (LV) ejection fraction partition values (17,18), accurate and reproducible determination of LV size and systolic function is paramount. Contrast administration improves the agreement of echocardiographically determined LV ejection fraction with reference techniques such as cardiac magnetic resonance and computed tomographic imaging (19–21), and reduces interobserver variability, even in patients with good baseline endocardial border delineation (22).

It is important to realize that complications occurring after any medical procedure may be attributable to the procedure itself or may be due to progression of the underlying disease state (“pseudocomplication”). Pseudocomplication was well defined for cardiac catheterization by Hildner et al. decades ago (23,24). These investigators examined “complications” that occurred from 24 h before to 72 h after a scheduled cardiac catheterization. They found an event rate of 0.81% (with 0.24% mortality) in the day before the procedure and an event rate of 0.81% (with no deaths) in the post-procedural interval. Thus, major cardiac events, including death, are relatively common in patients who are “sick enough” to warrant invasive cardiovascular testing. To our knowledge, such a study has never been performed in patients scheduled for echocardiography. What we do know is that echocardiography is the procedure of choice (and often the only diagnostic procedure possible) in critically ill patients; common inpatient indications for echocardiographic evaluation include “hypotension,” “shock,” “status post cardiac arrest,” and “tamponade.” It is important to differentiate between association and causation; without knowledge of the ambient event rate, any incremental risk of contrast agents (or any other intervention) cannot be known.

A review of the 4 cases in which patients died during or shortly after Definity® administration supports the possible role of pseudocomplication (1). Patient #1 was a 67-year-old man with an ischemic cardiomyopathy who experienced a cardiac arrest 1 min after beginning an exercise stress test (and 30 min after receiving Definity®). Patient #2 was an elderly man hospitalized in a cardiac intensive care unit with a recent myocardial infarction and severely reduced LV systolic function. Approximately 4 h after admission to the intensive care unit, he underwent contrast-enhanced echocardiography after first receiving a sedative for agitation. Shortly after completion of the echocardiogram, he suffered cardiac arrest. Patient #3 was a 70-year-old man with a history of coronary artery bypass grafting, heart failure, and deep venous thrombosis. He underwent echocardiography with contrast to evaluate worsening heart failure. Approximately 5 min after completion of the study, he became cyanotic and hypotensive and subsequently died. A massive pulmonary embolism was reported as the likely cause of death. Patient #4 was a 34-year-old morbidly obese woman (body weight >350 lbs) who was admitted to an intensive care unit for severe trilobar pneumonia. Her concomitant medical problems included postpartum cardiomyopathy. She required mechanical ventilation and multiple intravenous vasopressor agents. She arrested immediately after the injection of Definity®. A post-mortem examination revealed multiple pulmonary emboli and a large right ventricular thrombus.

Even if all of the reported events occurred as a direct result of contrast administration (which is unlikely, because a significant proportion must be attributable to pseudocomplication), this result would still indicate an approximate 1:500,000 risk of death based on events acknowledged by the FDA and manufacturer data on total patient doses since product approval. It is important to put this number in proper perspective. The mortality rate for diagnostic coronary angiography is approximately 1:1,000 (25), and the risk of myocardial infarction or death with exercise treadmill testing is approximately 1:2,500 (26). The lifetime risk of fatal malignancy after stress single-photon emission computed tomography or radionuclide ventriculogram examination is estimated at 1:1,000 to 1:10,000 (27,28). This latter risk is greatest in relatively young patients and in women but is generally ignored in the U.S. in part because of physician and patient ignorance regarding the biologic effects of ionizing radiation, but it also may be attributable to the lack of immediate risk. Despite these finite risks of serious complication, coronary angiography, exercise testing, and nuclear scintigraphic examinations are performed without trepidation, and with good reason—all allow early diagnosis and treatment of coronary artery disease, which remains the primary cause of death in the U.S.

What alternatives are available in patients with nondiagnostic transthoracic echocardiograms and concomitant ultrasound contrast agent contraindications? When LV systolic function is the principal clinical question, radionuclide ventriculography may be performed. This test is used in many centers for serial evaluation of LV size and systolic function in oncology patients receiving potentially cardiotoxic chemotherapeutic regimens. Given the significant risk
of a fatal secondary malignancy (27,28), which can only be heightened with repetitive studies, this alternative would seem to be a poor one. Additionally, nuclear testing is very difficult to perform at the bedside or in the critically ill. In most patients, transesophageal echocardiography will be the procedure of choice. Although a “minimally invasive” examination, serious complications, including laryngospasm (0.14%), hypotension (0.3%), hypoxia (0.3%), and death (0.01%), have been reported in a large series of patients (29). Additionally, the risk of esophageal perforation is 0.02% with flexible upper endoscopy (30). The risk of perforation with transesophageal echocardiography is likely significantly greater given the lack of direct visualization during intubation. Finally, methemoglobinemia occurring as the result of the application of topical lidocaine or benzocaine is increasingly being reported (31).

What will likely occur as a result of this latest FDA warning? If previous experience is any predictor, significant anxiety will be generated for both patients and health care providers. Perhaps personal injury lawyers will begin advertising for “injured” clients. In fact, even the requirement to monitor blood pressure and the electrocardiogram for 30 min after the procedure will have a chilling effect upon the use of contrast agents. Echocardiography laboratories are organized for rapid patient throughput for cost effectiveness and do not typically have facilities or personnel for prolonged monitoring of ambulatory patients. Given the absence of reported severe events and the safety record in ambulatory patients, the necessity and efficacy of such monitoring is surely questionable. Ultrasound contrast sales will certainly languish, likely forcing existing agents off the market, and discouraging future investment and innovation in new drug development.

What is our suggestion for resolving the controversy surrounding this decision? First, we believe the FDA Medical Imaging Division should convene a panel of cardiologists with and without experience in imaging modalities, including echocardiography, to fully assess the adverse events that have been attributed to Definity® and determine the most appropriate corrective action. At present, the Medical Imaging Division resides in the Office of Oncology Drug Products and may benefit from cardiology or cardiac imaging expertise in fully evaluating this issue. Medical imaging is the largest single contributor to Medicare costs; it would seem appropriate that evaluators with true cardiac imaging expertise help adjudicate the safety and efficacy of these modalities. Second, we recommend that any future FDA warnings acknowledge the possible influence of pseudocomplication, the proven efficacy of the modality in question for accurate diagnosis of cardiovascular disease, and the known and theoretical risks of alternative testing that may be necessary. Only then will physicians and patients possess the facts to make informed and rational choices in the selection of diagnostic tests.

REFERENCES


