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EXPEDITED PUBLICATION **Viewpoint**

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

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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.

Abbreviations and Acronyms

FDA = Food and Drug Administration

LV = left ventricular

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

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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.

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REFERENCES

1. New U.S. Food and Drug Administration prescribing information for Definity approved October 10th, 2007. Available at: http://www.fda.gov/cder/foi/label/2007/021064s007lbl.pdf. Accessed October 15, 2007.
2. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualization with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. Am Heart J 1999;138:163–8.
3. Mulvagh SL, DeMaria AN, Feinstein SB, et al. Contrast echocardiography: current and future applications. J Am Soc Echocardiogr 2000;13:331–42.
4. Geny B, Mettauer B, Muan B, et al. Safety and efficacy of a new transpulmonary echo contrast agent in echocardiographic studies in patients. J Am Coll Cardiol 1993;22:1193–8.
5. Feinstein SB, Cheirif J, Ten Cate FJ, et al. Safety and efficacy of a new transpulmonary ultrasound contrast agent: initial multicenter clinical results. J Am Coll Cardiol 1990;16:316–24.
6. Crouse LJ, Cheirif J, Hanly DE. Opacification and border delineation improvement in patients with suboptimal endocardial border definition in routine echocardiography: results of the Phase III Albunex Multicenter Trial. J Am Coll Cardiol 1993;22:1494–500.
7. Cohen JL, Cheirif J, Segar DS, et al. Improved left ventricular endocardial border delineation and opacification with OPTISON (FS069), a new echocardiographic contrast agent. Results of a phase III Multicenter Trial. J Am Coll Cardiol 1998;32:746–52.
8. Kitzman DW, Goldman ME, Gillam LD, Cohen JL, Aurigemma GP, Gottdiener JS. Efficacy and safety of the novel ultrasound contrast agent perflutren (Definity) in patients with suboptimal baseline left ventricular echocardiographic images. Am J Cardiol 2000;86:669–74.
9. Skyba DM, Camarano G, Goodman NC, Price RJ, Skalack TC, Kaul S. Hemodynamic characteristics, myocardial kinetics and microvascular rheology of FS-069, a second generation echocardiographic contrast agent capable of producing myocardial opacification from a venous injection. J Am Coll Cardiol 1996;28:1292–300.
10. Lindner JR, Song J, Jayaweera AR, Sklenar J, Kaul S. Microvascular rheology of Definity microbubbles after intra-arterial and intravenous administration. J Am Soc Echocardiogr 2002;15:396–403.
11. Porter TR, Xie F. Visually discernible myocardial echocardiographic contrast after intravenous injection of sonicated dextrose albumin microbubbles containing high molecular weight, less soluble gases. J Am Coll Cardiol 1995;25:509–15.
12. Porter TR, Xie F, Kricsfeld A, Deligonul U, Kilzer K. Reduction in left ventricular cavity attenuation and improvement in posterior myocardial contrast with higher molecular weight intravenous perfluorocarbon-exposed sonicated dextrose albumin microbubbles. J Am Soc Echocardiogr 1996;9:437–41.
13. Rainbird AJ, Mulvagh SL, Oh JK, et al. Contrast dobutamine stress echocardiography: clinical practice assessment in 300 consecutive patients. J Am Soc Echocardiogr 2001;14:378–85.
14. Vlassak I, Rubin DN, Odabashian JA. Contrast and harmonic imaging improves accuracy and efficiency of novice readers for dobutamine stress echocardiography. Echocardiography 2002;19:483–8.
15. Dolan MS, Riad K, El-Shafei A. Effect of intravenous contrast for left ventricular opacification and border definition on sensitivity and specificity of dobutamine stress echocardiography compared with coronary angiography in technically difficult patients. Am Heart J 2001;142:908–15.
16. Thanigaraj S, Nease RF Jr., Schechtman KB, Wade RL, Loslo S, Perez JE. Use of contrast for image enhancement during stress echocardiography is cost-effective and reduces additional diagnostic testing. Am J Cardiol 2001;87:1430–2.
17. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management Of Patients With Acute Myocardial

Infarction). Available at: www.acc.org/clinical/guidelines/stemi/index.pdf. Accessed November 14, 2007.
18. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guidelines update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task Force on Practice Guidelines/Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf. Accessed November 14, 2007.
19. Hundley WG, Kizilbash AM, Afridi I, Fatima F, Peshock RM, Grayburn PA. Administration of an intravenous perfluorocarbon contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: comparison with cine magnetic resonance imaging. J Am Coll Cardiol 1998;32:1426–32.
20. Thomson HL, Basmadjian AJ, Rainbird AJ, et al. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodeling measurements: a prospective; randomly assigned, blinded study. J Am Coll Cardiol 2001;38:867–75.
21. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. J Am Coll Cardiol 2004;44:1030–5.
22. Nayyar S, Magalski A, Khumri TM, et al. Contrast administration reduces interobserver variability in determination of left ventricular ejection fraction in patients with left ventricular dysfunction and good baseline endocardial border delineation. Am J Cardiol 2006;98:1110–4.
23. Hildner FJ, Javier RP, Ramaswamy K, Samet P. Pseudo complications of cardiac catheterization. Chest 1973;63:15–7.
24. Hildner FJ, Javier RP, Tolentino A, Samet P. Pseudo complications of cardiac catheterization: update. Cathet Cardiovasc Diagn 1982;8:43–7.
25. Johnson LW, Lozner EC, Johnson S, et al. Coronary arteriography 1984–1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. I. Results and complications. Cathet Cardiovasc Diagn 1989;17:5–10.
26. Stuart RJ Jr., Ellestad MH. National survey of exercise stress testing facilities. Chest 1980;77:94–7.
27. Picano E. Sustainability of medical imaging. BMJ 2004;328:578–80.
28. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. Circulation 2007;116:1290–305.
29. Seward JB, Khandheria BK, Oh JK, Freeman WK, Tajik AJ. Critical appraisal of transesophageal echocardiography: limitations, pitfalls, and complications. J Am Soc Echocardiogr 1992;5:228–305.
30. Dawson J, Cockel R. Oesophageal perforation at fibreoptic gastroscopy. Br Med J 1981;283:583.
31. Marcovitz PA, Williamson BD, Armstrong WF. Toxic methemoglobinemia caused by topical anesthetic given before transesophageal echocardiography. J Am Soc Echocardiogr 1991;4:615–8.