Ultrasound contrast agents capable of transpulmonary passage following intravenous injection have been commercially available since the 1990s. These agents are microbubbles, which are smaller than red blood cells and persist long enough (due to reduced rate of gas diffusion) to reach the left ventricle (LV).\(^1\)\(^3\) Ultrasound contrast agent applications included LV cavity opacification, enhancement of spectral Doppler signals and evaluation of myocardial perfusion at rest or post-stress.\(^3\) The commercially available second-generation ultrasound agents are approved by the US Food and Drug Administration (FDA) only for the enhancement of LV endocardial delineation in patients with baseline suboptimal examinations.\(^3\) There are currently two commercially available ultrasound contrast agents in the US: Optison\(^\text{TM}\) (perflutren protein-type A microspheres, GE Healthcare, Buckinghamshire, UK) and Definity\(^\text{®}\) (perflutren lipid microspheres, Lantheus Medical Imaging, North Bellirica).

**Efficacy of Ultrasound Contrast Agents**

Although tissue harmonic imaging has significantly enhanced the diagnostic quality of baseline transthoracic echocardiography,\(^6\) the increasing prevalence of obesity and lung disease has added an extra layer of challenge; at least 10–15% of echocardiograms are technically difficult or non-diagnostic despite the use of harmonic imaging. The proportion of non-diagnostic studies is significantly increased during stress echocardiography and in echocardiograms performed in the intensive care unit.\(^3\)

In non-selected patients, contrast-enhanced echocardiography leads to more accurate assessment of LV volumes and ejection fraction compared with magnetic resonance imaging.\(^8\)\(^,\)\(^9\) Even with the use of harmonic imaging, ultrasound contrast enhances accuracy and reproducibility in calculation of LV systolic function.\(^8\) In selected patients with excellent echocardiographic windows and adequate endocardial visualisation of all segments with harmonic imaging, the utilisation of contrast echocardiography reduces inter- and intra-reader variability in the assessment of LVEF.\(^7\)

In patients with abnormal LV systolic function undergoing evaluation for LV remodeling, the use of ultrasound contrast agents reduces reader variability and increases accuracy compared with harmonic imaging with computed tomography as a reference standard.\(^9\) In intensive care patients, the use of ultrasound contrast agents increases the diagnostic yield of both individual myocardial segment evaluation and overall LV function assessment, and should be considered in all patients with non-diagnostic studies.\(^5\) Contrast echocardiography also improves segmental evaluation during dobutamine stress echocardiography\(^10\)\(^,\)\(^11\) and in mechanically ventilated patients,\(^11\) leading to an increased diagnostic yield. Additionally, contrast-enhanced echocardiography reduces the downstream utilisation of alternative testing resources, making ultrasound contrast agents cost-effective for rest and stress imaging.\(^12\)\(^\text{-}^\text{15}\)

**Adverse Effects and Contraindications Based on Pre-marketing Studies**

In pre-marketing studies, Optison\(^\text{TM}\) was administered to 279 patients.\(^16\) Forty-seven patients (16.8%) reported at least one adverse event. Of these, one event was serious and required treatment with antihistamines for hypersensitivity manifestations of dizziness, nausea, flushing and temperature elevation. No deaths were reported during the clinical studies. Headache (5.4%) was the most commonly reported side effect. One thousand, seven hundred and sixteen patients received Definity in pre-marketing clinical trials.\(^17\) Of these, 144 (8.4%) had at least one treatment-related adverse reaction. There were eight deaths, which were attributed to underlying disorders. There were 11 other serious adverse events, including one hypersensitivity reaction with urticaria and pruritus; other patients experienced dizziness, chest pain, dyspnoea or back pain. Headache (2.3%) and back and renal pain (1.2%) were the most common side effects, and resolved spontaneously without treatment.

The use of ultrasound contrast agents is contraindicated in patients with right-to-left, bi-directional or transient right-to-left cardiac shunts that can allow microspheres to bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation, potentially resulting in microvascular occlusion and ischaemia. These agents should also not be injected intra-arterially or in patients who have a known hypersensitivity to perflutren. The use of Optison is also contraindicated in patients with an allergy to egg (albumin).

**US Food and Drug Administration Boxed Warning – October 2007**

In October 2007, the US FDA mandated labelling revisions for both commercially available perflutren-containing ultrasound contrast agents...
largely based on four reported deaths that were temporally related (but not clearly causally attributable) to ultrasound contrast agent injection. The labelling revisions included a ‘Boxed Warning’ highlighting the potential for “serious cardiopulmonary reactions”, new disease state contraindications including worsening or clinically unstable heart failure, acute myocardial infarction or acute coronary syndrome, serious ventricular arrhythmia or high risk for arrhythmia based on QT interval prolongation, and respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension. The FDA also mandated a 30-minute monitoring period for all patients following contrast agent injection.

Implications of the US Food and Drug Administration Warning

The FDA warnings and contraindications effectively restricted the use of contrast echocardiography in acutely ill patients; both published data and clinical experience indicated that these were the patients who were most likely to derive diagnostic benefit from the addition of an ultrasound contrast agent. Immediately following the October 2007 FDA product labelling changes, use of ultrasound contrast agents in the US decreased dramatically, with many medical centres discontinuing contrast echocardiography altogether.

Many echocardiographers were immediately critical of the FDA action, noting that there was no direct evidence for causality in the deaths reported in close temporal association to ultrasound contrast agent injection. Experts also noted the previously documented excellent safety profile of the commercially available agents, the possible confounding effect of ‘pseudocomplication’ (death or other adverse outcome due to progression of underlying disease and not diagnostic testing or therapeutic intervention) and the known increased risk of other more invasive testing (such as transoesophageal echocardiography), which would now be necessary in many patients.18,19 Within the past year, several large-scale safety studies have been published that have objectively defined the safety profile of ultrasound contrast agents in nearly 200,000 patients.

Recently Published Safety Data

In a research letter published in the Journal of the American Medical Association, Herzog reported on 16,025 patients on the Hennepin County database who received an ultrasound contrast agent. Optison was used in 3,051 studies and Definity was used in nearly 200,000 patients. In a large multicentre, retrospective analysis conducted by the American Society of Echocardiography (ASE),22 data on 78,383 contrast-enhanced studies were reported (66,164 Definity and 12,219 Optison), including ~10,000 critically ill patients hospitalised in intensive care units. In this study, there were only eight serious adverse events (0.01%), four of which were serious and secondary to an anaphylactoid reaction (0.006%); none of these occurred in the critically ill. There were no deaths attributable to ultrasound contrast agent use. These data were consistent with the very low serious adverse event rate in the Hennepin County database.20

Main et al. utilised the Premier Perspective Database, the nation’s largest inpatient drug utilisation database,21 to analyse mortality in 4,300,966 patients who underwent inpatient echocardiography with 58,254 contrast-enhanced studies.24 Short-term mortality rates (death on the day of or day following echocardiography) were similar in patients undergoing echocardiography with or without the use of an ultrasound contrast agent (1.06 versus 1.08%; p=0.613). Multivariable logistic regression analysis (correcting for case mix and clinical co-variates) revealed that patients receiving Definity were 24% less likely to die acutely compared with patients undergoing unenhanced echocardiography.24

Shaikh reported on 5,069 patients who underwent the stress echocardiography procedure; an ultrasound contrast agent was administered to 2,914 of these patients. A higher proportion of both inpatients and patients undergoing dobutamine stress had contrast-enhanced studies. Despite the fact that patients receiving an ultrasound contrast agent tended to be older and were more likely to have reduced LV systolic function, there were no deaths in the group receiving contrast. One uncomplicated acute myocardial infarction and one anaphylactoid reaction occurred in the contrast agent group (p=0.51). Thus, while ultrasound contrast agents were more likely to be used in older hospitalised patients with depressed LV systolic function, there was no increase in the rates of major adverse events.25

A second study evaluating the safety of ultrasound contrast agents during stress echocardiography was reported by the Cleveland Clinic. A series of 4,786 patients who underwent contrast-enhanced stress echocardiograms (2,022 with dobutamine stress and 2,764 with exercise stress) were compared with a control group of 5,012 patients matched for test year and type who did not receive an ultrasound contrast agent. There was no difference in serious adverse event rate,
death within 24 hours, cardiac arrest or sustained ventricular tachycardia between the contrast and non-contrast groups.\textsuperscript{27}

Based on these new data (either published or in press in 2008), it is reasonable to conclude that: serious adverse events consistent with anaphylactoid reactions occur in \textasciitilde1\texttimes10\textsuperscript{3} patient doses; there is no increased mortality in hospitalised patients undergoing contrast echocardiography compared with patients undergoing echocardiography without an ultrasound contrast agent, despite the fact that patients receiving an ultrasound contrast agent exhibit more co-morbidities and higher acuity of illness; and contrast administration is safe in stress echocardiography.

Subsequently, through FDA review of additional information received after October 2007, and in accordance with the findings of an FDA Cardio-Renal and Safety Advisory Committee meeting on 24 June 2008, the FDA determined that, in some patients, the benefits from the diagnostic information that could be obtained through the use of Definity or Optison may outweigh the risks for serious cardiopulmonary reactions, even among those patients at particularly high risk for these reactions.\textsuperscript{28,29}\textsuperscript{20} Although a ‘Boxed Warning’ continues to highlight the potential for “serious cardiopulmonary complications”, all of the disease state contraindications issued in October 2007 have been revised to ‘warnings’, and the post-contrast 30-minute monitoring period now applies only to patients with pulmonary hypertension and unstable cardiopulmonary conditions. The FDA also recently announced that both manufacturers (Lantheus Medical Imaging and GE Healthcare) have agreed to conduct two studies designed to further evaluate the safety of Definity and Optison that will include a large retrospective study using a hospital database to determine acute mortality in hospitalised patients undergoing echocardiography with and without an ultrasound contrast agent, and an invasive haemodynamic study to evaluate for changes in pulmonary artery pressure and resistance immediately following contrast agent administration.\textsuperscript{30}

\textbf{Conclusions}

The ‘Boxed Warning’ disease state contraindications and mandated 30-minute monitoring period issued by the FDA in October 2007 had a chilling effect on ultrasound contrast agent use in the US. Seven recently published studies have shown that: serious adverse events consistent with anaphylactoid reactions occur in \textasciitilde1\texttimes10\textsuperscript{3} patient doses; there is no increased mortality in hospitalised patients undergoing contrast echocardiography compared with patients undergoing echocardiography without an ultrasound contrast agent, despite the fact that patients receiving an ultrasound contrast agent exhibit more co-morbidities and higher acuity of illness; and contrast administration is safe in stress echocardiography. Based on these data and other considerations, the FDA recently revised product labelling for both agents, and clinicians can once again perform contrast echocardiography in those patients most likely to derive diagnostic benefit. Although these agents are ‘safe’, physicians and sonographers performing contrast echocardiography should be aware of the potential for a rare anaphylactoid reaction, and should be familiar with and have access to medications (most importantly epinephrine) to treat allergic-type reactions.

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