

Contrast echocardiography: Putting things into perspective – a Canadian Cardiovascular Society/Canadian Society of Echocardiography joint commentary

Robert Amyot MD FRCPC¹, Eric Yu MD Med FRCPC², George Honos MD FRCPC³,
Jonathan Choy MD FRCPC⁴, Greg Schnell MD FRCPC⁵, Howard Leong-Poi MD FRCPC⁶

In a recently published Canadian Cardiovascular Society/Canadian Society of Echocardiography Position Paper on Contrast Echocardiography in Canada, we reviewed the clinical diagnostic utility of ultrasound contrast agents (UCAs) in echocardiography (1). These agents are approved in Canada for left ventricular (LV) opacification in suboptimal echocardiograms to enhance endocardial borders and ventricular chambers, and assess regional wall motion. Despite improvements in the quality of echocardiographic imaging, an estimated 5% to 10% of rest echocardiograms and 20% to 30% of stress echocardiograms remain suboptimal (2-4). The use of UCAs improves diagnostic accuracy and contributes to a cost-effective pattern of care (3). In previous clinical studies, UCAs have been shown to be safe and effective in numerous circumstances such as improving the accuracy of qualitative assessment of global LV systolic function as well as quantitative assessment of LV volumes and ejection fraction, improving the accuracy and interobserver agreement of LV regional wall motion evaluation, increasing the reproducibility and interobserver agreement in stress echocardiography interpretation, and helping to define specific anomalies (myocardial rupture, pseudoaneurysms, intracardiac thrombi, aortic dissection, LV noncompaction, apical hypertrophic cardiomyopathy, etc) (1). UCAs enhance Doppler signals and have been used during transesophageal echocardiography for left atrial appendage thrombus detection and assessment of aortic dissection (1).

REGULATORY AND SAFETY CONCERNS

In October 2007, the United States (US) Food and Drug Administration (FDA) prompted a 'black box' warning to be added to the monograph of perflutren-based UCAs (5). Health Canada quickly followed by emitting a safety alert including similar considerations (6). On review of the available postmarketing safety data, the FDA raised significant concerns about the safety of perflutren-based UCAs. New rules markedly restricting the use of UCAs in clinical practice within the US were issued. Conditions precluding the use of these agents included acute coronary syndromes, acute myocardial infarction, and worsening or clinically unstable heart failure.

Review of cases

We have reviewed the four cases (5) of cardiac arrest that occurred within 30 min of UCA administration, which have caused particular concern and motivated the safety alert. The four cases were polymedicated, symptomatic patients with documented heart disease, significant impairment of LV systolic function and serious comorbidities.

One patient was intubated for concomitant, life-threatening pulmonary conditions and needed two pressor agents for hemodynamic support before UCA administration. A second patient with a history of diabetes and known ischemic cardiomyopathy experienced cardiac arrest during treadmill stress testing, 30 min after receiving a UCA during resting echocardiography. A third patient with recent myocardial infarction, very low ejection fraction, agitation and progressive clinical deterioration went into cardiac arrest a few hours after admission to a coronary care unit. A fourth patient with a history of myocardial infarction and triple coronary artery bypass graft surgery underwent echocardiography for worsening heart failure. He developed symptomatic hypotension and cyanosis, and experienced cardiac arrest. The suspected cause of death was massive pulmonary embolism. These four patients suffered a cardiac arrest within 30 min of UCA injection. However, in all cases, the cause of death was deemed unrelated to contrast administration by treating physicians.

Recently, a similar case occurred in a Canadian centre (personal communication), the details of which were forwarded to Health Canada. An elderly patient with previous myocardial infarction and other significant comorbidities underwent coronary artery bypass graft surgery, after a non-ST elevation myocardial infarction. The initial postoperative period was characterized by hemodynamic instability but the patient improved after a few days and was transferred to the ward. Ten days after the operation, the patient displayed increased shortness of breath, tachycardia, hypotension, rising white blood cell count and deteriorating renal function. Transthoracic echocardiography was performed, and a UCA was administered to assess LV systolic function because of suboptimal visualization of the endocardium. The patient was clinically stable during image acquisition and the contrast-enhanced echocardiographic images revealed an LV ejection fraction of less than 15%. The patient suffered a cardiac arrest 5 min after UCA administration. Autopsy results demonstrated severe dilation of both ventricular chambers, empyema and aspiration bronchopneumonia. The cause of death was believed to be unrelated to UCA administration.

DISCUSSION

While we should not ignore these incidents, it is impossible to conclude that there is a cause-effect relationship between UCA use and these fatal events. This is especially true in patients with severe cardiac conditions and significant comorbidities for whom a fatal cardiac

¹Hôpital du Sacré-Coeur, Montréal, Quebec; ²University Health Network, Toronto, Ontario; ³Centre Hospitalier Universitaire de Montréal, Montréal, Quebec; ⁴University of Alberta Hospital, Edmonton; ⁵Foothills General Hospital, Calgary, Alberta; ⁶St Michael's Hospital, Toronto, Ontario
Correspondence: Dr Howard Leong-Poi, 7-052 Bond Wing, St Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8.

Telephone 416-864-5201, fax 416-864-5571, e-mail leong-poi@smh.toronto.on.ca
Received for publication July 3, 2008. Accepted August 17, 2008

event may reflect disease progression and severity. Other experts within the field have also raised the issue of the confounding effects of 'pseudocomplication' in the interpretation of these adverse events (7). This is supported by mortality data from a recently published retrospective analysis (8) of 16,671 consecutive echocardiograms performed on hospitalized patients, demonstrating a similar, low (0.4%) mortality rate within 24 h of echocardiography, regardless of whether patients received (n=6196) or did not receive (n=12,475) a UCA during the study. In a similar retrospective study that was recently presented at the annual Scientific Session of The American College of Cardiology (9), investigators examined the clinical outcomes of 23,659 consecutive transthoracic and stress echocardiograms that used UCAs, compared with approximately 6000 studies that did not use UCAs. No deaths or serious adverse events occurred within 30 min in the group that received UCAs. At 24 h, there were three nonfatal myocardial infarctions and one death in the contrast-agent group, none of which were attributed to UCA use. This was compared with seven nonfatal myocardial infarctions and one death in the 6000 patients who did not receive contrast agents. From the numbers stated in the FDA alert, the incidence of death associated with UCAs is less than one in 200,000 patients, and the risk of serious adverse reactions is one in 10,000 patients. Of course, because these serious events occurred after a review of the post-marketing safety data of perflutren-based UCAs, there is a potential for bias due to under-reporting. However, an underestimation seems less likely in the case of rapid onset (within 30 min of administration), fatal events such as those that prompted the UCA safety alert from regulatory agencies.

There have been a total of 9500 doses of Definity (Lantheus Medical Imaging, USA [formerly Bristol-Myers Squibb Medical Imaging, USA]) sold in Canada and over 2,000,000 in the US since its introduction in 2001 (Bristol-Myers Squibb Medical Imaging, personal communication). Optison (GE Healthcare, USA), the other perflutren-based agent included in the FDA alert, is not marketed in Canada. We have all previously used these agents in hospitalized patients with unstable clinical conditions such as acute myocardial infarction, decompensated heart failure, cardiogenic shock and mechanical ventilation for respiratory failure, which are conditions that preclude the use of UCAs under the October 2007 updated product monograph in the US. Echocardiography remains the imaging test of choice to assess cardiac structure and function in these unstable patients with severe medical conditions because of its clinical utility, wide availability, safety and portability. Unfortunately, these echocardiograms are more likely to be nondiagnostic due to poor visualization of the LV endocardium. In these patients, the use of UCAs improves the diagnostic yield of echocardiography and provides important information on ventricular function that referring physicians require for adequate management (10). The inability to use UCAs has the potential to adversely affect patient care. Other diagnostic tests that may be pursued, such as cardiac magnetic resonance imaging, cardiac computed tomography and cardiac catheterization, are less widely available, more expensive, require transportation of these potentially unstable patients and have their own inherent risks. Thus, in our experience, UCAs have been a safe, clinically useful and valuable tool in the practice of echocardiography in Canada.

As physicians, the safety of our patients remains the number one priority; therefore, we take this safety alert very seriously. However, optimal care involves balancing the possible risks to the patient with the expected value of any diagnostic procedure on guiding subsequent medical management. Every day, Canadian physicians are faced with decisions that impact patient lives. We carefully consider both the risks and benefits on an individual basis when ordering any diagnostic test. For example, diagnostic coronary angiography carries a risk of myocardial infarction, stroke or death of one in 1000 that must be weighed against the value of determining the presence and the extent of coronary artery disease (11,12). Moreover, a mere transesophageal echocardiogram, a logical complement to many nondiagnostic transthoracic exams, carries a risk of death of one in 10,000 (13).

The October 2007 product monograph updates had an immediate impact on the practice of echocardiography. In response to the FDA alert, cardiologists and echocardiographers made an impassioned plea to the FDA to systematically review the previous and recent evidence of contrast efficacy and safety, and to reconsider the black box warning. In Canada, we also made an appeal to Health Canada to provide rational and balanced regulations for the use of UCAs. Based on available evidence, we believe that while monitoring is always advisable in symptomatic, hospitalized patients with cardiac disease regardless of whether they are undergoing UCA studies, the use of routine cardiac monitoring in stable, ambulatory cardiac patients, and especially those without a history of cardiac disease, is questionable. In addition, as physicians, we would like the opportunity to continue our practice of assessing the risks and benefits of a contrast echocardiographic study, even in unstable patients in whom the benefits of the improved diagnostic yield of echocardiography using UCAs may outweigh the extremely low risks associated with the administration of these agents. Our intent is not to ignore the potential risks of these agents. Thus, we have suggested establishing a registry of patients undergoing UCA studies that will closely track echocardiographic contrast use in our patients, and prospectively monitor for serious adverse reactions. A similar registry is planned within the US. Furthermore, we have proposed a multicentre outcomes study in Canadian patients who receive UCAs, to further define the benefits and potential risks of their use. In this fashion, we can accurately establish the true safety profile and inherent risks of these agents in contemporary clinical practice.

SUBSEQUENT EVENTS

In an unprecedented move, and after much discussion with physician groups, the FDA revised the black box warning on UCAs in April 2008 (14). Many of the contraindications, such as acute coronary syndromes, myocardial infarction and clinically unstable heart failure, have been removed and placed into the warnings section. In addition, the requirements for monitoring are now only restricted to patients with pulmonary hypertension and unstable cardiopulmonary conditions, who likely should be monitored regardless of UCA administration. According to the revised US labelling, the current contraindications to Definity use are known or suspected right to left shunt (further details are not specified, but are unlikely to include patent foramen ovale), hypersensitivity to perflutren and intra-arterial injection. In May 2008, a letter from Lantheus Medical Imaging (formerly Bristol-Myers Squibb Medical Imaging) in consultation with Health Canada was released on Health Canada's Web site, announcing a similar amendment in Canada (15).

At the recently completed Annual Scientific Sessions of the American Society of Echocardiography 2008 in Toronto, Ontario, an open forum discussion was held with key panel members from the FDA. At the conclusion of the session, commitments were made to continue open dialogue between involved parties, with ongoing monitoring of UCA use, both regarding the efficacy and safety of UCAs in clinical practice. The corresponding response from Health Canada and their proposed changes to the product monograph are expected very soon.

SUMMARY

The extremely low risks associated with UCAs and their proven benefits must be weighed against the risks and benefits of alternative diagnostic modalities. Rather than restricting the use of contrast echocardiography, insisting on its proper use would have seemed more appropriate if there was any biological plausibility between the five fatal events and UCAs. The recent change in the FDA's stance on the use and safety of UCAs reflects this approach, and is a step in the right direction. Finally, prospective studies are needed to differentiate between causality and fortuitous association, and clarify the link between contrast echocardiography and the extremely rare

occurrence of catastrophic events that, as of yet, were strictly described in patients with severe cardiac conditions and severe associated comorbidities.

DISCLOSURES: Robert Amyot has received honoraria and consultant fees from Bristol-Myers Squibb Medical Imaging/Lantheus Medical Imaging. Eric Yu has received honoraria from Bristol-Myers Squibb Medical Imaging and research grant support from Acusphere. George Honos has no conflicts to disclose. Jonathan Choy has received honoraria from Bristol-Myers Squibb Medical Imaging. Greg Schnell has received honoraria from Bristol-Myers Squibb Medical Imaging. Howard Leong-Poi has received honoraria and research support from Bristol-Myers Squibb Medical Imaging/Lantheus Medical Imaging and consultant fees from Point Biomedical.

REFERENCES

1. Honos G, Amyot R, Choy J, Leong-Poi H, Schnell G, Yu E. Contrast echocardiography in Canada: Canadian Cardiovascular Society/Canadian Society of Echocardiography position paper. *Can J Cardiol* 2007;23:351-6.
2. Marwick TH, Nemic JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting. *J Am Coll Cardiol* 1992;19:74-81.
3. Shaw LJ. Impact of contrast echocardiography on diagnostic algorithms: Pharmaco-economic implications. *Clin Cardiol* 1997;20(Suppl 1):I39-48.
4. Mulvagh SL, DeMaria AN, Feinstein SB, et al. Contrast echocardiography: Current and future applications. American Society of Echocardiography Task Force on Standards and Guidelines for the Use of Ultrasonic Contrast in Echocardiography. *J Am Soc Echocardiogr* 2000;13:331-42.
5. New U.S. Food and Drug Administration prescribing information for Definity, approved October 10, 2007. <<http://www.fda.gov/cder/foi/label/2007/021064s007lbl.pdf>> (Version current at October 1, 2008).
6. Health Canada. drugs and health products: Advisories, warnings, and recalls, October 19, 2007. <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/definity_hpc-cps_e.html> (Version current at January 27, 2008).
7. Main ML, Goldman JH, Grayburn PA. Thinking outside the "box". The ultrasound contrast controversy. *J Am Coll Cardiol* 2007;50:2434-7.
8. Kusnetzky LL, Khalid A, Khumri TM, Moe TG, Jones PG, Main ML. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: Results in 18,671 consecutive studies. *J Am Coll Cardiol* 2008;51:1704-6.
9. Dolan MS, Dodla S, Xie F, Cloutier D, Porter T, Labovitz AJ. Safety and efficacy of commercially available ultrasound contrast agents in a clinical setting. *J Am Coll Cardiol* 2008;51(Suppl 1):409-7.
10. 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.
11. Klinke WP, Kubac G, Talibi T, Lee SJ. Safety of outpatient catheterization. *Am J Cardiol* 56:639-41.
12. Noto TJ, Johnson LW, Krone R, et al. Cardiac catheterization 1990: A report of the registry of the society for cardiac angiography and interventions (SCA&I). *Cathet Cardiovasc Diagn* 91;24:75-83.
13. Seward JB, Khandheria BK, Oh JK, Freeman WK, Tajik AJ. Critical appraisal of transesophageal echocardiography: Limitations, pitfalls, and complications. *J Am Soc Echocardiogr* 1992;5:288-305.
14. New U.S. Food and Drug Administration prescribing information for Definity, approved April 8, 2008. <<http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4369b1-02.pdf>> (Version current at October 1, 2008).
15. Health Canada. Drugs and health products: Advisories, warnings, and recalls. <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/definity_hpc-cps_2-eng.php> (Version current at October 1, 2008).