REVIEW ARTICLE

Safety of ultrasound contrast agents: “Primum non nocere”?

Bernard COSYNS¹, MD; Agnès PASQUET², MD, PhD; Guy VAN CAMP¹, MD, PhD; Sophie HERNOT¹, MS; Steven DROOGMANS¹, MD; Philippe UNGER³, MD, PhD; Johan DE SUTTER⁴, MD, PhD; Patrizio LANCELLOTTI⁵, MD, PhD

On behalf of the Belgian Working Group on Non-Invasive Cardiac imaging

¹UZ Brussel, Cardiology and ICMI, Free University of Brussels; ²Cliniques universitaires Saint-Luc, Université Catholique de Louvain; ³Cliniques universitaires Erasme, Free University of Brussels; ⁴AZ Maria Middelaers, University of Gent; ⁵CHU Sart Tilman, University of Liege, Belgium.

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Historical background

Diagnostic ultrasound contrast agents (UCA) are mainly indicated to enhance endocardial border delineation in patients with technically difficult echocardiographic examinations¹.

They have proven to increase the accuracy and reproducibility of regional and global left ventricular (LV) function assessment at rest²⁻⁴ and during stress^{5,6}. UCA are also used for qualitative or quantitative determination of myocardial blood flow⁷, to increase the intensity of Doppler signals. New therapeutic and diagnostic applications, such as drug delivery system and molecular imaging, are now emerging⁸. In Belgium, UCA are refunded when ultrasound echocardiography without a contrast agent is not conclusive in the following applications: (i) At rest, when the quality of images obtained without contrast agent makes the visualization of at least 5 contiguous segments of a total of 17 not conclusive, and, (ii) during stress when the quality of the images obtained without contrast agent makes the visualization of at least 2 contiguous segments of a total of 17 not conclusive. The segmentation of the left ventricle is based on the recommendations of the American Heart Association. The examinations

will be conducted by devices with software for harmonic imaging with a low mechanical index less than or equal to 0.3, allowing the mandatory digital archiving of images before and after contrast. Evidence showing that the above conditions are met, must be held available to the insurer by the medical provider. For echocardiography, the documents would be subjected to peer review.

Although, UCA still account for a small proportion of diagnostic examinations⁹, it was estimated that in 2006, 1 million diagnostic examinations with UCA were performed and that by the end of 2007, Definity[®] (the European name is Luminity[®]) has been administered to approximately 2 million patients since approval in 2001^{9,10}. In cardiac applications, the reporting of some adverse events after UCA has led to some restriction imposed by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). A post-marketing analysis of 157,838 studies of Sonovue[®] (Bracco, Milan, Italy) reported 19 cases of severe, non-fatal (0.012%) and three cases of fatal adverse events (0.002%) after the use of this contrast agent¹¹. Based on these data, EMA recommended not to use Sonovue[®] in cardiology in May 2004. These recommendations were partly reversed in November 2004 but there are still some restrictions (exclusion of patients with acute coronary syndromes and unstable heart disease) to the infusion of Sonovue[®]¹². In a similar way, post-marketing analysis from the U.S. reported 10 deaths after the administration of Definity[®] (Bristol-Myers Squibb Medical Imaging, North

Address for correspondence: Bernard Cosyns, MD, Division of Cardiology, In vivo cellular and molecular imaging (ICMI) centre, UZ Brussel, Vrije Universiteit van Brussel, Laarbeeklaan, 101, B-1090 Brussels, Belgium. E-mail: bcosyns@skynet.be

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Billerica, Massachusetts, USA) and 1 after the administration of Optison® (Amersham Health, Amersham, UK). At least 6 of these occurred 1 to 12 hours after dosing and were attributed to serious underlying conditions and/or other medications. Four fatal cases, however, occurred less than 30 minutes after the administration of Definity®: 1 after a stress test, 2 in patients with severe heart failure, and 1 in a ventilated patient with severe respiratory failure, sepsis, and multiple pulmonary emboli. These 4 deaths occurred over a 6-year period. In October 2007, the FDA issued an alert requesting “black-box” warnings on the perflutren-based ultrasound contrast agents Definity® and Optison®. Additionally, the FDA recommended that these agents “be contraindicated in patients with unstable cardiopulmonary status, including patients with unstable angina, acute myocardial infarction (AMI), respiratory failure, or recent worsening congestive heart failure”¹³. In May 2008, several contraindications were removed by the FDA, and replaced by warnings on the use of UCA. FDA has continued to highlight the risk of serious cardiopulmonary reactions during or within 30 minutes following the administration of these products and recommended that high-risk patients with pulmonary hypertension or unstable cardiopulmonary conditions be closely monitored during and for at least 30 minutes post administration of these contrast agents¹⁴.

Potential side effects of UCA

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”).

ANAPHYLACTOID REACTIONS

This hypersensitivity reaction is non IgE-mediated and does not require prior sensitization. It can decrease in severity or even disappear with subsequent administration¹⁵. It occurs relatively frequently with liposomal drugs (up to 7%). The mild forms are associated with palmar erythema and back pain, the severe forms are associated with hypotension, bronchospasm and/or hypoxaemia. It can be mediated by both complement activation and thromboxane release¹⁶. Serious central nervous system reactions, including seizures, seizure-like reactions, and altered consciousness, have also been reported rarely and may or may not be associated with immediate hypersensitivity reactions. Lipid particles are likely to produce this C activation-related pseudo allergy-like syndrome (CARPA). The factors influencing CARPA are the surface charge, the lipid dose, the size (surface area), the presence of non-ionic polymer at surface (polaxamer, PEG) and the presence of pre-

formed anti-lipid antibodies. All the microbubbles (lipid, polymeric, albumin) have the potential to activate complement on their surface. Most commercially available lipid microbubbles possess a net charge and have been designed with non-ionic polymers on their surface (polaxamer, PEG). A CARPA-like syndrome can occur, but it is rare (1/10,000) and it is unknown if it is causally related to any of the reported deaths. The treatment in adults is epinephrine, beta2-agonists, antihistaminic drugs and methylprednisone 125 mg intravenously for late reaction.

UCA BIOEFFECTS

Bioeffects of UCA combined with ultrasound exposure are now well documented as time varying pressure and microcavitation. It also generates heat, shear stress, produces oxygen radicals and haemolysis. UCA may induce sonoporation, capillary rupture, erythrocyte extravasation and endothelial cell damage¹⁷⁻²¹. All these effects are dose-dependent and are related to microbubble shell composition, the frequency of insonification, the power of the ultrasound beam and the duration of exposure. In animals, it has been shown that these bioeffects may induce transient decrease in LV systolic function, aggregation, coalescence, lodging, ventricular arrhythmias and microvascular injury²²⁻²⁴.

Clinical significance of bioeffects

In animal studies, in conditions never met in humans, high ultrasound energy (no tissue attenuation), prolonged duration of insonification and high microbubble concentrations are examples of the exaggeration of UCA adverse events.

In clinical studies, ventricular premature beats were previously reported with the use of UCA but this was not confirmed in other studies^{25,26}. Some authors did not find clinically relevant increases in serum markers for myocardial necrosis, inflammation and oxidative stress after contrast echocardiography²⁷. More recently, another group observed subtle changes in biomarkers after contrast echocardiography in humans. They found a significant increase in the arterio-venous difference (coronary sinus versus arterial level) of troponine I only in those patients with prolonged exposure to high mechanical index (MI) of 1.5 intermittent imaging and with the use of PESDA (home made Perfluorocarbon-enhanced Sonicated Dextrose Albumin)²⁸. Tissue Doppler imaging is considered as a very sensitive technique to diagnose even small subclinical alterations of LV systolic and diastolic function. No abnormalities of regional deformation parameters were observed after UCA infusion, using this technique⁵.

Recent retrospective studies have shown safety of contrast using various UCA (Definity[®], Optison[®] and Sonovue[®]) and machine settings (left ventricular opacification or low power imaging) at rest and during stress²⁹⁻³². A study in the United States included 963 patients receiving Optison[®] and 523 receiving Definity[®] during stress echocardiography and analysed adverse cardiovascular and pulmonary effects. The incidence of side effects did not significantly differ among the 3 groups (Optison[®], Definity[®], and no contrast)³³. More recently, Dolan et al. retrospectively analysed 42,408 patients at 3 different institutions who had baseline suboptimal images and/or underwent myocardial perfusion imaging and received contrast agents; 18,749 of these underwent stress echocardiography. No deaths or acute myocardial infarction (AMI) were observed within 30 min; 1 death and 5 nonfatal AMI were observed within 24 h. This was not different from a matched cohort of 15,989 patients who did not receive UCA. At 1 h and at 30 days after contrast administration, no significant differences in death rates or AMI were observed between patients who did or did not receive contrast during their stress echocardiogram³⁴.

Therefore, clinical evidence shows that contrast echocardiography is rather safe in practice.

Relevance of potential side effects in clinical practice

Everyone using UCA should be ready to recognize and to treat the potential side effects of these agents. It is now recommended that patients should be closely monitored for hypersensitivity reactions and diagnostic procedures should be carried out under the direction of a physician experienced in the management of hypersensitivity reactions, including severe allergic reactions, which might require resuscitation. Importantly, additional monitoring of vital signs, electrocardiography, and cutaneous oxygen saturation (for 30 minutes) is not required in all patients but should be limited to patients with pulmonary hypertension or unstable cardiopulmonary conditions.

Until definite data become available, it is prudent to use the minimum effective dose of contrast at the lowest possible MI (<1.0) and to minimize the amount of ultrasound exposure. However, when perfusion data are needed, flash imaging with transient high MI or high MI with ECG-triggering have been shown to be safe at rest and under stress conditions. A dose-response relationship has been described for agents that can cause CARPA³⁵, and because a bolus injection may expose the bloodstream to a more sudden influx and a higher concentration of microbubbles, it may be more likely to induce a severe allergic reaction than a diluted infusion. Although there is no evidence to confirm this hypothesis, it is recommended to use diluted infusion.

The balance of risk to benefit

RISKS WITH OTHER DIAGNOSTIC PROCEDURES

Thus, the fatal event rate with UCA was approximately 1/500,000. Other non-invasive tests are not without small but definite risks. The fatal event rate of a treadmill exercise test is 1/2500³⁶ or is 1/10,000 with a transoesophageal echocardiogram³⁷.

Patients receiving gadolinium-based contrast media during magnetic resonance imaging have been shown to develop urticarial rash (0.04%) and anaphylactoid shock (0.01%)³⁸. The mortality from single-photon emission computed tomography is reported 0.05%³⁹, and the mortality from coronary angiography 0.03% to 0.26%⁴⁰ combined with other peripheral vascular and cerebrovascular morbidities.

THE CRITICALLY ILL PATIENT

Although UCA have proven utility in the diagnosis and management of critically ill patients⁴¹⁻⁴⁴, concern persists regarding the safety of these compounds, particularly in these patients. Recently published single-centre data demonstrated no increased mortality in hospitalized patients undergoing echocardiography with UCA in comparison with patients undergoing noncontrast-enhanced examinations⁴⁵. These findings were recently corroborated in large multicentre cohorts^{30,46}. Additionally, multivariate logistic regression modelling demonstrated a significantly lower risk of mortality in the UCA group compared with the no contrast group (24% decreased risk), a finding that may be surprising given recent safety concerns⁴⁶. In a recent prospective study performed early after AMI, administration of echo contrast did not induce any significant change in vital signs, physical examination, or ECG. There were no serious adverse events, and minor events occurred only in five patients⁴⁷.

THE RISK OF MISSING AN IMPORTANT DIAGNOSIS WITHOUT UCA

Considering the critical issue of left ventricular rupture (LVR) with pseudoaneurysm formation after ST-elevation AMIs, there are approximately 500,000 ST-elevation AMIs in the U.S. annually, of which 1% to 6% involve LVR⁴⁸. Free wall rupture may result in pseudoaneurysm, whereby the extravasation of blood into the pericardial space is prevented by adherence of the parietal pericardium to the underlying epicardium. A prompt surgical correction is always indicated for pseudoaneurysm to prevent rupture¹⁰. The sensitivity of transthoracic echocardiography for the diagnosis of left ventricular (LV) pseudoaneurysm is only 26%,

often because of inadequate imaging windows or failure to obtain a good tomographic view⁴⁹. However, the appearance of an intravenous contrast agent in the pericardial space is not dependent on tomographic slices and is diagnostic of LV pseudoaneurysm⁵⁰. In a study by García-Fernández et al., UCA were used for the diagnosis of LV pseudoaneurysm in 19 cases. In thirteen of them, contrast was required to make the diagnosis whereas in 4 other patients, the diagnosis was suspected by noncontrast echocardiography but confirmed by contrast administration. In the two remaining patients, suspected LV pseudoaneurysm was ruled out by contrast echocardiography, thereby preventing unnecessary emergency operations⁵¹. On the other hand, UCA frequently result in the diagnosis of LV apical thrombus in AMI, which is a major risk factor for death or stroke⁵². In other circumstances, the addition of contrast agents results in potentially lifesaving changes in therapy especially in critically ill patients with hypotension, heart failure, or respiratory failure^{43,44}. Therefore, in most of these circumstances, the benefit of UCA far outweighs their risks.

Future perspectives

With suboptimal image quality, using contrast echocardiography appears to be indicated. UCA echocardiography also provides important information about myocardial perfusion. The prognostic significance of myocardial contrast echocardiography has been demonstrated^{53,54}. However, the net clinical benefit of a more accurate assessment of the LV early after AMI with UCA echocardiography remains to be determined. Multi-centre randomized studies are ongoing to demonstrate how myocardial contrast echocardiography can change patient management early after AMI. A registry of patients who received a contrast agent within 24 h after myocardial infarction or other conditions of clinical instability is also required in order to achieve a revision of the contraindications of Sonovue®.

To some extent, the UCA bio-effects may open opportunities for therapeutic applications⁸. However, the overlap between toxic and therapeutic effects of UCA remains unclear, and should be established. Recent experiments indicate that ultrasound exposure parameters can be optimized for therapeutic applications⁵⁵.

In summary, warning and educating health care providers about previously unrecognized risks is important but clinical evidence shows that contrast echocardiography is safe in practice. Applying the principle "First do not harm", the benefit of UCA far outweighs their risks in most circumstances.

Conflict of interest: none to declare.

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