Bio-effects of ultrasound contrast agents in daily clinical practice: fact or fiction?

Guy Van Camp*, Steven Droogmans, and Bernard Cosyns

Department of Cardiology, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium

This editorial refers to ‘Release of cardiac bio-markers during high mechanical index contrast-enhanced echocardiography in humans’ by D. Vancraeynest et al.,

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Ultrasound contrast agents (UCAs), delivered as peripheral venous injections, have been developed to enhance the ultrasound image quality. The current application, recognized by the FDA and European Medicines Agency (EMEA) is the enhancement of the left ventricular endocardial border or left ventricular opacification (LVO). These microbubbles with a diameter and an intravascular velocity similar to red blood cells travel through the myocardial capillaries and enable us to visualize myocardial perfusion during myocardial contrast echocardiography (MCE).1 These agents are also used to quantitate myocardial perfusion most of the time, especially for research purposes.2,3

Like all other contrast agents used in medicine, adverse events can also occur with UCAs.4 Allergic reactions though important are inherent to the use of contrast agents. Their existence, although sometimes very serious (anaphylactoid reactions), imply that the use of UCAs in clinical practice can only be supported if the additional diagnostic information is clinically relevant enough for patient management. The UCAs can only be used by experienced hands and in an environment where facilities for emergency care are immediately available.

Above all the previously mentioned ‘acceptable’ adverse events for a contrast agent, two major observations have questioned the safety of UCAs. First, the concomitant use of contrast agents and ultrasound leads to bio-effects demonstrated in experimental studies. Second, post-marketing analysis of 157 838 studies of Sonovue® brought to light 19 cases of severe non-fatal (0.012%) (strong relationship with UCAs) (18 of 19 were anaphylactoid or vasovagal reactions) and three cases of fatal adverse events (0.002%) (causal relationship uncertain).5 For the first time, Vancraeynest et al.6 showed that MCE can cause sub-clinical release of bio-markers in humans. This observation could be the missing link between the demonstrated in vitro bio-effects of UCAs and some of the clinically reported adverse events with Sonovue®. What are the facts? What has been demonstrated in vitro in animals and in humans?

UCAs contain microbubbles with a diameter of <5 μm, filled with a perfluorocarbon gas, and surrounded by a shell. Because of these characteristics, they can pass through the pulmonary capillary filter. Due to their acoustic properties, they considerably enhance the backscattering capabilities of blood, thereby imaging the cavity of the left ventricle and also the myocardium. Once they travel into the ultrasound field, they oscillate. These oscillations can result in linear backscatter at low acoustic pressure, nonlinear signals with harmonic frequencies at medium acoustic pressure, and microbubble disintegration at high acoustic pressure.7 Microbubbles are compressible, and at low acoustic pressure, microbubbles grow and shrink symmetrically around their equilibrium size (stable or non-inertial cavitation). At higher acoustic pressure, however, the expansion and contraction of microbubbles usually become unequal and exaggerated, leading to their destruction (inertial cavitation). Microbubble destruction by ultrasound is the basic principle for the quantification of myocardial blood flow by MCE.2 Bio-effects of UCAs have been demonstrated in numerous in vitro studies. Even linear bubble oscillations are sufficient to achieve rupture of lipid membranes.8 Sudden violent collapse of microbubbles can produce high-velocity fluid micro-jets that may penetrate into the adjacent membranes leading to pore formation (sonoporation).9,10 Inertial cavitation, which depends on microbubble shell composition, ultrasound frequency, pulse duration, and acoustic power, can lead to secondary shock waves, transient local high temperatures, and shear stress.11–13 On the one hand, these bio-effects in vitro must draw the clinician’s attention towards potential harmful adverse events in patients; on the other hand, it opens the door towards potential applications of UCAs in gene and drug delivery.14

The most common finding in animal studies examining the potential tissue damage and the risk of UCAs together with ultrasound was capillary rupture and haemorrhage or dye extravasations.15,16 It is, however, very dangerous to extrapolate these results towards the real-life scenario. Ultrasound energy (no tissue attenuation in the animal studies), duration of insonification, and microbubble concentrations are some examples of the exaggeration of UCA’s adverse events suggested by these animal studies.

* Corresponding author. Tel: +32 2 476 32 52; fax: +32 2 477 68 40. E-mail address: guy.vancamp@uzbrussels.be

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Prolonged contrast agents’ destruction in the same scan plane is unlikely in human studies. In daily practice, the scan plane is frequently changed to evaluate multiple myocardial regions. These changes continuously shift the myocardial layer with microbubble destruction, and thereby reducing the possible bio-effects of UCAs. During the study no patient experienced clinically relevant adverse effects (no premature ventricular beats mentioned). Despite these remarks, the authors performed a difficult and technically very demanding study with a clear message. Using high-MI contrast echocardiography with PESDA, and intermittent imaging every other beat for 15 min maintaining the probe at a fixed apical position, they found a significant increase in the arterio-venous difference of cTnI.

In conclusion, in extreme situations, rarely seen in clinical practice, the concomitant use of ultrasound and contrast agents can lead to bio-effects in vitro, ex vivo, in animal studies, and in humans. The clinical relevance of these bio-effects in humans during real-life contrast echocardiography remains an unanswered question. It is, of course, possible that even subtle bio-effects can induce fatal adverse events in unstable patients with extensive coronary artery disease. In these patients, it seems reasonable to weigh the benefit of the use of contrast agents during echocardiography against the possible adverse events and to take into account the risk of alternative examinations that could be done instead of the contrast echocardiography. Once the decision is made that UCAs will be used, techniques using low volumes of contrast agents with low-MI imaging should be preferentially used. Each echolaboratory using UCAs should have experience with the use of UCAs and should be able to treat serious allergic reactions.

In spite of these rather modest safety concerns, UCAs have positively and considerably changed the diagnostic power of echocardiography. They can be used in daily practice to optimize our echocardiographic images and increase the diagnostic information with only a very low rate of adverse events.

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References


