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

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This editorial refers to 'Release of cardiac bioarkers during high mechanical index contrast-enhanced echocardiography in humans' by D. Vancraeynest et al., on page 1236

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 Medecines 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). These agents are also used to quantitate myocardial perfusion most of the time, especially for research purposes.

Like all other contrast agents used in medicine, adverse events can also occur with UCAs. 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. Secondly, 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). For the first time, Vancraeynest et al. 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. 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. Bio-effects of UCAs have been demonstrated in numerous in vitro studies. Even linear bubble oscillations are sufficient to achieve rupture of lipid membranes. Sudden violent collapse of microbubbles can produce high-velocity fluid micro-jets that may penetrate into the adjacent membranes leading to pore formation (sonoporation). 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. 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.

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. 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.

Serious adverse events with MCE in humans are rare. Ventricular premature beats were reported by van der Wouw et al. but this was not confirmed in other studies. Cosyns et al.\textsuperscript{19} could not find any tissue Doppler abnormality of the left ventricle in patients. Since tissue Doppler is considered as a very sensitive technique to diagnose even small, subclinical alterations of left ventricular systolic and diastolic functions, this observation is certainly reassuring. The large clinical experience accumulated so far in several clinical trials and in routine clinical practice of more than 2 million patients showing the very low side-effect potential of UCAs confirms their low toxicity potential. The three fatal adverse events in unstable patients with advanced coronary artery disease encountered with Sonovue\textsuperscript{4} however, suggest that this UCA might play a triggering role in the development of a fatal event in this group of high-risk patients.\textsuperscript{5} The lower adverse event rate of Optison\textsuperscript{40} (serious adverse event rate ≤ 0.002 vs. 0.014% for Sonovue\textsuperscript{4} and no fatal adverse events with Optison\textsuperscript{50}) is remarkable. As the shell of Sonovue\textsuperscript{50} contains polyethylene glycol which is known to be associated with the occurrence of allergic reactions, this chemical of the UCA could be responsible for these adverse reactions. Another explanation for some of the adverse events and for the fatal adverse events could be the occurrence of bio-effects at the level of the coronary microcirculation. Knebel et al.\textsuperscript{20} did not find clinically relevant increases in serum markers for micro-necrosis, inflammation, and oxidative stress after contrast echocardiography, but in some patients cTnI increased (threefold methodical variation). Vancraeynest et al. looked towards more subtle changes in biomarkers after contrast echocardiography. They found a significant increase in the arterio-venous difference (coronary sinus vs. arterial level) of cTnI only in those patients with high-MI (MI 1.5) intermittent imaging (every other beat) and with the use of PESDA (home made perfluorocarbon-enhanced sonicated dextrose albumin). This could be interpreted as the first demonstration of bio-effects of contrast echocardiography in humans. The following remarks have to be made, however, concerning the methods used in this paper. Thickness, compressibility, and elasticity of the microbubble shell are important factors in their susceptibility to ultrasound-mediated destruction.\textsuperscript{21} These properties may be very different among the available contrast agents. The results obtained in the present study with PESDA are difficult to extrapolate with other contrast agents. Increase in cTnI was only seen in the high-MI intermittent imaging group. The vast majority of contrast examinations worldwide are used, however, for endocardial border delineation. In this situation, LVO settings use lower MI and real-time imaging, thus considerably reducing the chance for bio-effects. The authors used continuous infusion of contrast. A continuous infusion of UCAs is used in the first place for the quantification of myocardial perfusion. As mentioned earlier, this is mainly used in research. In all the other situations, bolus injections are used permitting the administration of lower volumes of UCAs and also reducing the cost. The authors also used a stable triggering interval every other beat. This is never done in clinical practice. Quantification of myocardial perfusion is only possible by increasing the pulse interval. Refilling of the normal myocardium takes almost always more than one cardiac cycle. The probe was also maintained for 15 min in the same apical position. 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.\textsuperscript{4} 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

Clinical vignette

In-line filtration of intravenous fluids retains 'spearhead'-shaped particles from the vascular system after open-heart surgery

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Looking at the potential benefit of in-line filtration in reducing major complications occurring during intensive care unit stay, we would like to present the electron microscopy analysis of a filter used in a 17-year-old girl after aortic valve replacement. The patient received all drugs and fluids through a Pall Posidyne NEO filter with 0.2 μm pores size. Drugs given through the filter membrane included furosemide, spironolactone, hydrocortisone, ranitidine, paracetamol, and cefazoline by bolus injection or continuous infusion. The filter was used for 72 h before being removed and analysed. We were able to visualize 51 mm² of the membrane’s top layer by scanning electron microscopy and detected various particles of different size and shape adherent to the surface and the presented pictures were taken (Panels A–D). These images are representative of the size and shape of particles found, many of which are notable for their angular shape and crystalline appearance.

We hypothesize that microparticles, such as these, that would have been infused in the absence of the filter may cause severe local endothelial damage and possibly predispose to complications such as respiratory distress syndrome, thrombosis and systemic inflammatory response syndrome, or, in the worst case, multiorgan dysfunction. We are therefore currently conducting a clinical trial to evaluate the potential benefit of microfilters in the paediatric intensive care setting.

The girl had an uneventful stay on the intensive care unit and was discharged to the ward after 36 h.

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