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Contrast agents for echocardiographic studies within 24 h after myocardial infarction

Harald Becher

Cardiac Investigation Annexe, John Radcliffe Hospital, University of Oxford, Headley Way, Oxford OX3 9DU, UK

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Back to normal in the US

In April 2008, the US Food and Drug Administration (FDA) performed a safety review of the US-approved perflutren microsphere contrast agents (Definity and Optison) and revised a previous black box warning. The new contraindications are much less restrictive than the previous contraindications and satisfy the needs of clinical echocardiography. These changes have come after an intensive debate with the American Society of Echocardiography but also with significant European support. The correction of the contraindication for contrast agents is a good example, how inadequate decisions by the health administration can be reversed by competent and decisive actions of scientific and professional bodies like the ASE and EAE.

Before April 2008, the use of contrast agents was contraindicated in patients with unstable cardiopulmonary status, including patients with unstable angina, acute myocardial infarction, respiratory failure, or recent worsening congestive heart failure. The contraindications were established temporarily after the reports of 199 serious cardiopulmonary reactions including 11 deaths during and shortly after the administration of contrast agents in post-marketing use. Ten of the events were observed with Definity over 6 years with more than 2 million applications; one fatal event was reported with Optison for 1 million applications. At least six of these cases (five Definity and one Optison) occurred 1–12 h after dosing and were attributed to serous underlying conditions.

The FDA revised the benefit/risk assessment for patients with unstable conditions and acknowledged that some of the fatal events may be coincidental and not related to the contrast media. Only four fatal events with Definity occurred within 30 min after the application of contrast agents. Within this time frame, a negative role of contrast agents appears to be possible, but this is difficult to prove or exclude. Indeed, two patients had severe heart failure and one patient was ventilated because of respiratory failure, sepsis, and multiple emboli. The FDA and European Medicines Agency (EMEA) usually are concerned about a temporal relation of an adverse event and administration of the drug. They assume a possible causal relation as long as there is no proof of another explanation. But even if we assume that all four cases are related to the ultrasound contrast agent, the fatal event rate would be only 1 in 500 000 for Definity and zero for Optison. This rate is far less than the fatal event rate in exercise and Dobutamine stress echocardiography.[1] Meanwhile, several studies demonstrate the safety of ultrasound contrast agents in more than 20 000 patients including stress echocardiography and myocardial perfusion imaging using the flash-replenishment technique.[2–5] In order to provide further safety data, external, independent safety monitoring boards for the agents will be established by the manufacturers.

So, it is time to be less worried about the safety of contrast echocardiography and it is good news to have ultrasound contrast agents not contraindicated in unstable conditions. However, as good physicians we still have to be prepared for a serious adverse event, e.g. hypersensitivity reactions, even if they are very rare. Like in the angiography suite, there should always be appropriate equipment and skilled personnel for resuscitation available during administration of contrast agents. According to the FDA, the risk for severe adverse reactions may be increased among patients with pulmonary hypertension or unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, serious ventricular arrhythmias, or respiratory failure, including patients receiving mechanical ventilation). In these patients, vital signs, electrocardiography, and cutaneous oxygen saturation have to be monitored during the contrast agents application and for at least 30 min after DEFINITY® and OPTISON® administration.

Back to normal . . . *not* in Europe!

Surprisingly, the manufacturer of LUMINITY® (name of Definity in Europe) announced a temporary cessation of the marketing and supply of LUMINITY in Europe. There

Corresponding author. Tel. +44 1865 220 325; fax: +44 1865 740 409.
E-mail address: harald.becher@orh.nhs.uk

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may be purely commercial reasons for that decision. For clinical echocardiography, OPTISON is not yet available in Europe. Thus, the only available contrast agent is SonoVue®. However, SonoVue has not been included in the FDA review, because it is not licensed in the US. For SonoVue, the contraindications have not changed yet! SonoVue remains contraindicated in acute coronary syndromes, patients with heart failure III and IV, serious ventricular arrhythmias, and respiratory failure.

Need for performing a contrast study within 24 h after myocardial infarction

In the setting of an acute myocardial infarct, urgent and repeated echocardiographic examinations may be necessary to evaluate LV function, intracardiac thrombi, and other complications of myocardial infarction. Contrast agents have been shown to be useful to improve the image quality (endocardial definition) in 2D and 3D echocardiography.[6] Therefore, it appears to be straightforward to use contrast echocardiography for better image quality in those with suboptimal image quality. Contrast echocardiography also provides important information about myocardial perfusion. Using the state-of-the-art ultrasound scanners, LV cavity opacification is usually associated with myocardial tissue opacification, if the tissue is viable. Thus, contrast echocardiography after a coronary intervention shows the amount of non-reflow and necrosis in the myocardium. The prognostic significance of myocardial contrast echocardiography has been demonstrated: The extent of microvascular damage during myocardial contrast echocardiography was superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodelling.[7,8]

But what is the real clinical benefit of a more accurate assessment of the LV early after acute myocardial infarction? The best way to address this question is to ask what would have been happened to the patients should they not have had a contrast echocardiography study. To my knowledge, there are no controlled clinical studies at all addressing the question, how the contrast agents applications changed the management of patients in acute myocardial infarction. Until such time that adjunctive therapies following primary percutaneous coronary intervention are shown conclusively to alter the outcome in relation to myocardial perfusion, the role of myocardial contrast echocardiography in this scenario will be limited.[7] At present, it is the approved indication for LV opacification and endocardial border delineation, which makes contrast agents valuable for patient management: by reviewing case studies, Grayburn[1] recently demonstrated the catastrophic sequences of inaccurate assessment of LV function and misdiagnosis of complications such as pseudoaneurysms and thrombi. Even if there would be a moderate risk by the contrast agent, the risk/benefit still would be very favourable for using contrast agents in acute myocardial infarction!

Nucifora *et al.*[9] provide further reassurance about the safety of LUMINITY in the acute phase of myocardial infarction: in 115 consecutive patients with ST-elevation, myocardial infarction contrast echocardiography was performed with LUMINITY. Administration of echo contrast did not induce any significant change in vital signs, physical examination, and ECG. There were no serous adverse events, and minor events occurred only in five patients. Of course, this study cannot rule out all concerns about the safety of ultrasound contrast agents in unstable patients. Firstly, only patients were included after coronary intervention. These patients are probably in a lower risk group compared with patients who would get a contrast agent before the intervention. Secondly, the number of patients is not large enough for a definite answer to our safety questions. However, I agree with the authors that the results of this pilot study should encourage studies in larger cohorts.

What needs to be done?

In Europe, we need ultrasound contrast agents that can be used within the first 24 h after myocardial infarction. There are conditions, where there is no real alternative to the diagnostic value of bedside LV opacification. In the debate with the FDA, the clinical and scientific echocardiographic community has demonstrated their impact on the health administration. We should use this momentum in the discussions with the EMEA in order to achieve a revision of the contraindications of SonoVue. Multi-centre randomized studies are needed to demonstrate how myocardial contrast echocardiography can change patient management. Finally, we need a registry of patients who have got a contrast agent within 24 h after myocardial infarction or other conditions of clinical instability.

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