Current Indications for Contrast Echocardiography

a report by
Harald Becher1 and Robert Olszewski1,2

1. John Radcliffe Hospital, Oxford, 2. Military Medical Institute, Warsaw

Contrast echocardiography has become an indispensable tool in non-invasive imaging. In the last decade new contrast agents and contrast-specific imaging technologies have simplified the clinical use of contrast agents and dramatically improved the images acquired. However, there is a price to pay: extra time, the costs of the agent and a small risk of intolerance reactions. Significant improvements have been achieved in other cardiac imaging modalities that supplement or compete with echocardiography. Therefore, it appears reasonable to review the clinical indications of the approved ultrasound contrast agents.

Available Contrast Agents and Suitable Imaging Techniques

At present three contrast agents are licensed for left ventricular (LV) opacification and endocardial definition: SonoVue (Brgacco, Italy), Luminity (BMS, US) and Optison (GE, US). The latter is currently not available. All of these agents provide intensive opacification of the left heart chambers when administered intravenously.

All agents are suspensions of microspheres filled with a perfluorocarbon gas and are a similar size to red blood cells. Ultrasound contrast agents are intravascular tracers: they opacify the blood in the cavities and in the myocardial vessels. Since the blood volume within the myocardial vessels makes up only 7% of the myocardial tissue, myocardial opacification is always much less intensive than the cavity opacification, providing excellent contrast for endocardial delineation (see Figure 1).

The myocardial opacification following intravenous contrast application can be used to assess myocardial thickening and perfusion. The dosages of contrast needed for LV opacification – 0.1–0.3 ml – are minimal compared with contrast agents in other imaging modalities such as X-ray. These small dosages are possible because of the very sensitive contrast-specific imaging technologies that have been implemented in all state-of-the-art ultrasound systems. The settings of the ultrasound scanners and the contrast dosages are standardised, making contrast echocardiography an easy-to-use technique. Recent developments such as power modulation and power-pulse inversion use very low non-destructive power transmission techniques (mechanical index <0.2) and allow for realtime imaging. Contrast-specific imaging modalities have been implemented into 3D echo scanners. The indications for contrast echocardiography do not differ between 2D and 3D echocardiography, but in general higher dosages of contrast agent are required for 3D compared with 2D echocardiography (see Figure 2).

Approved Indication for Contrast Echocardiography – To Improve Endocardial Border Definition

Current indications for contrast agents in Europe state that their use is targeted to “patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance LV endocardial border delineation” (see figures 1 and 3). In other words, contrast echocardiography represents a tool to improve image quality. Many patients have suboptimal images despite the advances of ultrasound technology. The use of contrast echocardiography is desirable when the anticipated image improvement may alter patient management. Contrast agents also improve the signal-to-noise ratio in colour and spectral Doppler echocardiography. This can be used to rescue noisy Doppler studies, in particular studies of aortic valves and pulmonary venous flow.

Assessment of Myocardial Opacification – An Integral Part of Contrast Echocardiography

Ultrasound contrast agents have been licensed for the improvement of endocardial border definition by LV opacification. However, LV opacification is inevitably associated with myocardial opacification, in particular when the newer contrast-specific imaging modalities are used (see Figure 4). Assessment of myocardial opacification provides very important information on top of the evaluation of the wall motion. Questionable findings of wall motion can be clarified by assessing LV opacification, and vice versa. Homogeneous myocardial opacification and quick opacification of the myocardial vessels after LV opacification indicate normal myocardial perfusion and provide further confirmation of normal wall motion. This is particularly helpful in stress echocardiography. Reduced opacification in the subendocardial layers
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UK LUMINITY® PRESCRIBING INFORMATION

PRESENTATION: Solution for dispersion for injection or infusion (150 microgram/ml perfusate). Each ml contains a maximum of 6.4 x 10^6 perfusate-containing lipid microspheres, with a mean diameter range of 1.1-2.5 micrometres (µm).

INDICATIONS: For diagnostic use in patients in whom non-contrast echocardiography was suboptimal and who have suspected or established coronary artery disease, to provide opacification of cardiac chambers and improvement of left ventricular endocardial border delineation at both rest and stress.

DOSAGE: Before use, the product must be activated using a mechanical shaking device the VIALMIX®. For intravenous use only. Bolus intravenous injection using non-linear contrast imaging technique at rest and stress - multiple injections of 0.1 to 0.4 ml (total dose not > 1.6 ml); then 3 to 5 ml bolus of sodium chloride 9 mg/ml (0.3%) or glucose 50 mg/ml (5%) solution for injection. Bolus intravenous injection using fundamental imaging technique at rest - 10 microlitr injected by slow bolus intravenous injection; then 10 ml bolus of sodium chloride 9 mg/ml (0.3%) or glucose 50 mg/ml (5%) solution for injection. Intravenous infusion using non-linear contrast imaging technique (rest and stress) or fundamental imaging technique at rest - intravenous infusion of 1.3 ml added to 50 ml sodium chloride 9 mg/ml (0.3%) or glucose 50 mg/ml (5%) solution for injection; rate of infusion not > 10 milliliter. Other methods of administration not recommended. Safety and efficacy have not been established for fundamental imaging technique for stress echocardiography and in children < 18 years. For further information, see SPC.

CONTRAINDICATIONS: Hypersensitivity to perfluor or to any of the excipients.

WARNINGS AND PRECAUTIONS: Caution when used in patients with right-to-left, bi-directional or transient right-to-left cardiac shunts, on mechanical ventilation or with clinically significant pulmonary disease, as safety has not been established. Use only after careful consideration and monitor closely during administration in patients with certain states of cardiac and pulmonary disease. For further information, see SPC.

DRUG INTERACTIONS: None known.

SIDE EFFECTS: Common: Headache and flushing. Others: Allergic-type reactions. For further information, see SPC.

LEGAL CATEGORY: POM.

AUTHORISATION NUMBERS/BASIC NHS PRICE: LUMINITY® 150 microgram/ml solution for dispersion for injection or infusion; EU/106361/001; £244.00 for 4 x 1.5 ml vials.

MARKETING AUTHORIZATION HOLDER: Bristol-Myers Squibb Pharma Belgium Sprl, Chaussée de la Hulpe, 185/Terhulpsesteenweg 109, B-1170 Brussels/Bruxsel, Belgium.

FURTHER INFORMATION FROM: Bristol-Myers Squibb Medical Imaging, Udrbridge Business Park, Sanderson Road, Udrbridge, Middlesex UB8 1DH. Freephone 0800 731 1736. Medical Information.


In the UK, adverse events should be reported to Bristol-Myers Squibb Pharmaceuticals Ltd Medical Information on 0800 731 1736. Information about adverse event reporting can also be found at www.yellowcard.gov.uk.

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References:

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Contraindications for SonoVue contrast echocardiography in 2004: “SonoVue is contraindicated for use in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, acute cardiac failure, class II/IV cardiac failure or severe rhythm disorders because in these patients allergy-like and/or vasodilative reactions may lead to life-threatening conditions. Not to be used in evolving or ongoing myocardial infarction; typical angina at rest within seven days; significant worsening within seven days; other factors suggesting clinical instability such as deterioration of electrocardiogram (EKG), lab or clinical findings.”

Similar contraindications have recently been established by the US Food and Drug Administration (FDA) for Definity (Luminity in Europe); it is very likely that the EMEA will follow these guidelines. These contraindications barely affect the use of contrast agents in stress echocardiography for assessment of inducible ischaemia, where it is common practice to exclude unstable patients and symptomatic patients at rest. The safety of contrast dobutamine stress echocardiography has been demonstrated in two large trials. However, patients with poor LV function and class II/IV heart failure are often referred for viability studies. According to the new contraindications, these patients should not undergo contrast echocardiography.

Risk/Benefit Considerations
Assessment of risk/benefit means comparing the risks of the procedure – here contrast echocardiography – with the risks of an incorrect diagnosis when not using the contrast agent. For instance, a new wall motion abnormality is not detected in stress echocardiogram because the wall is not adequately imaged, the diagnosis may be inaccurate and subsequent management of the patient may be wrong. Although there appears to be strong evidence that patients with a missed diagnosis of coronary artery disease have an unfavourable outcome, in fact there are only limited data to quantify the extent to which this may occur. It appears to be easier to assess the risk/benefit when considering false-positive studies. Usually, coronary angiography is requested in the case of a false-positive stress echocardiogram. This will expose the patient to significant radiation; there is also a procedural risk that certainly exceeds the risk of an adverse event when using an ultrasound contrast agent. Therefore, it is very important to take a decision as to whether to continue with a study that has suboptimal images or to consider other possibilities to ensure the patient receives the best possible medical treatment. Even when the risk of serious adverse events is very low, there should be a clear benefit from the application of the contrast agent to justify its use. In patients undergoing stress echocardiography, the benefit of using a contrast agent certainly outweighs the small risks, in particular when the current contraindications are not ignored.

Comparison with Other Imaging Technologies
There are three aspects to be considered when comparing different imaging technologies (see Table 1): the accuracy, the risk/benefit and the cost-effectiveness. Cardiac MRI, computed tomography (CT) and nuclear methods are known to be considerably more expensive than contrast echocardiography. Several multicentre and numerous single-centre trials, as well as series of case reports, have demonstrated the accuracy of contrast echocardiography for assessment of LV volumes and ejection fraction (for an overview see reference 4).

The reproducibility of contrast-enhanced echocardiography is as good that of MRI. For assessment of global and regional LV
function, there are large controlled trials including several hundred patients. The accuracy of stress echocardiography is no worse than that of myocardial scintigraphy. Multislice CT is a new technology that displays the coronary arteries rather than looking for myocardial ischaemia. There is an ongoing debate as to whether non-invasive coronary angiography really provides the best information for the management of patients; however, there is consensus that functional assessment of coronary stenoses with stress tests cannot be given up.

Contrast echocardiography could hardly be advocated if there were an imaging technology with similar indication for the same indication with similar accuracy but a better risk/benefit ratio. The contrast agents applied during MRI, CT and single-photon emission CT (SPECT) examinations pose immediate-term risks, while the radiation used in SPECT and cardiac CT pose long-term risks. The latter may become important if repeated examinations are necessary. For single tests, however, the incidence of side effects appears to be very low for all imaging technologies. Therefore, it is difficult to establish a significant superiority of one method over another in terms of safety. Data from clinical trials for EMEA or FDA approval are available, but do not provide enough information on rare side effects. Post-marketing surveillance, anecdotal reports on adverse events and a few articles on local registries are other sources to compare different technologies. However, these studies represent different populations and different methods of clinical care.

**Echocardiography Is the Method of Choice for Repetitive Cardiac Imaging**

In many patients the clinical course requires several appointments for cardiac imaging. Radiation dosages become an issue in those patients who require non-invasive or invasive coronary angiography and coronary interventions. This has to be taken into account when patients need functional imaging. MRI and echocardiography should be used rather than nuclear methods. Contrast application can close the gap between MRI and echocardiography in those patients with suboptimal images. Even with the use of contrast, echocardiography remains a very cost-effective test that can be easily integrated into the workflow, either as an outpatient appointment or as treatment on the ward.

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Dear Colleagues,

Cardiovascular imaging has been chosen as the theme for the European Society of Cardiology (ESC) Congress 2008. A comprehensive update will be provided, with a focus on technical innovations in imaging and implementation in clinical cardiology. Part of these sessions will be presented in the focus sessions with live transmission from various locations in Europe.

Other live focus sessions will be dedicated to intervention, in which technical and practical skills are presented and shared with the audience in an interactive manner. In addition, there will be more practical read and meet the expert sessions. Emphasis is placed on clear take-home messages that can easily be transposed into clinical practice by the medical professionals who take part in the ESC congress. The newest guidelines will be presented and discussed in dedicated sessions.

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