Current indications for contrast echocardiography imaging

H. Becher*, C. Lofiego, A. Mitchell, J. Timperley

John Radcliffe Hospital, Oxford, UK

Abstract The assessment of regional ventricular function is dependent on good endocardial definition. Suboptimal images can be converted to diagnostic recordings in the majority of patients by contrast agents, which have become an indispensable aid in rest and stress echocardiography. In particular for stress echocardiography image quality is essential and contrast administration is of great importance. However this diagnostic procedure must be performed following the indications which reflect the risks of the procedure and consider the benefits of an accurate diagnosis on further patient management. The contraindications recently introduced in the use of the echo-contrast agent SonoVue for acute cardiac patients reflect the same contraindications which have been applied in stress echocardiography for several years. Clinical trials and post-marketing surveillance have demonstrated that this approach is safe with no fatalities reported.

For all ultrasound contrast media, side effects have been reported but they are usually mild. However, rare allergic and potentially life threatening reactions may occur and the investigators have to be prepared for such an event with appropriate drugs stored in the echo department.

In a recent retrospective analysis in 751 consecutive stress echocardiograms the use of contrast during dobutamine stress echocardiography was not associated with an increased risk of side effects. The incidence of side effects was very low and different in patients receiving Optison, SonoVue or without contrast agent.

Conclusion: Ultrasound contrast agents are licensed for improvement of endocardial border definition. Data from clinical trials and wide clinical experience indicate an excellent risk/benefit ratio if the current contraindications are applied.

Introduction

In recent years numerous clinical studies have demonstrated the clinical utility of contrast echocardiography in the endocardial border delineation and evaluation of LV function.

The assessment of regional ventricular function is dependent on good endocardial definition. Suboptimal images can be converted to diagnostic recordings in the majority of patients by contrast agents which have become an indispensable aid in rest and stress echocardiography (Fig. 1).

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 left ventricular endocardial border delineation". In other words contrast echocardiography represents a tool to improve image quality. Many patients have poor images despite the advances of US technology. The use of contrast echocardiography is desirable when the anticipated image improvement may alter patient management following the evaluation of risk/benefit of procedure and possible side effects.

Improvement in patient management

Not all patients in whom image quality is suboptimal need an ultrasound contrast agent to improve endocardial border delineation. According to the guidelines of the American Society
of Echocardiography there is an indication for contrast echocardiography when the endocardial border definition in 2 or more segments is poor. However, in a rest echocardiogram it is often possible to make the right clinical decisions even when the endocardial definition is poor in more than 2 segments: for instance in a 82-year-old patient with dilated LV, akinetic inferior wall and poor endocardial definition of the lateral wall further management will not be dependent on the contractility in the lateral wall (Fig. 2).

A different situation occurs during stress echo examinations. The accuracy of stress echocardiography depends on the image quality; suboptimal images even in parts of the LV cannot be accepted. The complexity of protocol and the risks of ischaemia can only be justified if the test is diagnostic. Therefore high image quality is vital. These considerations are reflected in the most recent published guidelines of the British Society of Echocardiography for the clinical application of Stress Echocardiography. In these guidelines USCM utilization is mentioned for first time: “If image quality is suboptimal, i.e. endocardial borders are barely or not visible in 2 or more myocardial segments, application of ultrasound contrast agents should be considered or the patient should be referred for another imaging test like myocardial scintigraphy or MRI.”

**Safety of contrast echocardiography**

For ultrasound contrast agents side effects have been reported but they are usually mild. However, “rare allergic potentially life-threatening reactions may occur and the investigators have to be prepared for such an event.” How frequent are these serious adverse events? Data collected during Post-Marketing Surveillance referred to more than 200 000 of SonoVue vials used, indicate that serious adverse events (SAE) are rare (0.01%). The signs and symptoms of most of these SAEs indicate an underlying allergy-like mechanism and they were considered by European Medicines Agency (EMEA) in the context of idiosyncratic, hypersensitivity reactions. This kind of reactions (allergy-like) is well known from contrast agents in...
Other imaging modalities (see section Comparison with other imaging technologies).

During Post-Marketing Surveillance three patients died in temporal relation to the application of SonoVue. These patients had no symptoms of an allergic reaction. This raised the question of a causal relationship or just coincidence with a spontaneous cardiac event. Indeed, all three patients had advanced coronary disease with high spontaneous risk of acute events: at high risk for short term (spontaneous) mortality; severe left main stenosis; untreated multivessel disease. All three patients had signs or symptoms indicating clinical instability. All reporting physicians and several independent external cardiology experts requested to comment on these cases, regarded causality as very unlikely. However, because of the temporal relationship between the fatalities and the application of SonoVue, EMEA established new contraindications for SonoVue-Contrast Echocardiography: "SonoVue is contraindicated for use in patients with recent acute coronary syndrome or clinically unstable ischemic cardiac disease, acute cardiac failure, Class III/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 7 days significant worsening within 7 days; other factors suggesting clinical instability such as deterioration of ECG, lab or clinical findings." 

These new contraindications do not allow contrast echocardiography in patients with unstable coronary syndromes and advanced heart failure. However, they do not affect the use of SonoVue in stress echocardiography, where it is common practice to exclude unstable patients and symptomatic patients at rest. This means that the new contraindications established by EMEA are almost identical with the criteria that have been already applied for stress echo for assessing myocardial ischaemia.

The safety of Contrast Dobutamine stress echocardiography has been demonstrated in 2 large trials; the registry of the John Radcliffe Hospital Oxford included 751 consecutive patients who underwent Contrast Dobutamine Stress echocardiography (Table 1). The study included the safety data during 18 months in 299 patients administered with SonoVue and 120 with Optison. No significant difference was observed in the incidence of adverse events in patients with and without contrast administration. The incidence of arrhythmias or significant changes in blood pressure was very low and in concordance with data from literature on native stress echocardiography.

No allergic events were seen. Recently the safety data of 1486 patients who underwent contrast dobutamine stress echocardiography with Optison have been published with similar results. However since side effects are very rare, we need to collect data on a wider patient population to establish the real incidence.

Comparison with other imaging technologies

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. Furthermore if there is an imaging technology for the same indication with a better risk/benefit ratio the use of contrast echocardiography could hardly be advocated. Considering the low incidence of side effects of all imaging technologies it is difficult to establish a significant superiority of one method over another method concerning safety. Data from clinical trials for EMEA or FDA approval are available but do not give enough information on rare side effects. Post marketing surveillance, anecdotal reports on adverse events and few articles on local registries are other source to compare different technologies. However, these studies represent different populations and clinical care.
In clinical practice only myocardial scintigraphy is a real alternative for stress echocardiography if it is non-diagnostic. Stress SPECT has a 0.26 SAE-rate, patients are exposed to radiation and anaphylactic SAE are also reported (<0.5% Cardiolite) 18,19. MRI may be an alternative in a few centres; it is contraindicated in patients with pacemakers and implantable defibrillators; in patients at early phase post-bypass surgery, gadolinium associated side effects have been reported 20. Due to the limited stress studies performed compared to stress echocardiography or SPECT, no final judgment on risk profile is possible. Considering all the information available for the different imaging modalities there appears to be no evidence to prefer one technology for reasons of safety.

Risk/benefit considerations

For all imaging modalities the risk/benefit has to be assessed by considering the consequences of suboptimal imaging for the patient management. Assessment of risk/benefit means to compare the risks of the procedure - here contrast echocardiography - with the risks of an incorrect diagnosis when not using the contrast agent. If 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 it appears to be very convincing that patients with a missed diagnosis of coronary artery disease have an unfavorable outcome, there actually are only limited data to quantify to which extent this might happen. In the case of false positive studies it is easier to establish a favorable risk/benefit ratio: If a patient has a positive stress echocardiogram usually a coronary angiography is requested. This will expose the patient to significant radiation and implantable defibrillator; in patients at early phase post-bypass surgery, gadolinium associated side effects have been reported 20. Due to the limited stress studies performed compared to stress echocardiography or SPECT, no final judgment on risk profile is possible. Considering all the information available for the different imaging modalities there appears to be no evidence to prefer one technology for reasons of safety.

In conclusion, data from clinical trials and wide clinical experience indicate an excellent risk/benefit ratio for contrast echo and for SonoVue if the current contraindications are applied.

References

19. Ranhusky A, Kempthorne-Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion

