Clinical benefits of contrast-enhanced echocardiography during rest and stress examinations

Roxy Senior*, Girish Dwivedi, Sajad Hayat, Tiong Keng Lim

Department of Cardiovascular Medicine, Northwick Park Hospital, Harrow, Middlesex, HA1 3UJ, England, United Kingdom

Abstract

Despite the recent introduction of tissue harmonic imaging in echocardiography, 10-15% of patients have poor endocardial border definition. This may lead to erroneous assessment of regional and global left ventricular (LV) function or to further diagnostic imaging with another modality thus increasing the costs for the healthcare system. The recent development of second generation contrast echocardiography agents such as SonoVue has resulted in several studies showing the value of these agents to outline endocardium clearly, thereby improving assessment of LV function. The use of these contrast agents has also opened the possibility of automated and quantitative LV function assessment, making it more accurate and reproducible. Other major clinical uses of these contrast agents are evaluation of LV masses such as thrombus and tumors, and better definition of LV structure such as delineating LV aneurysm, pseudoaneurysm; and non-compaction of LV and apical cardiomyopathy. Furthermore, the use of these contrast agents during stress not only improved the assessment of wall motion but also made possible the evaluation of myocardial perfusion, thereby increasing diagnostic accuracy for the detection of coronary artery disease.

Introduction

Accurate assessment of regional and global left ventricular (LV) function and structure is pivotal in the clinical management of patients with suspected cardiovascular disease. Several studies have previously confirmed that markers of LV function such as LV ejection fraction (LVEF), wall motion score indices, end-systolic volume and regional wall motion assessment are powerful predictors of outcome in patients with cardiac disease. Indeed, markers of LV remodelling following acute myocardial infarction in patients with heart failure are even more powerful indices of outcome. While echocardiography is the most widely used and inexpensive tool for the assessment of cardiac structure and function, it is unable to obtain adequate images in about 30% of patients. The inability to clearly identify endocardial border has resulted in unacceptable reproducibility for assessment of LVEF and regional wall thickness. Furthermore, in day to day clinical practice, assessment of markers of LV function by echocardiography has been qualitative, subjective and experience dependent. This has also resulted in suboptimal efficacy for the detection of coronary artery disease during stress echocardiography.

Contrast echocardiography for enhanced endocardial border delineation of left ventricle

Despite substantial improvement of endocardial definition by using tissue harmonic imaging, there is still a significant number of patients in whom endocardial definition remains inadequate for
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Fig. 1. Images in apical 4-chamber view with diastolic frames (left-hand panel) and systolic frames (right-hand panel). The top images are acquired during fundamental imaging which shows poor delineation of the endocardium especially of the distal septum, apex and lateral wall both during systole and diastole. Following SonoVue® (Bracco, Milan) injection (bottom panel), there is marked improvement of the endocardial border visualization of the left ventricle both during systole and diastole.

Proper assessment of LV function is important for diagnosis and management of cardiovascular disease. Contrast echocardiography can improve the visualization of the endocardial border, leading to more accurate measurement of LV function. SonoVue® (Bracco, Milan, Italy) is a second generation contrast agent made of microbubbles containing sulphur hexafluoride gas and stabilized by phospholipids. In a multicenter study of 218 patients, SonoVue showed a significant improvement in identifying endocardial border in comparison with unenhanced fundamental imaging (fig. 1). The images in this study were read blinded by four off-site observers. A significant improvement in the endocardial visualization score (0 = not well visualized, 1 = barely visible, and 2 = well visualized) was obtained with SonoVue at all doses (0.5, 1, 2, and 4 ml) and was more marked in the apical views (fig. 2). Similar results were obtained following SonoVue administration in patients with suboptimal non-contrast-enhanced echocardiographic images. In another study, SonoVue was compared with Albunex (Molecular Biosystems/Mallinkrodt) and saline in 264 patients with suboptimal endocardial border visualization using fundamental echocardiography. SonoVue produced a significant enhancement in the endocardial border delineation, P < 0.0001, at the two highest doses compared to Albunex and saline. Moreover, following SonoVue administration, a significant reduction in the number of patients with suboptimal endocardial border delineation compared to Albunex and placebo was also obtained (fig. 3, overleaf). Other studies have similarly confirmed the value of contrast-enhanced assessment of endocardial border.

Lindner et al. convincingly demonstrated the superiority of contrast enhancement with harmonic imaging compared to fundamental contrast imaging for the evaluation of endocardial border. Figure 4 shows an example where tissue harmonic imaging failed to identify endocardial border in the apical-lateral wall, which was brought out clearly by contrast echocardiography. In another study, Spencer et al. demonstrated in a large group of patients with poor images that contrast enhancement resulted in a significantly higher segmental salvage rate compared to harmonic imaging alone.

**Does contrast echocardiography improve assessment of LV function?**

Reproducible and accurate measurement of LV function provide valuable diagnostic and prognostic information in patients with cardiovascular disease. To answer the question whether contrast-enhanced echocardiography improves the evaluation of LV volumes and LVEF, Hundley et al. compared...
measured these from data acquired before and after intravenous contrast echocardiography and compared these measurements with quantitative assessments obtained by magnetic resonance imaging. The use of contrast improved the echocardiographic assessment of LV volumes and LVEF. The percentage of subjects in whom the correct echocardiographic classification of normal, mild to moderately reduced or severely depressed LVEF was achieved improved significantly after contrast enhancement. These findings were most striking in study subjects who had two or more adjacent poorly visualised segments.

However, in a larger study consisting of 110 patients, the accuracy of intravenous contrast echocardiography was found to be significantly better than unenhanced tissue harmonic imaging when compared to CMR irrespective of image quality. The LV volumes assessed by tissue harmonic imaging were consistently smaller, while those assessed during contrast echocardiography were less small compared to CMR. This is probably because tissue harmonic does not track the endocardium as well as contrast echocardiography and hence results in tracking noise in the left ventricle cavity, which is perceived as endocardial border. In this study contrast echocardiography was also more reproducible than tissue harmonic echocardiography. This fact was further demonstrated in a multicentre study using SonoVue.

Recently the advent of low-power contrast echocardiography has allowed simultaneous as-

Fig. 3. Percentage of patients with inadequate endocardial border delineation which changed following SonoVue® (Bracco, Milan) or saline/Albunex.

Fig. 4. Apical 4-chamber view. Left-hand panel: tissue harmonic imaging showing poor endocardial definition in the apico-lateral LV wall. Right-hand panel: contrast echocardiography clearly outlines all LV walls.
assessent of myocardial perfusion and function. While low-power myocardial perfusion has been extensively investigated, the ability of this technique to assess LV function was not extensively studied. However, a recent study, which already had investigated the usefulness of detection of myocardial perfusion following AMI, further evaluated the ability of contrast echocardiography to assess LV remodelling 7-10 days after AMI. All patients also underwent CMR at 7-10 days after AMI. Low-power contrast echocardiography was more accurate and reproducible than tissue harmonic imaging when CMR was considered the standard. Furthermore, low-power contrast echocardiography correctly identified patients with various grades of LVEF. This is important because LVEF after AMI is one of the major determinants not only of outcome but for decision-making regarding implantation of an automatic defibrillator.

In another study, Yu et al. also demonstrated the feasibility and accuracy of LVEF and LV volumes using contrast echocardiography. This was also demonstrated in critically ill patients in intensive therapy unit settings where accurate assessment of LV function is mandatory for proper management, under adverse imaging circumstances. Reilly et al. further evaluated these patients comparing the results with transoesophageal echocardiography and concluded that the use of intravenous contrast harmonic echocardiography significantly improved the feasibility and accuracy of estimated LVEF over tissue harmonic imaging. This study also demonstrated that contrast echocardiography is cost-effective in this setting.

Imaging techniques for assessment of LV function

Evidence suggests that harmonic contrast echocardiography gives the best signal-to-noise ratio for LV opacification. However, high transmit power may result in apical microbubble destruction. Furthermore, high transmit power due to its greater bubble destruction effect may also result in larger volumes of contrast to be injected in patients with large cardiac volumes to adequately opacify LV for proper endocardial definition. Thus, to minimise bubble destruction especially at the apex during contrast harmonic echocardiography, the transmit power should be reduced to intermediate levels and focal zone should be kept at intermediate depth. When mechanical index (MI) is used to define transmit power, an MI of >1 is high. It should be reduced to 0.5-0.6. With the advent of low-power imaging technologies, i.e. power pulse inversion, power modulation and coherent imaging, one can now achieve even better segmentation of LV cavity from the myocardial tissue. However, the frame rate drops quite significantly, but recent developments have resulted in improving the frame rate to approximately 25-30 MHz.

Automated quantification of LV function - the ultimate goal!

Even though automated endocardial border detection techniques have been developed, their ability to provide consistent reproducible results has been confounded by inadequate image quality. Although the use of contrast opacification of LV improves endocardial definition, the fact that it disturbs the balance between the low-intensity blood pool and higher-intensity myocardial tissue makes automated endocardial border detection unsuitable. The lower-power imaging modes selectively enhance microbubble-generated reflections because the microbubbles continue to reflect ultrasound non-linearly compared to the myocardial tissue which at the lower power behaves linearly. This may facilitate automated endocardial detection. The new power modulation technique which utilises low power has a higher sensitivity to weak echoes generated by low concentration of contrast media; this significantly reduces the attenuation and at the same time assesses the myocardial perfusion. Using this technique, it is feasible to automatically delineate endocardial border, colour encode and subsequently quantify global and regional LV wall motion (fig. 5). Studies are now underway to test the reproducibility of contrast-enhanced automated border detection for LVEF and regional function.

Fig. 5. Colour kinesis with contrast echocardiography showing the feasibility of qualitatively assessing regional wall motion.
Other applications of LV contrast opacification

Assessment of LV thrombus remains a difficult entity even with harmonic tissue imaging. Harmonic generation is poor in the near field. Noise, clutter and reverberation in the near field make fundamental echocardiography an almost useless technique to confidently identify apical masses. Contrast echocardiography under these circumstances provides unequivocal diagnosis (fig. 6). This has been clearly shown in a recent study by Thanigaraj et al. Another condition of the heart that may prove elusive to diagnosis by native echocardiography is apical hypertrophic cardiomyopathy. A recent case report from our laboratory clearly showed the utility of contrast echocardiography for the diagnosis of this entity (fig. 7). Non-compaction of LV has recently been identified in more patients with the advent of contrast echocardiography.

Stress echocardiography

One of the major challenges of modern cardiology is the detection or exclusion of flow-limiting coronary artery disease (CAD). Stress echocardiography is an established diagnostic method for the assessment of myocardial ischemia. Its widespread availability, feasibility in almost all circumstances, non-invasiveness, and relatively low cost has led to general acceptance of this diagnostic method. Interpretation of both pharmacologic and dynamic stress echocardiography is based on the evaluation of LV wall thickening and motion at rest and during stress. Clear visibility of the LV endocardium is essential for reliable assessment of wall motion abnormalities. Various factors, such as lung disease, obesity, or chest deformities, may impair image quality thus limiting reader confidence, decreasing diagnostic accuracy, and resulting in poor reproducibility. Image quality appears to be
one of the key factors determining the diagnostic accuracy of stress echocardiography.\textsuperscript{35}

**Improvement of LV cavity visualization using contrast agents**

Numerous studies have demonstrated improvement of endocardial border delineation during stress testing\textsuperscript{36-41} after administration of a transpulmonary contrast agent. In a multi-center study with SonoVue, two blinded observers compared native and contrast-enhanced stress echocardiographic images of 172 patients with unsatisfactory image quality at rest during an off-site assessment. The study demonstrated that contrast harmonic imaging was superior to all other imaging modalities regarding interobserver variability. The number of nondiagnostic tests, defined as the presence of at least two adequately delineated LV segments, decreased significantly rendering more than 95% of the previously unsatisfactory echocardiograms interpretable.\textsuperscript{42}

**Diagnostic value of contrast stress echocardiography**

Although improvement of LV visualization and reader confidence has been described in numerous studies, the impact on the diagnostic yield of stress echocardiography has not been investigated in depth. Uehara and coworkers\textsuperscript{43} reported improvement of the diagnostic accuracy for the circumflex artery only; this was due to most pronounced enhancement of endocardial border delineation in the lateral wall of the LV corresponding to the perfusion bed of this vessel. Another study\textsuperscript{44} compared sensitivity and specificity of dobutamine stress echocardiography in 112 patients with good LV visualization at rest with that in 117 patients with poor image quality during native imaging who underwent contrast echocardiography. These investigators found that in patients with poor image quality the use of contrast during dobutamine stress echocardiography significantly improved endocardial border delineation and resulted in a sensitivity and specificity for detection of CAD, comparable to that achieved with the native dobutamine stress in patients with good image quality.

The ability of contrast echocardiography to simultaneously assess perfusion potentially makes stress echocardiography a sensitive technique to detect flow-limiting CAD. Experimental studies have clearly indicated that identification of perfusion defect enhances the ability of dobutamine echocardiography not only to detect flow-limiting CAD but also to correctly identify multi-vessel disease, which has prognostic importance.\textsuperscript{45,46} Recent clinical studies have indicated that myocardial perfusion abnormality detection significantly enhanced the ability of dobutamine echocardiography for the detection of CAD\textsuperscript{47-49}. In those patients who are unable to exercise or undergo dobutamine echocardiography (e.g. life-threatening arrhythmias, severe LV dysfunction) or when these tests are difficult to interpret, (e.g. LBBB, pacing, systemic etc), vasodilator myocardial contrast echocardiography may be performed. Vasodilator MCE has been found to be accurate and even superior to SPECT for the detection of CAD\textsuperscript{50,51}.

In a novel study, Moir et al.\textsuperscript{52} used a dipyridamole-exercise MCE protocol whereby wall motion assessment was maximised, and exercise parameters were obtained together with data on myocardial perfusion. They found that wall motion assessment without contrast underestimated diagnosis and extent of CAD compared to wall motion and perfusion assessment using low-power MCE.\textsuperscript{52}

**Conclusion**

Contrast echocardiography, both at rest and stress, provides valuable clinical information by allowing simultaneous assessment of both function and perfusion at rest and during stress.

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