Head-to-Head Comparison of Fundamental, Tissue Harmonic and Contrast Harmonic Imaging With or Without an Air-Filled Contrast Agent, Levovist, for Endocardial Border Delineation in Patients With Poor Quality Images

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Recent developments in tissue harmonic imaging and intravenous contrast agents have enhanced left ventricular endocardial border delineation (EBD). In a total of 48 patients with poor quality images, apical 4- and 2-chamber views were obtained with fundamental, tissue harmonic and contrast harmonic imaging with or without intravenous Levovist, an air-filled contrast agent. The left ventricle (LV) was divided into 12 segments, and the EBD of each segment was scored: (1) not visible, (2) barely visible, (3) well delineated. The EBD index (EBDI), defined as the sum of the endocardial scores divided by 12 was obtained for each patient. Of a total of 576 LV segments, 231 were scored as 1 by fundamental imaging and that number decreased to 125 segments by tissue harmonic imaging and 116 segments by fundamental imaging with Levovist. The number of segments scored as 1 decreased to 38 segments by tissue harmonic imaging with Levovist, and to 29 segments by contrast harmonic imaging with Levovist. The EBDI by fundamental imaging was 1.85±0.29, which improved significantly with the addition of Levovist (2.10±0.36, p<0.001) and was nearly identical to that by tissue harmonic imaging (2.15±0.32, p=NS). Tissue and contrast harmonic imaging with Levovist further enhanced the EBDI (2.43±0.26, 2.51±0.27, respectively). Levovist enhances EBD, even in the fundamental mode, to the level obtained with tissue harmonic imaging. Tissue harmonic and contrast harmonic imaging are the best modalities for enhancing EBD after Levovist injection. (Circ J 2002; 66: 494–498)

Key Words: Contrast agent; Harmonic imaging; Levovist; LV opacification

Two-dimensional echocardiography is the method of choice for evaluating left ventricular (LV) systolic function in various cardiovascular diseases because it is non-invasive and versatile. The prerequisite for accurate and reliable assessment of LV function is clear visibility of the entire endocardium in each cross-sectional image, but the conventional imaging methods result in approximately 20% of studies being suboptimal, particularly of the anterior and the lateral wall.2 With the advent of tissue harmonic imaging, that percentage has fallen, but 5–10% of cases still have suboptimal results.1,3 The introduction of transmural contrast agents has further reduced the number of suboptimal cases and are useful for endocardial border delineation (EBD) at rest and during stress echocardiography.1,4–8 From September 1999, an-air-filled contrast agent, Levovist, became commercially available in Japan for LV border delineation and myocardial perfusion. The rapid advancement in ultrasound technology and improved understanding of microbubble properties, together with a different dosing regimen in Japan (2.5 g vial up to 300 mg/ml) vs Europe (4.0 g vial up to 400 mg/ml) could account for the differing results from previous studies.9–11 Thus, we have to standardize the use of Levovist for LV border opacification. In addition, many clinicians and sonographers in Japan still use ultrasound machines without harmonic equipment and they want to know whether fundamental imaging with Levovist will enhance their assessment of LV function in day-to-day clinical practice. The aim of this study was to determine (1) which modality is best suited for enhancing LV border delineation with Levovist and (2) whether Levovist would improve EBD, even with fundamental imaging, in technically difficult cases.

Methods

The study group consisted of 48 patients (30 men, 18 women; mean age: 69±13 years) who had incomplete endocardial visualization of 2 or more endocardial segments in apical 4- and 2-chamber views (12-segment model) by fundamental imaging. Informed consent was obtained from all patients who participated in this study. Exclusion criteria were pregnancy, galactosemia, hyperreactivity to Levovist, and unstable hemodynamic status.

Study Protocol

Image Acquisition Without Levovist Optimal fundamental imaging in the apical 4-chamber view was obtained using a commercially available echocardiographic system
with a broadband transducer (S4, SONOS5500, Philips Medical Systems, Andover, MA). A high mechanical index (>1.4) and adjustment of the lateral gain control were used to enhance EBD. Overall gain, compression, time-gain-compensation and the focus level were adjusted in each patient. After getting the best image, 3 consecutive cardiac beats in the apical 4-chamber view and apical 2-chamber view were digitally acquired and stored on the magneto-optical disk. The SONOS5500 is equipped with 2 harmonic modes: harmonic fusion imaging (so-called tissue harmonic imaging) and contrast harmonic imaging. The major differences in the 2 modes are the mechanical index and the internal gains. For tissue harmonic imaging, the mechanical index is set highest (>1.4), whereas for contrast harmonic imaging, it is set around 1.0. In order to adjust the brightness of the myocardium similarly for each modality, the gain was relatively higher in the contrast harmonic mode than in tissue harmonic mode. Otherwise, the same procedure was performed.

**Image Acquisition With Levovist**

The addition of 7-8 ml of sterile water into the 2.5 g Levovist vial (Tanabe Seiyaku, Inc, Tokyo, Japan and Schering AG, Germany) constituted 8 ml of Levovist solution (300 mg/ml). Because the dose required for optimum delineation of the LV endocardial border during fundamental imaging is higher than for harmonic imaging,12 either 2 ml (tissue harmonic and contrast harmonic imaging) or 4 ml of Levovist (fundamental imaging) was administered intravenously followed by a slow saline flush from an in-dwelling cannula inserted into the antecubital vein. Taking the accumulation effect of Levovist into consideration for the subsequent injection, the sequence of the imaging mode was randomized in each patient, and we waited at least 3 min between injections to eliminate or disperse the microbubbles in the circulation. The focus was set at the upper third of the LV to decrease bubble destruction in the near field. Other system settings were adjusted before the contrast injection. To enhance the full opacification of the LV cavity and to accomplish minimal bubble destruction until the Levovist entered the LV cavity, intermittent diastolic triggering every sixth cardiac beat in the apical 4-chamber view was initiated just before the contrast injection. Immediately after the LV cavity was completely filled with contrast, we changed to the continuous mode, and digitally acquired 3 consecutive cycles of apical 4- and 2-chamber views as quickly as possible. The images were stored on the magneto-optical disk.

**Image Interpretation**

The LV was divided into 6 segments in both the apical 4-chamber view (basal, mid and apical interventricular septum and lateral wall) and 2-chamber view (basal, mid and apical anterior and inferior wall). EBD was classified using a 3-point scoring system ((1) not visible, (2) barely visible and (3) well delineated) in each of the 12 segments by 2 observers blinded to the clinical data. If a discrepancy appeared, a third observer assessed the image and consensus was reached. The EBD index (EBDI), defined as the sum of endocardial scores divided by 12, was obtained in each imaging mode.

**Statistical Analysis**

Data are expressed as mean ± SD. The differences in the endocardial scores among the 6 groups were tested at first with analysis of variance for repeated measures, and then for multiple comparisons with Wilcoxon signed rank test. Discontinuous variables were analysed using chi-square test. A probability value of p<0.05 (or p<0.01 when multiple comparisons were attempted) was considered significant.

**Results**

The patient demographics are listed in Table 1. There were no differences in heart rate and diastolic pressure and systolic blood pressure before and after contrast injection for each mode of imaging. By fundamental imaging, 17 patients had a wall motion abnormality and the mean value of the wall motion score index was 1.14±0.29 (range: 1.00–2.17).

**Uninterpretable Segments**

Of a total of 576 segments from 48 patients, the regional LV endocardial border was not seen in 231 segments when using fundamental imaging. An average of 4.8 of 12 segments per patient (40%) were uninterpretable for the endocardial border (Score 1), and these segments were often observed in the anterior or lateral wall. The number of uninterpretable segments decreased with harmonic imaging (125 segments in tissue harmonic imaging, 114 segments in contrast harmonic imaging). Of the 231 segments with score 1 from fundamental imaging, 115 segments became score 2 or 3 with fundamental imaging combined with Levovist, and of these 115 segments, which were became interpretable after Levovist injection, a segmental wall motion abnormality was observed in 18 segments (hypokinesia in 11, akinesis/dyskinesia in 7). Harmonic imaging with Levovist further enhanced EBD, and 193 and 202 segments became score 2 or 3 by tissue harmonic with Levovist and contrast harmonic with Levovist, respectively. Of 202 segments, which became interpretable by contrast harmonic with Levovist, a wall motion abnormality was observed in 28 segments (hypokinesia in 15, akinesis/dyskinesia in 13). A representative case is shown in Fig 1.

**Endocardial Border Delineation Index**

The EBDI for each modality is shown in Fig 2. Harmonic imaging or the addition of Levovist in each imaging significantly improved the EBDI compared with fundamental imaging (p<0.001). The EBDI obtained from fundamental imaging with Levovist was nearly identical to that for

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tissue harmonic imaging (2.10±0.36 vs 2.15±0.32, p=NS). The best results were obtained by harmonic imaging with Levovist. The interobserver agreement was 94% (κ=0.93) using the 3-point scoring system.

Comparison Between Fundamental Imaging With Levovist and Tissue Harmonic Imaging for Regional Endocardial Border Delineation

The result of tissue harmonic imaging alone and fundamental imaging with Levovist for EBD in each segment is shown in Fig 3. Compared with fundamental imaging alone, both methods significantly improved EBD in the majority of segments, although these improvements on a regional basis were somewhat different for each modality. Table 2 shows the rate of improvement of an endocardial segments score of 1 in each modality compared with fundamental imaging alone. Although the total number of segments that improved was nearly identical between fundamental imaging with Levovist and tissue harmonic imaging, fundamental imaging with Levovist improved more apical EBD than tissue harmonic imaging. On the other hand, tissue harmonic imaging enhanced more endocardial borders in the mid to basal segments.

Comparison Between Tissue Harmonic Imaging and Harmonic Imaging With Levovist for Regional Endocardial Border Delineation

Compared with tissue harmonic imaging alone, harmonic imaging with Levovist significantly improved EBD in the mid to apical regions (Fig 3, Table 2). Although there was not a statistically significant difference, contrast harmonic imaging with Levovist showed the highest value in a majority of segments. Although contrast agents may produce attenuation and degradation of images, especially from the basal LV, there was no significant difference in the degradation rate between the base and apex in this study.

Discussion

This study demonstrated that harmonic imaging with an air-filled contrast agent, Levovist, can enhance EBD in patients with poor quality images. We also demonstrated that the addition of Levovist improved EBD even in fundamental imaging and this improvement resulted in images nearly identical to those obtained by tissue harmonic imaging. Many segments that were uninterpretable on...
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fundamental imaging became interpretable with the use of Levovist, and a wall motion abnormality could be detected in some segments. These results suggest that Levovist can unmask a wall motion abnormality not seen by fundamental imaging alone and thus enhance reliable assessment of LV systolic function. The strength of this study was the head-to-head comparison of each modality for enhancing EBD in the same patient group.

Technical Caveats

Levovist is an air filled first-generation contrast agent with a thin permeable shell comprising palmitic acid. Its microbubbles are highly echogenic and are sufficiently stable for transit through the pulmonary circuit. Both preclinical and clinical studies with Levovist demonstrate its capacity to traverse the pulmonary bed in sufficient concentrations to enhance both colour Doppler and, in some instances, the B-mode image itself. However, unlike second-generation intravenous contrast agents, it is easily destroyed by ultrasound energy and the air diffused readily into the blood making it inferior for dense LV opacification. To overcome these limitations, we applied the triggered mode until the LV cavity was completely filled with the contrast. Microbubble destruction is minimized by decreasing their exposure to ultrasound, which can be achieved by triggered imaging during microbubble transit through the right heart chambers, increasing the microbubble concentration in the LV cavity and enhancing LV border delineation. Although this enhancement was transient after continuous imaging resumed, this form of imaging can have a greater effect if the first 2 or 3 cardiac cycles after resuming imaging are captured and displayed in a cine-loop format. Another important setting is the level of focus. If it is set at the middle to lower level of the LV, preferential apical bubble destruction because of overlapping ultrasound beams causes less apical opacification and may preclude reliable apical EBD. Setting the focus at the apical level narrows the individual beam width and reduces the rate of bubble destruction, which enhances apical endocardial delineation. Finally, reduction of the mechanical index can decrease bubble destruction, but may not be ideal for Levovist because it is easily broken up even at a low mechanical index, and produces less signal enhancement.

Tissue Harmonic Imaging vs Fundamental Imaging With Levovist

This study demonstrated that the improvement in the EBDI was nearly identical between tissue harmonic imaging and fundamental imaging with Levovist. However, the improvement differed somewhat with regard to the LV site. Tissue harmonic imaging enhances EBD in patients with poor acoustic windows. The intensity of the generated second harmonic signal is proportional to the distance from
the transducer, so a stronger signal will come back from the basal to mid LV than from the apical LV, which is what we found in this study. Fundamental imaging with Levovist showed better apical endocardial delineation than did tissue harmonic imaging, probably because the generation of native second harmonic frequency in the near field may be insufficient, even though near field artefacts are suppressed. Although the best results were obtained with harmonic imaging with Levovist, its use with fundamental imaging has some potential for improving endocardial visualization, especially in the apical regions.

Study Limitations

The observers were not blinded to the type of imaging modality while scoring, but in any case the distinctive features of each modality could not exclude this bias. Although we made a head-to-head comparison of 3 imaging modalities for enhancing LV border delineation, there was no gold standard for its reliability. Improvement in LV border delineation does not always accompany accurate assessment of LV systolic function. However, conversion of a non-diagnostic into a diagnostic study would enhance our ability to reliably assess LV function in daily clinical practice. With multiple doses of contrast agent in the same patient, there may have been cumulative effects that could have confounded the results. Although this effect could not be entirely eliminated, randomization of the imaging sequence in each patient could equally affect overall results.

The dose of contrast agent for fundamental imaging might have been insufficient because it should be approximately 3 times higher than that used for harmonic imaging. However, 4 ml of Levovist can be used as maximal dose, which allows for 2 injections in different windows or different stages during a stress study from 1 vial.

In the case of severe left ventricular dysfunction and/or a dilated LV cavity, accurate EBD might be difficult because of the swirling of microbubbles in the cavity.

Clinical Implications

Our results demonstrated LV border delineation improved using Levovist with both fundamental and harmonic imaging in patients with poor acoustic windows. However, fundamental imaging should only be used when harmonic imaging is not available, because harmonic imaging uses a lower dose of Levovist and better appreciation of LV borders. A significant number of suboptimal examinations can be salvaged using intravenous contrast injections, which should enhance the quality of echocardiographic examination in the daily clinical setting.

References