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# Improvement of Endocardial Border Delineation During Dobutamine Stress Echocardiography With Levovist™

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**Abstract**

***Objectives***. This study evaluated whether the use of Levovist™ improves endocardial border delineation during dobutamine stress echocardiography.

***Methods***. Thirty patients(20 men and 10 women)were enrolled in this study. Dobutamine was infused intravenously using an incremental regimen of 5, 10, 20, 30, and 40 μg/kg/min, each dose for 3 min. Levovist(277 mg/m*l*), dissolved in 9 m*l* of 5% dextrose, was infused intravenously. Two m*l* was infused at rest, 10, and 20 μg/kg/min. Three m*l* was infused at peak dobutamine dosage. Echocardiograms were recorded on videotapes. A endocardial border delineation score index(EDSI)was used for image analysis. The EDSI was obtained from each of 12 segments of the left ventricular wall(30 patients)in the rest and peak stress periods, before and after Levovist. Data from a total of 1,440 segments were analyzed separately.

***Results***. The mean EDSI at rest was 2.2 ± 0.6 without contrast medium, and 2.4 ± 0.7 with contrast medium($p < 0.05$). The mean EDSI during peak stress was 2.0 ± 0.7 without contrast medium, and 2.2 ± 0.6 with contrast medium($p < 0.05$). The wall-by-wall EDSI revealed that the delineation of apical-septal, mid- and apical-lateral, apical-inferior, and apical-anterior segments was improved significantly with Levovist in the rest and peak stress periods.

***Conclusions***. Delineation of the apical-septal, mid- and apical-lateral, apical-inferior, and apical-anterior segments was improved significantly with Levovist during dobutamine stress echocardiography.

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**Key Words**

■**Contrast echocardiography** ■**Stress echocardiography (dobutamine)**
■**Contrast media (Levovist™)** ■**Coronary heart disease**

## INTRODUCTION

Dobutamine stress echocardiography(DSE)is an effective procedure for the diagnosis of coronary artery disease[1,2]. Accurate delineation of the endocardial border is important in the use of DSE. Characteristics of the ultrasound system and individual patient factors, such as obesity, emphysema, and chest deformity, all affect endocardial border delineation. However, dobutamine is a synthetic catecholamine that has strong $beta_1$-receptor and mild $alpha_1$- and $beta_2$-receptor agonist activity[1]. Dobutamine induces sinus tachycardia, cardiac arrhythmias, and symptomatic side effects such as

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chest pain, hypotension, nausea, *etc*.[3], so DSE can only provide accurate endocardial border delineation in the non-stress setting. Use of the second harmonic mode has improved endocardial border delineation and the feasibility of performing DSE[4–6], but problems due to patient-dependent factors still occur. Contrast agents can enhance endocardial border delineation in the non-stress setting[7–11], and so may improve endocardial border delineation during DSE[12–14].

The present study evaluated the use of the ultrasound contrast agent "Levovist™" to improve endocardial border delineation during DSE.

## SUBJECTS AND METHODS

### Patients

Thirty patients, 20 men and 10 women, aged 53 to 78 years (mean 69 ± 7.5 years) underwent DSE for the investigation of ischemia between July and October 2002. All patients had stable clinical status.

### Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed as previously described[3,15]. Dobutamine was infused intravenously using an incremental regimen of 5, 10, 20, 30, and 40 μg/kg/min, each dose given for 3 min. Intravenous atropine (up to 1 mg) was given if the target heart rate was not achieved at the peak dose of dobutamine infusion (40 μg/kg/min). The endpoints for DSE were: development of a new wall-motion abnormality or worsening of a preexisting wall motion abnormality in one or more contiguous segments, achievement of 85% of the maximal heart rate (220 beats/min minus age), end of dobutamine infusion and atropine infusion, or emergence of significant side effects. Blood pressure was recorded at each stage. Twelve-lead electrocardiography was recorded at the baseline and peak dobutamine dosage.

### Levovist

Levovist (2.5 g; Tanabe Seiyaku, Inc., Schering AG) was diluted to 277 mg/m*l* with 9 m*l* of 5% dextrose and infused intravenously. Two m*l* was infused at rest, 10, and 20 μg/kg/min. Three m*l* was infused at peak dosage. Levovist (a first-generation contrast agent) consists of galactose microparticles adhering to palmitic acid-stabilized microbubbles filled with air. Levovist is a fragile contrast material, so is gradually deactivated after mixing with 5% dextrose. Levovist quality declines between rest and the peak dobutamine dosage because of the elapsed time. We compensated for this reduced quality with increased quantity. However, if the Levovist was deactivated before the peak dose was reached, we administered another dose of Levovist to achieve left ventricular opacification.

### Echocardiographic analysis

Ultrasonography was performed with an ATL HDI 5000 system (ATL) using a P4-2 transducer. Second harmonic mode was used for all stress tests. The apical views and parasternal views without contrast (Levovist) were acquired first. Levovist was then infused intravenously and the apical view was acquired. Dobutamine infusion was started after image acquisition at rest. Images at peak stress were taken with these same procedures. Echocardiograms were recorded on videotapes. The left ventricle was divided into a 16-segment model according to the recommendation of the American Society of Echocardiography[16]. The images of the left ventricle with Levovist contrast medium did not provide the parasternal view because of invasion by the acoustic shadowing from the right ventricle. Therefore, only the parasternal view was taken without Levovist. We omitted four segments (basal-anteroseptal, mid-anteroseptal, basal-posterior, and mid-posterior) from the analysis because these segments are usually assessed in the parasternal view.

### Image analysis

The endocardial border delineation score index (EDSI) was used[12]. The score was 0 for no endocardial segment visible, 1 for poor endocardial delineation, 2 for satisfactory delineation, and 3 for excellent delineation. The EDSI was obtained from each of the 12 segments at rest and during peak stress periods before and after Levovist. A total of 1,440 segments were analyzed separately. Two independent and experienced echocardiographers analyzed all images. The mean score was adopted in cases of discrepancy.

### Statistical analysis

The paired Student's *t*-test was used for continuous variables. A $p$ value of $< 0.05$ was considered statistically significant.

**Table 1 Comparison of the endocardial border delineation score index of segments at rest and peak stress periods**

| | Analysis of each wall endocardial border delineation score index | | | | | |
|---|---|---|---|---|---|---|
| | Rest Levovist (−) | Rest Levovist (+) | *p* value | Peak Levovist (−) | Peak Levovist (+) | *p* value |
| Septum | | | | | | |
| Base | 2.6±0.6 | 2.8±0.5 | NS | 2.4±0.8 | 2.5±0.7 | NS |
| Mid | 2.8±0.5 | 2.8±0.5 | NS | 2.6±0.6 | 2.6±0.6 | NS |
| Apical | 2.5±0.5 | 2.7±0.6 | <0.05 | 2.3±0.7 | 2.6±0.5 | <0.05 |
| Lateral wall | | | | | | |
| Base | 1.5±1.0 | 2.0±1.0 | <0.05 | 1.4±0.9 | 1.7±0.8 | NS |
| Mid | 1.8±0.9 | 2.3±0.9 | <0.05 | 1.8±0.9 | 2.2±0.7 | <0.05 |
| Apical | 2.3±0.7 | 2.5±0.7 | <0.05 | 2.2±0.7 | 2.5±0.7 | <0.05 |
| Inferior wall | | | | | | |
| Base | 2.4±0.8 | 2.4±0.9 | NS | 2.0±0.9 | 2.2±0.7 | NS |
| Mid | 2.5±0.8 | 2.6±0.7 | NS | 2.3±0.7 | 2.5±0.6 | NS |
| Apical | 2.3±0.7 | 2.6±0.7 | <0.05 | 2.1±0.7 | 2.5±0.6 | <0.05 |
| Anterior wall | | | | | | |
| Base | 1.6±0.9 | 1.8±1.0 | NS | 1.4±1.0 | 1.5±0.9 | NS |
| Mid | 1.9±1.0 | 2.1±1.1 | NS | 1.8±1.0 | 2.0±0.8 | NS |
| Apical | 2.1±0.8 | 2.3±0.9 | <0.05 | 1.9±0.9 | 2.3±0.7 | <0.05 |
| Mean | 2.2±0.6 | 2.4±0.7 | <0.05 | 2.0±0.7 | 2.2±0.6 | <0.05 |

Values are mean±SD.

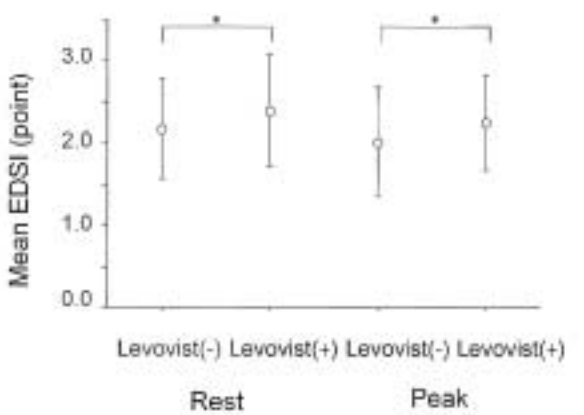


**Fig. 1 Mean endocardial border delineation score indexes in the rest and peak stress periods without and with Levovist**
*$p < 0.05$ paired *t*-test.
EDSI = endocardial border delineation score index.

## RESULTS

No patient suffered significant side effects. A total of 1,440 segments, 360 at rest without Levovist, 360 at rest with Levovist, 360 at peak stress without Levovist, and 360 at peak stress with Levovist, were analyzed.

The mean EDSI at rest was 2.2 ± 0.6 without contrast medium, and 2.4 ± 0.7 with contrast medium ($p < 0.05$). The mean EDSI at peak stress (dobutamine dosage) was 2.0 ± 0.7 without contrast medium, and 2.2 ± 0.6 with contrast medium ($p < 0.05$). The mean EDSIs in the peak and rest periods without and with Levovist are compared in **Fig. 1**. The EDSI of each segment in the rest and peak stress periods are listed and compared in **Table 1**. Images of the apical-septal, mid- and apical-lateral, apical-inferior, and apical-anterior segments were improved significantly with Levovist in the rest and peak periods. The images of basal-lateral segments were improved significantly with Levovist in the rest period. The images of other segments were not improved significantly (**Fig. 2**). Two representative cases are shown in **Figs. 3**, **4**.

## DISCUSSION

The present study showed that mean EDSI increased with the use of Levovist in the rest and peak stress periods. However, wall-by-wall EDSI analysis revealed that the images of only 5 of 12 segments (including all apical segments) were improved significantly with Levovist during these periods. Adequate apical segment images are difficult to obtain because most artifacts originate in these regions. The second harmonic mode reduced

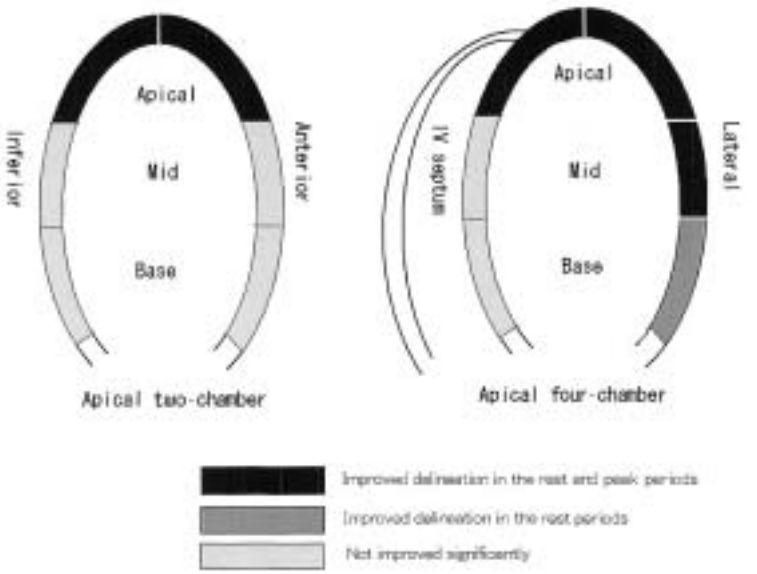


**Fig. 2 Effect of Levovist on border delineation of each segment in the rest and peak stress periods**

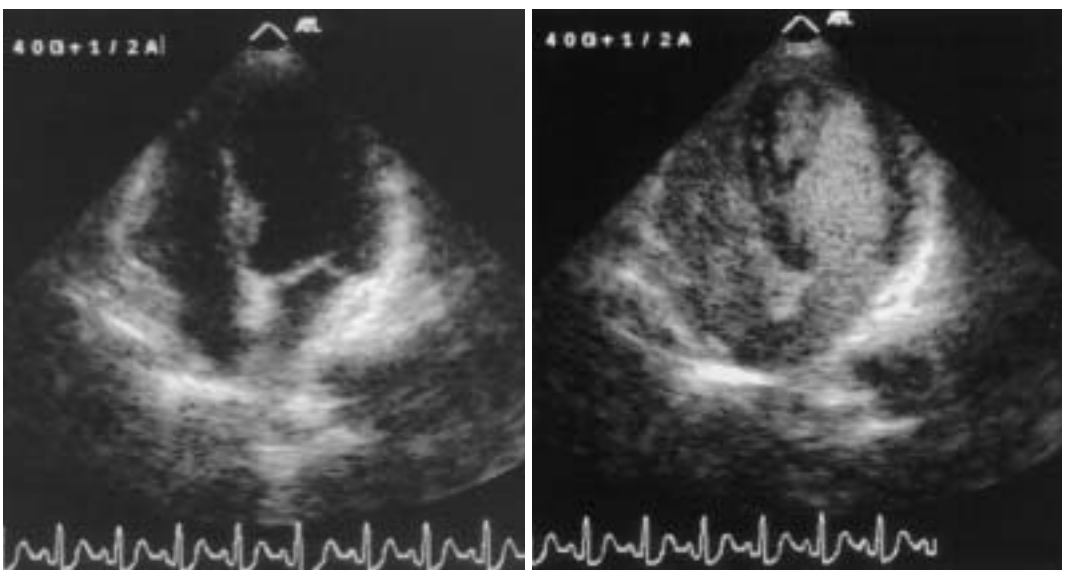


**Fig. 3 Representative example of a good quality image**
Images show the diastolic apical four-chamber view with (*right*) and without (*left*) contrast medium when the patient's heart rate was 138 beats/min. The endocardial border was clearly delineated with contrast medium.

but did not eliminate these artifacts[8]. Levovist is useful for obtaining adequate apical segment images in non-stress settings[7,17]. Our results show that Levovist is useful in both non-stress and stress settings. Basal-lateral segment images are improved in the rest period, but not in the peak stress period. This difference may be due to acoustic shadowing because the basal-lateral segment is sometimes affected by acoustic shadowing. We suppose that the basal-lateral segment is more frequently affected by acoustic shadowing during the peak stress period because of dobutamine induced tachycardia. Contrast material such as Levovist is expensive, so routine use is not recommended. Although our results show that mean EDSI improved in the rest (2.2 to 2.4) and peak (2.0 to 2.2) periods, these improvements were small (only 0.2) and cannot justify routine use of Levovist.

Selection of patients who might benefit from the

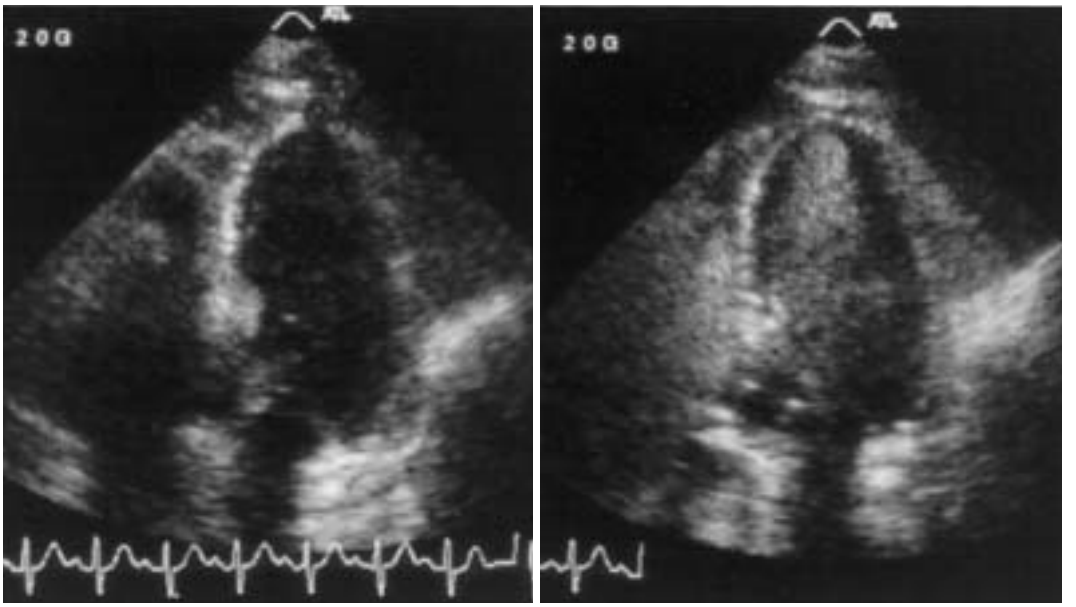

**Fig. 4 Representative example of a poor quality image**
Images show the diastolic apical four-chamber view with (*right*) and without (*left*) contrast medium when the patient's heart rate was 125 beats/min. This poor image quality is probably due to pulmonary emphysema and obesity (body mass index 31). Although this quality without contrast medium was suboptimal, the endocardial border, especially of the apical wall, was delineated with contrast medium.

use of contrast material is important. We classified our patients into three categories: Class A, the endocardial border was clearly delineated; Class B, the endocardial border was partly delineated and the obscure endocardial border included all apical segments or mid-lateral segments; and Class C, the endocardial border was partly delineated and the obscure endocardial border did not include any apical segments or mid-lateral segments. Levovist is unnecessary for Class A patients. Levovist is also unnecessary for Class C patients because the images of the obscure segments would not be improved. We recommend Levovist only for Class B patients, the only category to benefit from its use.

**Comparison with previous studies**

We showed that mean EDSI increased with the use of Levovist in the rest and peak periods. This finding is similar to that in previous studies using various contrast agents. The contrast agent Optison improved wall segment visualization during DSE[13]. Image quality was scored using a 5-point scale. To obtain this score, whole wall images were graded rather than images of each wall segments. Therefore, which segments would most benefit from the use of contrast agents was not determined. The contrast agent Albunex™ improved endocardial delineation score during DSE[14]. The septal segment and lateral segment images were studied taken from an apical four-chamber view. SH U 508A improved endocardial border delineation in suboptimal stress echocardiography[18]. Left ventricular angiography was used as the "gold standard". However, the study population was small, with five patients for dobutamine stress and five patients for dipyridamole.

The use of perfluorocarbon-exposed sonicated dextrose albumin microbubbles as contrast agents improved endocardial border delineation during dobutamine-atropine stress echocardiography[12]. Analysis of the images of each wall segment concluded that endocardial delineation was improved for all walls with contrast medium, especially the lateral and anterior walls. No difference in contrast was found between the apical, mid, and basal portions of each segment as seen in our study. We emphasize the importance of this difference because the ultrasound field during echocardiography is not even. Our three classes of patients are based on those differences. Our findings suggest selective use of contrast agent is appropriate.

**Limitations of the study**

The limitations of the study include the retro-

spective nature. The analysis of endocardial delineation was semi-quantitative, which introduces observer bias. The doses of Levovist（277 mg/m*l*）were 550 mg at rest and 830 mg at peak. We did not compare other doses or concentrations. The optimum concentration for left ventricular delineation may be 300 mg/m*l*[19]. More adequate images might be obtained with optimal doses and concentrations. We showed that Levovist improved endocardial delineation. However, our study did not address the sensitivity and specificity of DSE, because each case was not compared with a " gold standard " such as coronary angiography or myocardial scintigraphy. Whether improvement of endocardial delineation always enhances the diagnostic accuracy of DSE remains to be classified.

## CONCLUSIONS

Levovist improves endocardial delineation during DSE. The images of the apical-septal, mid- and apical-lateral, apical-inferior, and apical-anterior segments were improved significantly with the use of Levovist contrast medium.


## 要　約

### ドブタミン負荷心エコー図法におけるレボビスト™使用による心内膜面描出能の向上

坂倉　建一　　刀根　克之　　垣 本　斉　　小山　美貴　　関岡　清次

**目　的**: 本研究の目的は，ドブタミン負荷心エコー図法施行時に超音波造影剤レボビストを使用することによって，心内膜面描出能が改善するかどうかを検討することである．

**方　法**: 虚血性心疾患の疑いのある30例（男性20例，女性10例）が本研究に参加した．ドブタミンを経静脈的に投与し，3分ごとに5，10，20，30，40 μg/kg/minと増量した．レボビストは5%ブドウ糖液9 m*l*で溶解し，277 mg/m*l*の濃度とし，安静時，10，20 μg/kg/min，およびピーク時にそれぞれ，2 m*l*ずつ（ただし，ピーク時は3 m*l*）経静脈的に投与した．心エコー図はビデオテープに記録され，検査終了後にそのビデオテープを元に心内膜面描出スコアインデックス（EDSI）を算出した．EDSIは各患者において一つ一つの分画（12分画）から，ドブタミン投与前安静時と投与後ピーク時にそれぞれレボビスト使用前と使用後で算出した．合計1,440分画が分析された．

**結　果**: 安静時の平均EDSIはレボビスト投与前で2.2±0.6，レボビスト投与後に2.4±0.7（$p<0.05$）．ピーク時の平均EDSIはレボビスト投与前で2.0±0.7，レボビスト投与後に2.2±0.6（$p<0.05$）であり，レボビスト投与によって安静時，ピーク時ともに平均EDSIは有意に増加した．各分画ごとに検討すると，心尖部中隔，心尖部側壁，心尖部下壁，心尖部前壁，中部側壁において安静時，ピークともに有意にレボビストによってEDSIが増加した．

**結　論**: レボビストはドブタミン負荷心エコー図法中の心内膜面描出を改善する．とりわけ，心尖部中隔，心尖部側壁，心尖部下壁，心尖部前壁，中部側壁がレボビストによって有意に内膜面描出が改善する領域である．


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