Improved Left Ventricular Endocardial Border Delineation and Opacification With OPTISON (FS069), a New Echocardiographic Contrast Agent

Results of a Phase III Multicenter Trial

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Objectives. The echocardiographic contrast-enhancing effects and safety profile of ALBUNEX (a suspension of air-filled albumin microspheres) were compared with the new contrast agent OPTISON (formerly FS069: a suspension of albumin microspheres containing the gas perfluoropropane) in 203 patients with inadequate noncontrast echocardiograms.

Background. The efficacy of ALBUNEX has been limited by its short duration of action. By using perfluoropropane instead of air within the microsphere, its duration of action is increased.

Methods. Each patient received ALBUNEX (0.8 and 0.22 mL/kg) and OPTISON (0.2, 0.5, 3.0, and 5.0 mL) on separate days a minimum of 48 hours apart. Echocardiograms were evaluated for increase in left ventricular (LV) endocardial border length, degree of LV opacification, number of LV endocardial border segments visualized, conversion from a nondiagnostic to a diagnostic echocardiogram, and duration of contrast enhancement. A thorough safety evaluation was conducted.

Results. Compared with ALBUNEX, OPTISON more significantly improved every measure of contrast enhancement. OPTISON increased well-visualized LV endocardial border length by 6.0 ± 5.1, 6.9 ± 5.4, 7.5 ± 4.7, and 7.6 ± 4.8 cm, respectively, for each of the four doses, compared with only 2.2 ± 4.5 and 3.4 ± 4.6 cm, respectively, for the two ALBUNEX doses (p < 0.001). 100% LV opacification was achieved in 61%, 73%, 87%, and 87% of the patients with the four doses of OPTISON, but in only 16% and 36% of the patients with the two ALBUNEX doses (p < 0.001). Conversion of nondiagnostic to diagnostic echocardiograms with contrast occurred in 74% of patients with the optimal dose of OPTISON (3.0 mL) compared with only 26% with the optimal dose of ALBUNEX (0.22 mL/kg) (p < 0.001). The duration of contrast effect was also significantly greater with OPTISON than with ALBUNEX. In a subset of patients with potentially poor transpulmonary transit of contrast (patients with chronic lung disease or dilated cardiomyopathy), OPTISON more significantly improved the same measures of contrast enhancement compared with ALBUNEX and did so to the same extent as in the overall population. Side effects were similar and transient with the two agents.

Conclusion. OPTISON appears to be a safe, well-tolerated echocardiographic contrast agent that is superior to ALBUNEX.

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Since its introduction, ALBUNEX has had only partial success as an echocardiographic contrast agent (1–5). Unfortunately, when given intravenously, its power to enhance left ventricular (LV) structures has been limited by its relatively short duration of action. ALBUNEX consists of microspheres prepared by the sonication of human albumin in the presence of air.
OPTISON, formerly known as FS069, was developed to stabilize these microspheres and prolong their duration of action. To achieve this, a 1% solution of human albumin is sonicated in the presence of an inert gas, perfluoropropane. Like ALBUNEX, the product is fully manufactured and is ready for injection after simple resuspension. Preliminary studies have demonstrated the improved contrast effect and increased duration of OPTISON (6,7). We report here the first multicenter clinical trial of OPTISON. Its efficacy and safety are compared with ALBUNEX in patients with suboptimal routine echocardiograms.

Methods

Study design. This study was a prospective, multicenter comparison of two intravenous echocardiographic contrast agents, ALBUNEX and OPTISON. The principal objectives of the study were to compare the contrast-induced increase in LV endocardial border delineation, degree of LV chamber opacification, number of LV endocardial border segments visualized, conversion from a nondiagnostic to diagnostic echocardiogram, and duration of contrast effect of the two agents in patients with poorly defined noncontrast echocardiograms. The safety and tolerability of the two agents were also compared.

Patient selection. Patients were selected from those undergoing routine diagnostic echocardiography at 14 investigative sites. To be included, patients had to have poor LV endocardial border delineation, i.e., at least two of six endocardial segments in the apical four-chamber view not adequately visualized. The study was approved by the human subjects review committee at the participating institutions. Signed informed consent was obtained for each patient prior to enrollment in the study. For female patients of child-bearing potential, a negative serum pregnancy test within 24 h of enrollment in the study. For female patients of child-bearing potential, a negative serum pregnancy test within 24 h of enrollment in the study. For female patients of child-bearing potential, a negative serum pregnancy test within 24 h of enrollment in the study. For female patients of child-bearing potential, a negative serum pregnancy test within 24 h of enrollment in the study.

Exclusion criteria were: known or suspected hypersensitivity to blood, blood products or albumin; pregnancy or lactation; recent cerebrovascular event or transient ischemic attack within the previous 6 months; confinement to an intensive care unit or on a mechanical ventilator; New York Heart Association class IV congestive heart failure; LV ejection fraction <20%; or severe liver disease.

From this study population, a subgroup of patients was identified who had dilated cardiomyopathy or chronic pulmonary disease, conditions known to impair the transpulmonary transit of echo contrast agents. The study design required that 25% of the patients enrolled fall into this subgroup. Patients in this impaired function group were those with an LV ejection fraction of 20–40% or a history of clinically significant asthma, chronic bronchitis, emphysema, bronchiectasis, or pulmonary hypertension. The demonstration of safety of new contrast agents is important in this population. There are theoretical concerns about pulmonary microcirculatory compromise with echo contrast agents in these patients.

Contrast agents. ALBUNEX is a suspension of air-filled microspheres with a mean concentration of 3.0–5.0 × 10^6 microspheres/mL and a mean diameter of 3.0–5.0 μm. OPTISON is a suspension of perfluoropropane-filled albumin microspheres with a mean concentration of 5.0–8.0 × 10^6 microspheres/mL and a mean diameter of 2.0–4.5 μm. Like ALBUNEX, OPTISON is completely manufactured and is prepared for injection by rotating the vial for a few seconds. Each patient received ALBUNEX and OPTISON on separate days at least 48 h apart. The sequence of contrast administration was randomized: half of the patients received ALBUNEX and half received OPTISON on the first test session.

Two-dimensional echocardiography. Standard, continuous, fundamental, two-dimensional echocardiography was used. Prior to baseline imaging, ultrasound settings for each patient were optimized for the apical four-chamber view with the assistance of a grey-scale phantom (ATS Laboratories, Inc.). Once the clearest image of the phantom was obtained, the ultrasound settings for each patient were maintained throughout the testing sessions. For ALBUNEX, the apical four-chamber view was utilized. If feasible, the apical two-chamber and parasternal short axis and long axis views were also obtained after contrast injection. For OPTISON, the apical four-chamber, apical two-chamber, and parasternal short and long axis views were used throughout. All imaging was recorded on videotape (Fig. 1).

Image analysis. Echocardiograms were reviewed by a central core laboratory (Georgetown University Medical Center) blinded to patient history, contrast agent, and dose. All observations were made at baseline and after each dose of OPTISON and ALBUNEX following clearance of attenuation. LV endocardial border length, endocardial border delineation by segment, LV opacification, and diagnostic yield were the parameters assessed in a blinded manner by the core lab and are reported below. With the exception of LV endocardial border length and diagnostic yield, each observation was also made by the individual investigators in an unblinded manner for comparison purposes. The duration of contrast effect was assessed by the investigators only and is reported below.

LV endocardial border length. The apical four-chamber view was digitized off-line by a commercially available imaging system (Nova Microsonics Image Vue). Endocardial length was obtained by measuring and summing those segments that were well visualized. The increase in well-visualized endocardial border length due to each agent dose compared with noncontrast was calculated for systole and diastole.

LV endocardial border delineation by segment. The apical four-chamber view was divided into six segments. Each segment was graded visually from the videotape. A qualitative scale was used as follows: A = not well delineated; B = average delineation; C = good delineation; and D = excellent delineation.
delineation. The proportion of patients whose endocardial
delineation improved ≥1 segment at end-diastole (from grade
A to grade B, C or D) was calculated for each agent dose.

LV chamber opacification. Visual assessment from the video
tape images of LV peak filling was graded according to the
following qualitative scale: 0 = none (0% LV filling); 1 = faint
contrast (33% LV filling); 2 = intermediate filling (67% LV
filling); and 3 = full LV chamber opacification (100% LV
filling). The proportion of patients with each grade of LV
filling was calculated for each agent and dose, at systole, and
diastole.

Duration of contrast. From the imaging protocol, each
investigator was asked to calculate the duration of clinically
useful contrast effect for each agent dose.

Diagnostic yield. The rate of conversion from a nondiag-
nostic to a diagnostic echocardiogram with contrast was as-
essed. Patients were considered to have a nondiagnostic
noncontrast echocardiogram if the apical four-chamber view
had a minimum of four of six segments graded as “A” (not well
visualized) at end-diastole. Studies were determined to have
become diagnostic after contrast if they improved to five or six
segments judged as visualized (graded as B, C, or D).

Safety and tolerability. At the time of enrollment into the
study, a detailed clinical history was obtained from each
patient. A physical examination, 12-lead electrocardiogram
(ECG), vital signs, urinalysis, creatine phosphokinase isoen-
zymes, chemistry panel, complete blood count, prothrombin,
and partial thromboplastin times were also obtained. These
parameters, along with symptom notation, were repeated after
each set of contrast agent administrations and again at 48 h
poststudy. Throughout each testing session, oxygen saturation,
vital signs, and ECG rhythm recordings were made. The onset,
severity, duration of adverse events, and their possible rela-
tionship to each agent were noted.

Statistical analysis. LV endocardial border length was
analyzed as a two-way ANOVA with factors of protocol and
agent/dose level. Tukey-adjusted contrasts on comparisons
between the two ALBUNEX doses and all four OPTISON
doses were performed. Proportion of patients converting from
nondiagnostic to diagnostic, improving in one or more seg-
ments, with >67% filling and with >100% LV filling were all
analyzed by Chi-square test. Since these were all highly statis-
tically significant (p < 0.001 for all), pair-wise comparisons
between the two ALBUNEX doses and all four OPTISON
doses were made with Fisher’s exact tests and a Bonferroni
correction. For each parameter reported, the sample size
varied slightly. This occurred because either the baseline or
contrast image could not be read due to poor image quality or
technical errors in image acquisition. Data are reported as
mean ± standard deviation or number and percent of patients,
and represent the core lab analysis unless otherwise stated.

Results

Patient population. A total of 203 patients were enrolled in
the study (Table 1). Of these, 74 (37%) had either dilated
cardiomyopathy or chronic lung disease (impaired function
group). Seven patients received only one contrast agent. Three
patients received OPTISON on the first day but did not return
for ALBUNEX on the second day: one for bad weather
conditions, another withdrew without a reason, and one with-

Figure 1. Apical four-chamber views (end-diastole on left, end-systole
on right) from a single patient. Top, Before contrast, there is poor LV
endocardial border definition. Middle, After injection of 0.22 mg/kg of
ALBUNEX, there is minimal improvement in LV endocardial border
delineation and faint LV chamber opacification in diastole. In systole,
there is almost no contrast effect. Bottom, After injection of 0.5 mL of
OPTISON, there is 100% LV chamber opacification and almost
complete endocardial border delineation in both diastole and systole.
drew on the advice of a family member. Four patients received ALBUNEX on the first day but did not return for OPTISON on the second day: one for intravenous access problems, one for chest pain the evening after ALBUNEX injection, one for pneumonia complicating chronic lung disease 48 h after receiving ALBUNEX, and another for emergency coronary bypass surgery 5 d after ALBUNEX administration. None of these problems were considered related to ALBUNEX by the investigators.

LV endocardial border length. For all patients, the increase in LV endocardial border length at end-diastole (Fig. 2A) was greater with each dose of OPTISON (6.0 ± 5.1, 6.9 ± 5.4, 7.5 ± 4.7, 7.6 ± 4.8 cm) than with each dose of ALBUNEX (2.2 ± 4.5, 3.4 ± 4.6 cm), p < 0.001. Similarly, in the impaired function group, end-diastolic LV endocardial border length increased more with each OPTISON dose (6.2 ± 5.4, 6.6 ± 6.7, 7.8 ± 5.4, 8.0 ± 5.4 cm) than with each ALBUNEX dose (1.2 ± 4.5, 2.8 ± 4.4 cm), p < 0.001. End-systolic increases in LV endocardial border length for all patients (Fig. 2B) were also greater with each dose of OPTISON (3.5 ± 4.6, 4.5 ± 4.9, 4.8 ± 4.6, 5.4 ± 4.6 cm) than for each dose of ALBUNEX (0.8 ± 3.8, 1.4 ± 3.8), p < 0.001. Again, in the impaired function group, end-systolic LV endocardial border length increased more with OPTISON (3.8 ± 5.0, 5.2 ± 5.8, 5.1 ± 5.2, 6.7 ± 4.7 cm) than with ALBUNEX (0.5 ± 3.9, 1.6 ± 4.0 cm) p < 0.001.

LV endocardial delineation by segment. When endocardial delineation was evaluated by segment, the percentage of all patients improving by ≥1 segment was higher for each dose of OPTISON (81% [154/191], 90% [172/192], 93% [177/190], 94% [174/186]) than for either dose of ALBUNEX (64% [124/195], 74% [142/193]), p < 0.001. In the impaired function group, improvement in segment delineation was noted in more OPTISON patients (74% [51/69], 87% [61/70], 94% [65/69], 94% [62/66]) than in ALBUNEX patients (59% [41/70], 77% [54/70]), p < 0.001 for each comparison except for ALBUNEX 0.08 mL/kg versus OPTISON 0.2 mL, p = NS; ALBUNEX 0.22 mL/kg versus OPTISON 0.2 mL, p = NS; ALBUNEX 0.22 mL/kg versus OPTISON 0.5 mL, p < 0.01.

LV opacification of 100%. Full LV opacification at end-diastole (Fig. 3A) was achieved by a greater percentage of all patients with each of the four doses of OPTISON (61% [112/183], 73% [133/181], 87% [158/181], 87% [89/102]) than with each of the two doses of ALBUNEX (16% [16/100], 36% [68/187]), p < 0.001. Similarly, in the impaired function group, a higher proportion of patients with OPTISON (58% [40/69], 71% [46/65], 87% [59/68], 83% [30/36]) attained complete LV opacification compared with ALBUNEX (5% [2/37], 20% [14/71]), p < 0.001. At end-systole (Fig. 3B), OPTISON again produced full LV opacification in a higher percentage of all patients (48% [87/183], 59% [107/181], 69% [125/181], 75% [77/102]) than did ALBUNEX (7% [7/100], 9% [16/187]), p < 0.001. In the impaired function group, OPTISON also achieved complete LV opacification in more patients (46% [32/69], 62% [40/65], 79% [54/68], 75% [27/36]) than did ALBUNEX (3% [1/37], 4% [3/71]), p < 0.001.

LV opacification of ≥67%. This level of LV opacification at end-diastole (Fig. 4A) was achieved in a higher percentage of all patients with each of the four doses of OPTISON (81% [148/183], 90% [163/181], 94% [171/181], 95% [97/102]) than with either of the two doses of ALBUNEX (41% [41/100], 56% [104/187]), p < 0.001. Similarly, in the impaired function

Table 1. Patient Characteristics (n = 203)

| Age (yr) | 59 ± 13 |
| Male | 161 (79) |
| Hypertension | 118 (58) |
| Diabetes mellitus | 63 (31) |
| Myocardial infarction | 81 (40) |
| PTCA | 33 (16) |
| CABG | 43 (21) |
| Valvular disease | 29 (14) |
| Congestive heart failure | 66 (33) |
| Dilated cardiomyopathy | 47 (23) |
| Chronic lung disease | 35 (17) |

Data are mean ± SD or numbers of patients (%). CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
group, a higher proportion of patients with OPTISON (72% [50/69], 85% [55/65], 94% [64/68], 94% [34/36]) attained this degree of LV opacification compared with ALBUNEX (27% [10/37], 35% [25/71]), p < 0.001. At end-systole (Fig. 4B), OPTISON produced this level of LV opacification in a higher percentage of all patients (60% [110/183], 73% [133/181], 81% [147/181], 83% [85/102]) than did ALBUNEX (10% [10/100], 14% [26/187]), p < 0.001. In the impaired function group, OPTISON attained this degree of LV opacification in more patients (58% [40/69], 74% [48/65], 85% [58/68], 81% [29/36]) than did ALBUNEX (5% [2/37], 7% [5/71]), p < 0.001.

**Diagnostic yield.** The rate of conversion from a nondiagnostic to a diagnostic echocardiogram was evaluated with each dose of contrast agent judged to be the most efficacious (3.0 mL with OPTISON and 0.22 mL/kg with ALBUNEX) based on the endocardial border length and LV opacification analyses. The core laboratory identified 85 OPTISON patients and 85 ALBUNEX patients who were considered to have nondiagnostic baseline studies. Among all patients, a higher percentage of the OPTISON studies (74% [63/85]) converted to diagnostic echocardiograms compared with ALBUNEX (26%, 22/85), p < 0.001. Similarly, in the impaired function patients, there were more conversions with OPTISON (75%, 30/40) than with ALBUNEX (12%, 5/41), p < 0.001.

**Duration of contrast.** The duration of clinically useful contrast effect was greater for all patients with each dose of OPTISON (1.7 ± 1.3, 2.4 ± 1.8, 4.3 ± 2.5, and 5.2 ± 3.3 min) than with each dose of ALBUNEX (0.6 ± 0.6 and 0.8 ± 0.7 min), p < 0.001.

**Investigators’ assessments.** Left ventricular opacification and LV endocardial delineation by segment were evaluated by the investigators as well as the core lab. The investigators’ assessments related closely to those of the core lab. In response to the questionnaire regarding diagnostic confidence, investigators thought ALBUNEX produced a diagnostic study in 45% (92/203) of patients, whereas OPTISON was thought to produce a diagnostic study in 87% (176/203) of patients. Overall, investigators preferred OPTISON over ALBUNEX in 97% (184/203) of patients.

**Side effects.** Among all patients, there were no clinically significant changes in physical examination, vital signs, or ECG with either OPTISON or ALBUNEX. In particular, there were no significant changes in the heart rate, blood pressure, or oxygen saturation in the impaired function group. Five patients had mild decreases in oxygen saturation (mean decrease 8.0 ± 0.7%); four with OPTISON and one with ALBUNEX. These episodes were asymptomatic, transient, and resolved spontaneously. Side effects believed to be related to each agent are
Efficacy. For all patients, OPTISON was significantly superior to ALBUNEX in all measures of contrast enhancement, including increase in LV endocardial border length, LV opacification, endocardial segment delineation, diagnostic yield, and duration of contrast. It should be emphasized that the patients in this study had incomplete endocardial depiction on their routine echocardiograms. Despite selecting only patients with technically difficult images, OPTISON was able to improve LV opacification such that 87% of patients had 100% LV opacification at end-diastole. This degree of LV filling with OPTISON occurred in over three times the number of patients compared with ALBUNEX. As a result of improved endocardial border delineation and LV opacification, the investigators reported a greater sense of diagnostic confidence with OPTISON than with ALBUNEX.

Impaired function group. It has been shown previously that patients with reduced forward cardiac output, such as those with LV systolic dysfunction or pulmonary hypertension, have diminished LV opacification with ALBUNEX (16,17). It has been proposed that the reduced cardiac output causes a delay in the transpulmonary transit of contrast. This causes prolonged exposure of the microspheres to ultrasound and ultrasound-induced microsphere destruction as well as more time for diffusion of gas out of the microspheres with consequent microsphere shrinkage (16,17).

In the present study, 74 patients had chronic lung disease or dilated cardiomyopathy. As expected, there was decreased contrast effect with ALBUNEX in these patients. OPTISON, however, maintained its contrast effect in this subgroup. In fact, there was a trend toward increased LV endocardial border delineation and opacification, especially in systole, with OPTISON in this group compared with all patients (Figs. 2–4). Therefore, the greatest effects of OPTISON were in those patients in whom contrast echocardiography would have benefited the most. These patients typically have the poorest quality echocardiograms. One may surmise that the preservation of bubble size and concentration due to perfluoropropane in OPTISON resists the destruction of microspheres by ultrasound energy in these patients.

Systole versus diastole. It is well known that the contrast effects of ALBUNEX are significantly reduced during systole (18). This was observed in the present study (Figs. 2–4). While this phenomenon has been actively investigated, the precise mechanism has not been clearly defined. Microsphere destruction or compression during the high LV pressures of systole have been implicated (18–20). The contrast effect of OPTISON did decrease somewhat during systole in the present trial.

Discussion

This is the first multicenter clinical trial of OPTISON, a new generation echocardiographic contrast agent. Its superiority over ALBUNEX was demonstrated with continuous, fundamental imaging.

Characteristics of OPTISON. While ALBUNEX has achieved some success as an ultrasound contrast agent (1–5), its clinical usefulness has been limited by its relatively short duration of contrast effect. ALBUNEX consists of albumin microspheres filled with air, which in turn consists mainly of oxygen and nitrogen. Graham’s Law states that the rate of diffusion of gases is inversely proportional to the square root of their molecular weights (8). Because oxygen and nitrogen have low molecular weights (32 and 28 g/mol, respectively), they easily diffuse out of the albumin microspheres. They are also readily soluble in blood, another factor causing them to escape from the microspheres. As the gases escape, the microspheres become smaller. As particle size is the principal determinant of ultrasound backscatter (9), the contrast effect diminishes as microsphere size decreases. To obviate this, gases with less diffusivity and less solubility in blood have been explored for use with contrast agents (10,11). OPTISON is produced by the sonication of a 1% solution of human albumin in the presence of perfluoropropane, an inert gas approved by the FDA for use in ophthalmologic surgery (12). Its high molecular weight (188 g/mol) makes it less diffusible than air. It is also less soluble in blood. This significantly stabilizes microsphere size. As a result, more microspheres survive the transit through the pulmonary circulation for delivery to the left heart. In addition, higher concentrations of microspheres in itself is protective against destruction by ultrasound (13–15). The higher concentration of microspheres reaching the left heart is responsible for the increased contrast effect of OPTISON.

Table 2. Side Effects Considered to Be Agent Related

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Impaired Function Group</th>
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<tbody>
<tr>
<td></td>
<td>OPTISON</td>
<td>ALBUNEX</td>
</tr>
<tr>
<td></td>
<td>(n = 198)</td>
<td>(n = 202)</td>
</tr>
<tr>
<td>Transient altered taste</td>
<td>4 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Flushing/warmth</td>
<td>4 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Ecchymosis at intravenous site</td>
<td>0</td>
<td>1 (0.5%)</td>
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</table>

Data are numbers of patients.

shown in Table 2. There were no significant differences in side effects between the two agents. None required treatment.
but to a much lesser extent than ALBUNEX (Figs. 2–4). The higher concentration of microspheres delivered to the left ventricle must in some way counteract the effects of systolic pressures (14).

**Side effects.** The side effects of ALBUNEX have been well studied (2–5). Altered taste sensation has been the most common symptom. Similar side effects were noted with ALBUNEX in the present study. In this and in previous studies, side effects were mild, transient, and required no treatment (2–5). The absence of significant side effects with ALBUNEX may be due, in part, to its lack of hemodynamic alterations. In several studies, ALBUNEX did not change right- and left-sided cardiac pressures, LV contractility, or blood gases (13, 17, 21).

In the present investigation, the side effects observed with OPTISON were similar and occurred with the same frequency as with ALBUNEX. All were mild and resolved spontaneously. OPTISON was also well tolerated in another study of patients with coronary artery disease (6). As with ALBUNEX, OPTISON has been shown not to alter pulmonary and left heart pressures, LV contractility, myocardial blood flow, and blood gases (7, 21, 22). In the subgroup of patients in our study with pulmonary and/or cardiac dysfunction, the frequency of side effects was low. This observation is particularly important because of the theoretical concern that these patients are prone to pulmonary microcirculatory embarrassment after injection of microspheres. In fact, some studies of ultrasound contrast agents under development have specifically avoided patients with pulmonary disease (23). We conclude that the safety profile of OPTISON is excellent and equivalent to that of ALBUNEX.

**Limitations of study.** The true duration of OPTISON was underestimated in this study. Investigators were not specifically asked to determine its actual duration. When protocol imaging was complete, no further evaluations were made, even though OPTISON was still present on the echocardiogram. Neither harmonic nor intermittent imaging was employed. These techniques have been shown to enhance the contrast effects of ultrasound contrast agents and have great promise for the future (24, 25).

**Conclusions.** OPTISON is an excellent contrast agent that is superior to ALBUNEX for LV endocardial border delinea-

**References**


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