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Perflenapent Emulsion (EchoGen®): A New Long-Acting Phase-Shift Agent for Contrast Echocardiography

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Summary: Perflenapent emulsion (EchoGen®, SONUS Pharmaceuticals, Bothell, Wash.) is a phase-shift colloid that is the first of a new class of intravenously injectable fluorocarbon-based ultrasound contrast agents, representing a significant advance in contrast echocardiography. Unlike currently available contrast agents, perflenapent emulsion effectively opacifies the left ventricle and enhances endocardial border delineation. The persistence of the contrast effect permits interrogation in multiple echocardiographic views. Perflenapent emulsion should permit the use of echocardiography to visualize and localize myocardial perfusion deficits at rest by producing a negative contrast effect, allowing physicians to diagnose coronary artery disease, including the extent of a lesion's impact on the perfusion of the myocardium, in a timely and cost-efficient manner. Perflenapent emulsion is also easy to use and requires no preparation, reconstitution, or refrigeration.

Key words: perflenapent emulsion, EchoGen®, phase-shift colloid, contrast echocardiography, fluorocarbon

Introduction

Recent advances in contrast echocardiography have yielded significant improvements in image quality. However, available contrast agents may be cumbersome to use, have a short persistence in the bloodstream, and often cannot opacify the left heart. Perflenapent emulsion (EchoGen® SONUS Pharmaceuticals, Bothell, Wash.), a phase-shift colloid and the first of a new class of intravenously injectable fluorocarbon-based ultrasound contrast agents, addresses these shortcomings.[1] Perflenapent emulsion opacifies the left ventricle and also enhances endocardial border delineation. Its lack of attenuation at doses that produce myocardial enhancement can render otherwise suboptimal echocardiograms diagnostically useful. The use of this agent for contrast echocardiography may, in many cases, eliminate the need for angiography, ventriculography, nuclear medicine, and magnetic resonance imaging.[2]

The microbubbles produced by perflenapent emulsion persist in the ventricle during systole and make multiple passes through the portal vein.[1] The microbubbles are small enough to pass through the lungs and circulate in the vascular system,[1] enabling imaging of small blood vessels and tissues. (Data on file, SONUS Pharmaceuticals.) The persistence of the contrast effect (over 4 min in phase III cardiology studies and over 15 min in phase III radiology studies) permits interrogation in multiple echocardiographic views.[3] Perflenapent emulsion is administered in an antecubital vein, requires no preparation, and has a shelf life of at least 12 months at room temperature. (Data on file, SONUS Pharmaceuticals.)

Action, Elimination, and Proposed Indications

Perflenapent emulsion is a ready-to-use, sterile, nonpyrogenic, 2% aqueous emulsion of dodecafluoropentane (DDFP). It is stabilized by a surfactant in a 30% sucrose solution.[4] DDFP, a clear, colorless, and odorless perfluorocarbon, converts to a gas at body temperature.[1] Perfluorocarbons are inert to even intense ultraviolet radiation; thus, perflenapent emulsion does not have the potential to cause ozone depletion. (Data on file, SONUS Pharmaceuticals.)

Perflenapent emulsion contains droplets approximately 0.3 μm in diameter.[1] After hypobaric activation and intravenous administration, the liquid emulsion becomes a dispersion of microbubbles of DDFP, which, because of the substantial decrease in density of DDFP as a gas, have an average diameter of 6 to 8 μm. (Data on file, SONUS Pharmaceuticals.) The microbubbles circulate within the intravascular space,[1] providing strong backscatter and enhanced gray scale, color Doppler, and spectral Doppler ultrasound signals. (Data on file, SONUS Pharmaceuticals.) The microbubbles persist in solution much longer than microbubbles of air, carbon dioxide, or other gases because of the extremely low solubility of DDFP in water compared with oxygen and nitrogen and,

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in part, because the much larger DDFP molecules diffuse more slowly in blood.[1,2] The microbubbles circulate through the body in proportion to blood flow. (Data on file, SONUS Pharmaceuticals.)

Administration of perflenapent emulsion to healthy adult volunteers and patients results in rapid distribution into the vascular space and subsequent elimination without metabolism. The elimination half-life from blood ranges from 1.85 to 6.09 min. The distribution and elimination half-lives in expired air are 0.92 ±1.6 min and 5.19 to 28.13 min, respectively. (Data on file, SONUS Pharmaceuticals.) The only approved contrast agent, sonicated albumin (Albunex®, Mallinckrodt, St. Louis, Mo.), does not consistently pass through the pulmonary vasculature.[5,6]

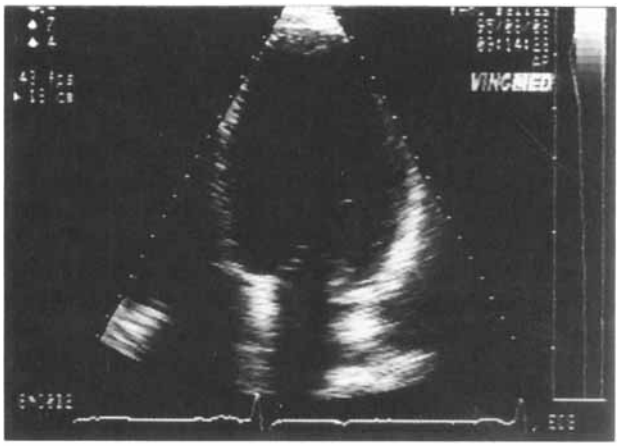
In patients with coronary disease undergoing echocardiography, the elimination kinetics of perflenapent emulsion in expired air are essentially identical to those in healthy adult volunteers and conform to a two-compartment model, with a distribution of 0.5 to 1.7 min and an elimination half-life of 1.6 to 18.09 min. (Data on file, SONUS Pharmaceuticals.)

Proposed indications for perflenapent emulsion include (1) use in echocardiography to provide contrast enhancement of ventricular chambers and improve endocardial border delineation in adult patients undergoing ventricular function and wall motion studies with suboptimal echoes, (2) use in the assessment of myocardial perfusion in adults to provide myocardial tissue enhancement of the left ventricular wall, and (3) Doppler signal enhancement. (Data on file, SONUS Pharmaceuticals.)

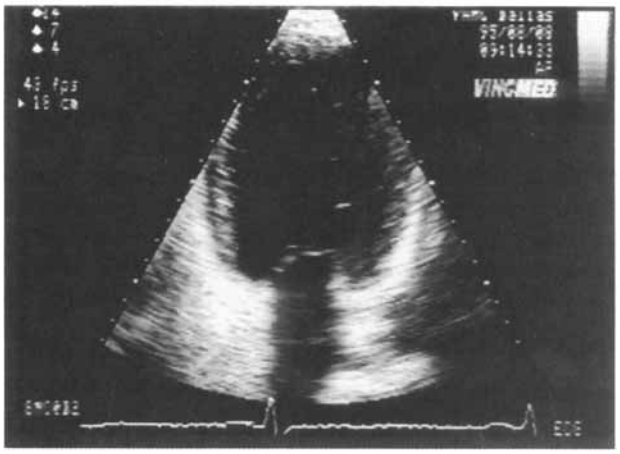
Phase II Clinical Trials

In all, 107 patients at 11 institutions—48 patients in five institutions in echocardiography and 59 patients in six institutions in radiology—were enrolled in phase II trials in the United States to evaluate perflenapent emulsion.[2] (Data on file, SONUS Pharmaceuticals.) The studies were multicenter, blinded, and placebo-controlled (saline) with ascending dosage protocols. Two independent, blinded readers provided a second assessment of efficacy. Videotape ultrasound scans were blinded by masking patient-identifying information.

Researchers working on the echocardiography study compared the percentage of echocardiographic scans after injection of saline solution with those after the injection of perflenapent emulsion. The comparison showed contrast enhancement of the blood pool, improved endocardial border delineation, and facilitated diagnosis of regional or global cardiac function.[2] Perflenapent emulsion produced contrast enhancement in the right ventricle and right atrium in 91.7% of patients and in the left ventricle in 75%. The average duration of contrast enhancement in the left ventricle was >2 min in the 0.05- and 0.10-ml/kg dosage groups. Contrast enhancement in the left ventricular chamber was significantly improved by perflenapent over saline at all dosages. Figure 1 shows an example of right- and left-sided chamber opacification with perflenapent emulsion.



(A)



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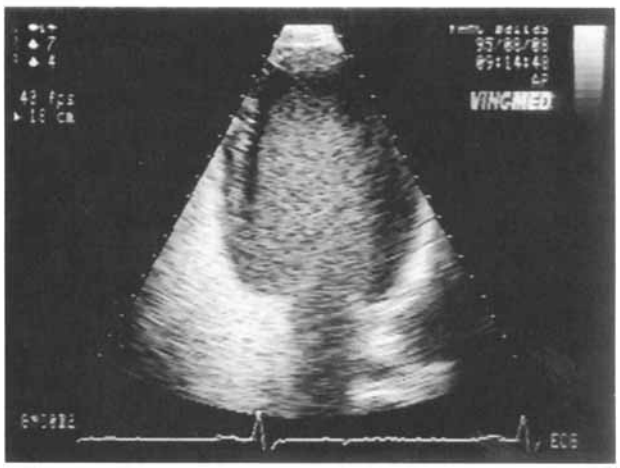

(C)

FIG. 1 Right- and left-sided chamber opacifcation using perflenapent emulsion. (A): Apical 4-chamber echocardiogram showing endocardial dropout. (B): After injection of perflenapent emulsion (EchoGen®), the right ventricle becomes densely opacified. (C): A few seconds later, both ventricles are opacified and the left ventricular endocardial surface can be clearly seen.

The investigators and blinded readers graded the overall endocardial border delineation at several locations after both saline solution and 2% perflenapent emulsion administration.[2] In 23% of patients, the left ventricular endocardial border was better delineated after administration of perflenapent emulsion. In 52% of cases, perflenapent emulsion assisted in the assessment of cardiac function by (1) providing blood pool contrast enhancement, (2) facilitating endocardial border delineation, (3) improving the quality of wall motion abnormalities, (4) improving the utility of ejection fraction detection, or (5) facilitating the visualization of valvular blood flow patterns.[2] Perflenapent emulsion also aided patient management in 19% of cases by (1) providing the primary diagnostic features of the study, (2) changing a diagnosis that was based on unenhanced images, (3) facilitating a diagnosis by disclosing findings not previously apparent on the unenhanced scan, (4) increasing confidence in the diagnosis, or (5) obviating the need for additional tests or referrals.

Current Findings from Phase III Clinical Trials

The technical limitations of echocardiography are such that suboptimal images are common. Even in patients with good acoustic windows, dropout of the endocardium in the apical views may limit the ability to determine ejection fraction and assess regional wall motion accurately.[3] (Data on file, SONUS Pharmaceuticals.)

In a phase III study of 254 patients, perflenapent emulsion resulted in intermediate or full left ventricular opacification in 83% of patients, compared with 54% with sonicated albumin.[3] This comparative study showed that perflenapent emulsion also increased duration of opacification (4.2 vs. 0.5 min); provided a superior contrast imaging window, that is, the time the presence of contrast actually improved the image (2.24 vs. 0.32 min); improved endocardial border delineation (88 vs. 45%); improved echocardiograms from suboptimal to diagnostically useful (51 vs. 9%); enhanced color Doppler (73 vs. 26%) and spectral Doppler (80 vs. 59%); facilitated assessment of wall motion (88 vs. 37%); increased myocardial opacification (40 vs. 8%); increased gray-scale level in the myocardium (59%); disclosed new diagnostic findings (63 vs. 20%); eliminated the need for additional studies (19 vs. 7%); assisted clinicians in reaching a diagnosis (88 vs. 40%); and improved the investigator's confidence in the diagnosis (76 vs. 24%).[3]

In another phase III trial, Hundley *et al.*[7] studied the ability of perflenapent emulsion to improve echocardiographic assessment of regional wall motion, left ventricular volumes, and ejection fraction in 35 patients. Each subject underwent a gated cardiac magnetic resonance imaging (MRI) scan followed immediately by contrast echocardiography. Magnetic resonance imaging views, precontrast echocardiograms, and postcontrast echocardiograms were assessed independently by blinded readers. Of 420 segments evaluable by MRI, 362 were seen by standard echocardiography and 413 were visualized after perflenapent emulsion. Figure 2 shows the improvement in echocardiographic scoring of regional wall motion (normal, hypokinetic, akinetic, or dyskinetic) after perflenapent emulsion. Echocardiographic wall motion was concordant with MRI in 76% of segments prior to perflenapent emulsion and 91% afterward ($p<0.0001$). Perflenapent also improved the echocardiographic assessment of left ventricular volumes and ejection fraction as shown in Table I. A significant reduction in the absolute difference between MRI and echocardiographic measurements of left ventricular volumes and ejection fraction was present after administration of perflenapent.

Perflenapent emulsion can also improve harmonic and power-mode Doppler imaging. One study evaluated its effect in 24 patients in whom visualization of the left ventricular endocardium had been suboptimal by two-dimensional echocardiography. (Data on file, SONUS Pharmaceuticals.) Apical two- and four-chamber views were recorded at baseline, after intravenous (IV) perflenapent (0.3 ml) with imaging at the fundamental frequency (2–3 MHz), and then with power-mode Doppler and harmonic power-mode with the transducer emitting at 1.8 MHz and receiving at 3.6 MHz. Two blinded observers performed off-line analysis of border delineation; for each stage, each view was separated into six segments and assigned a score (0 = no delineation; 1 = faint;

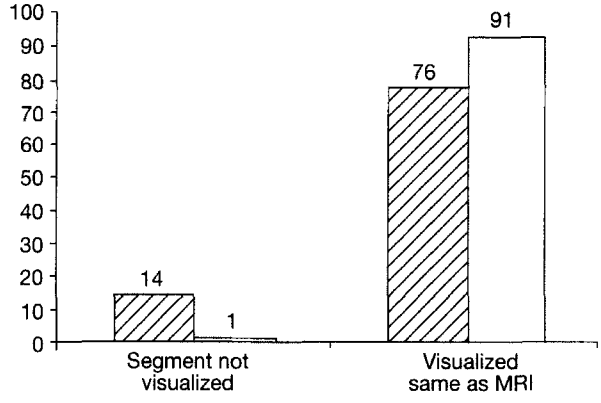

FIG. 2 Improvement in echocardiographic scoring of regional wall motion. Graph shows the percent of myocardial segments not visualized during echocardiography at left and the percent of segments in which wall motion was graded the same as MRI at right. Precontrast values are in striped bars, postperflenapent emulsion (EchoGen®) values in white bars. MRI = magnetic resonance imaging.

TABLE I Absolute difference between echocardiographic and MRI measurements

Variable	Precontrast echo-MRI	Perflenapent echo-MRI
End-diastolic volume (ml)	21 ± 13	15 ± 14[a]
End-systolic volume (ml)	17 ± 13	12 ± 9[a]
Stroke volume (ml)	14 ± 12	9 ± 7[a]
Ejection fraction (%)	8 ± 6	5 ± 3[a]

[a] $p < 0.05$ compared with precontrast value.

Abbreviation: MRI = magnetic resonance imaging.

Source: Data on file, SONUS Pharmaceuticals.

2 = intermediate; 3 = excellent delineation). The total score was divided by the number of segments to derive an index of border delineation. The mean ± standard deviation index for all segments at baseline was 0.95 ± 0.57; after administration of perflenapent emulsion it was 1.35 ± 0.52; with power-mode Doppler it was 1.74 ± 0.7, and with harmonic imaging it was 1.71 ± 0.71. When only the segments with faint or no visible endocardium at baseline were considered, the scores were 0.42 ± 0.22, 1.04 ± 0.58, 1.65 ± 0.82, and 1.62 ± 0.76, respectively. There was no significant difference between power-mode Doppler and harmonic imaging. (Data on file, SONUS Pharmaceuticals.)

Perflenapent, unlike sonicated albumin, also enhances color M-mode patterns and does not affect parameters used for differentiating normal from abnormal patterns. (Data on file, SONUS Pharmaceuticals.) Researchers studied 10 patients via the transthoracic approach using sonicated albumin (0.22 ml/kg) and perflenapent emulsion (0.05 ml/kg). Recordings were performed at baseline and during each injection. The velocity weighted mean was found further from the mitral valve during echocardiography with perflenapent emulsion and the spread of the velocity distribution in the major axis of the E wave increased significantly. These findings suggest that more velocities could be detected at the apex. Flow propagation features did not change. (Data on file, SONUS Pharmaceuticals.)

Safety and Adverse Events

Patients undergoing ultrasound studies of the heart and other target organs tolerate perflenapent emulsion well. A safety assessment of 743 patients who had received perflenapent emulsion and 151 patients who had received placebo during 21 clinical studies revealed no clinically important abnormalities in laboratory tests, pulse oximetry, vital signs, or electrocardiograms.[8] The overall incidence of adverse events occurring within 30 min of administration of perflenapent emulsion was comparable to that after administration of placebo and sonicated albumin.[8] Adverse events that occurred with a frequency of ≥ 1% within 30 min of perflenapent emulsion administration were vasodilation, taste aberration, pain, paresthesia, back pain, and headache.[8] Adverse events were of mild to moderate intensity, began within 10 to 20 min of administration, and resolved spontaneously within 10 to 20 min.

In phase I and II trials, vital signs, electrocardiogram, blood oximetry, serum and urine analyses, spirometry, neurologic status, discomfort, and adverse events were monitored before and up to 72 h after injection of perflenapent.[2] No safety parameter changed significantly in any dosage except for an increase in the serum total bilirubin, which remained in the normal range 8 h after injection in the general phase I trials.[2] Included were markers of anaphylaxis, serum histamine, and tryptase (an enzyme found in mast cell granules that has been used as a marker of mast cell activation); histamine did not change and tryptase was not detected in any subject.

In controlled clinical trials, patients who had experienced an adverse event with another contrast agent were at no increased risk of having an adverse event with perflenapent emulsion compared with the general population. (Data on file, SONUS Pharmaceuticals.) In patients with impaired renal function, perflenapent emulsion had no apparent effect on kidney function, as measured by blood urea nitrogen and creatinine levels. (Data on file, SONUS Pharmaceuticals.)

Appropriate test systems reveal no evidence of a mutagenic or teratogenic effect of perflenapent. (Data on file, SONUS Pharmaceuticals.) No impairment of fertility has been demonstrated in animal models. Studies in rats and rabbits at doses up to 30 times the human dose do not show impaired fertility or harm to the fetus due to the components of perflenapent. (Data on file, SONUS Pharmaceuticals.)

Carcinogenicity studies have not been carried out. It is not known whether perflenapent emulsion is excreted in human milk. Its safety and effectiveness in pediatric patients are not yet established. (Data on file, SONUS Pharmaceuticals.)

Dosage and Administration

Perflenapent emulsion (EchoGen®) is administered as an intravenous bolus at a dose of 0.05 ml/kg at a rate of 1.0 ml/s. The vials require no preparation and need not be refrigerated. (Data on file, SONUS Pharmaceuticals.) A white layer of settled emulsion droplets may form on the bottom of the vial, but this is not evidence of product separation and vigorous shaking is not required; gentle inversion or rolling of the vial resuspends the emulsion. (Data on file, SONUS Pharmaceuticals.)

Other contrast agents are not as convenient. For example, sonicated albumin (Albunex®, Mallinckrodt Medical, St. Louis, Mo.) requires refrigeration before use, hand rotation for 3 min to suspend microspheres, an injection time of more than 1 min after suspension, an IV infusion of saline solution, and multiple injections.[9]

Perflenapent emulsion is activated by holding a 30-ml syringe filled with the emulsion by the barrel in a horizontal position, by rapidly and continuously pulling back on the plunger to the full extent of the graduations on the syringe, and by immediately releasing the plunger to cause an audible pop. (Data on file, SONUS Pharmaceuticals.) The agent is then injected into an antecubital vein within 30 s of activation. In a study of 405 patients, there was only one failure from improper activation. (Data on file, SONUS Pharmaceuticals.)

The size and distribution of microbubbles immediately after activation is shown in Figure 3. Perflenapent emulsion has a room temperature shelf life of up to 12 months.

Proper activation has been performed correctly in all reported administrations. However, to determine whether improper activation has an effect on microbubble size, in vitro studies have been conducted to determine microbubble size following proper and improper hypobaric activation of perflenapent emulsion. Using a phase Doppler particle analyzer, bubble size was determined (1) following activation and a delay of 0, 5, 10, 30, 60, and 360 s; (2) following retraction and holding of the plunger for 10 s; (3) following slow release of the plunger to prevent a pop; and (4) with no activation. The results are

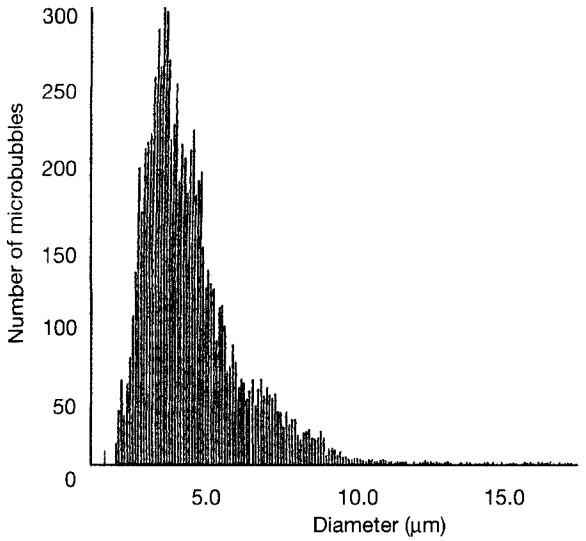

FIG. 3 Perflenapent emulsion is administered in a vein within 30 s of activation. The figure shows the size and distribution of microbubbles immediately following activation.

TABLE II Microbubble size in various conditions of activation

Activation condition	In vitro mean microbubble size (μm) (mean ± SD)
Activation followed by no delay	5.9 ± 0.8
Activation followed by 5 s delay	6.3 ± 0.2
Activation followed by 10 s delay	6.8 ± 0.3
Activation followed by 30 s delay	7.6 ± 0.2
Activation followed by 60 s delay	9.4 ± 0.2
Activation followed by 360 s delay	9.6 ± 0.1
Retract and hold plunger for 10 s	8.5 ± 0.3
Slow release of plunger to prevent a pop	7.2 ± 3.7[b]
No activation[a]	13.7[b]

[a] Only one sample analyzed.
[b] Extremely low number of bubbles produced, approximates background noise.
Abbreviation: SD = standard deviation.
Source: Data on file, SONUS Pharmaceuticals.

shown in Table II. The improper activation techniques investigated in this study have no major impact on the resultant mean microbubble size or distribution in vitro. Even under severe conditions of improper activation, microbubbles are < 10 μm and/or a small number of microbubbles are produced.

To determine the effect of the age of perflenapent emulsion on microbubble size, bubble size in activated samples from five different lots stored at 25°C (aged 6–88 weeks) and one lot stored at 40°C for 38 weeks was analyzed for microbubble size. The results are shown in Table III. Mean particle size increased with the age of the emulsion, but based on the results of these in vitro studies, mean particle size (between 210 and 1197 nm) has no statistically significant effect ($p \geq 0.05$) on microbubble size following hypobaric activation. Mean microbubble size ranged from 5.3 ± 0.0 to 6.9 ± 0.9 μm for all lots.

During clinical trials, there were no instances of an overdose of perflenapent. (Data on file, SONUS Pharmaceuticals.) The minimum lethal single dose of perflenapent emulsion in mice was found to be 4.0 ml/kg—more than 80 times the recommended human dose of 0.05 ml/kg. (Data on file, SONUS Pharmaceuticals.) The maximum single dose administered during clinical trials to healthy adult male volunteers was 0.35 ml/kg; the maximum cumulative dose was 0.70 ml/kg given as divided doses of 0.35 ml/kg 24 h apart. (Data on file, SONUS Pharmaceuticals.)

Clinical Benefits and Future Applications

Echocardiography is a safe, noninvasive method of assessing cardiac function. Unfortunately, echocardiography is often limited by inability to visualize the endocardial surface adequately. Perflenapent emulsion, by increasing contrast within ventricular chambers and providing better delineation of the endocardial borders, may salvage many otherwise suboptimal echocardiograms.[7,10]

In addition to improving echocardiographic visualization of left ventricular size and function, the ability of perflenapent emulsion to enhance color and spectral Doppler signals (Figs. 4, 5) should significantly aid in the diagnosis of valvular lesions, hemodynamic alterations, pulmonary hypertension, and left ventricular diastolic function. Further, perflenapent emulsion could be used to detect intracardiac shunts or other congenital abnormalities.

Often, severe coronary artery disease can be diagnosed only by evaluating the cardiovascular system during exercise or pharmacologic stress.[11] One of the main factors limiting the accuracy of stress echocardiography is inadequate visualization of the endocardial border. Because perflenapent emulsion enhances left ventricular border delineation, it may be able to increase the accuracy of exercise echocardiography.[12]

Perflenapent emulsion should permit the use of echocardiography to visualize and localize myocardial perfusion def-

TABLE III Particle and microbubble size in different aged lots of EchoGen®

Age (weeks)	Temperature (°C)	Emulsion mean particle size (nm)	In vitro mean bubble size (μm)
6	25	210	5.9 ± 0.8
6	25	229	6.1 ± 0.8
38	25	368	5.3 ± 0.0
86	25	450	6.9 ± 0.9
88	25	516	6.3 ± 0.1

Source: Data on file, SONUS Pharmaceuticals.

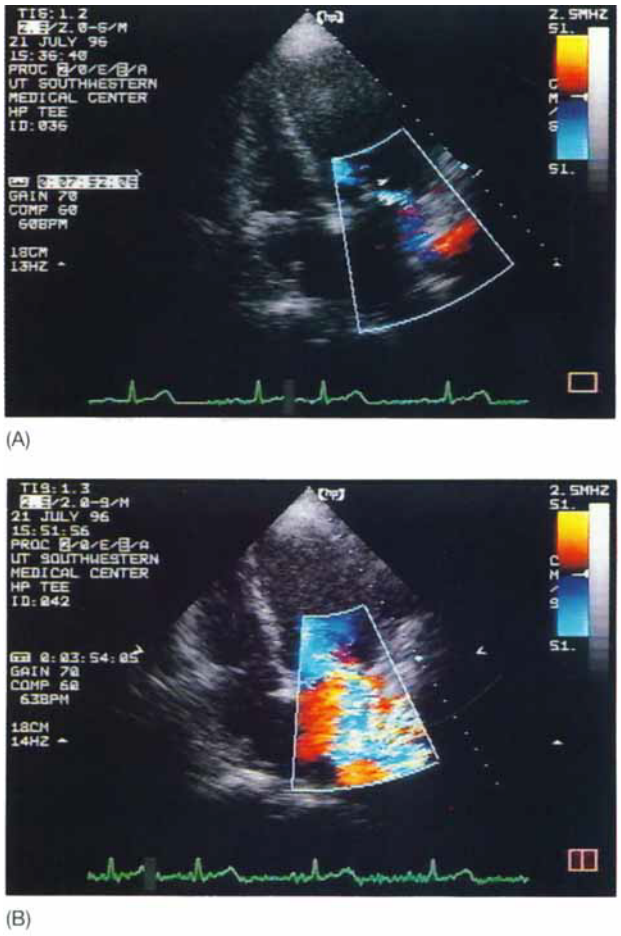

FIG. 4 Enhancement of spectral and color Doppler signals. (A) Color Doppler image showing a small mitral regurgitation jet directed along the lateral wall of the left atrium. The proximal flow convergence zone and vena contracta could not be visualized. (B) After perflenapent emulsion (EchoGen®), the color flow jet is easily imaged and its proximal flow convergence zone and vena contracta are visible.

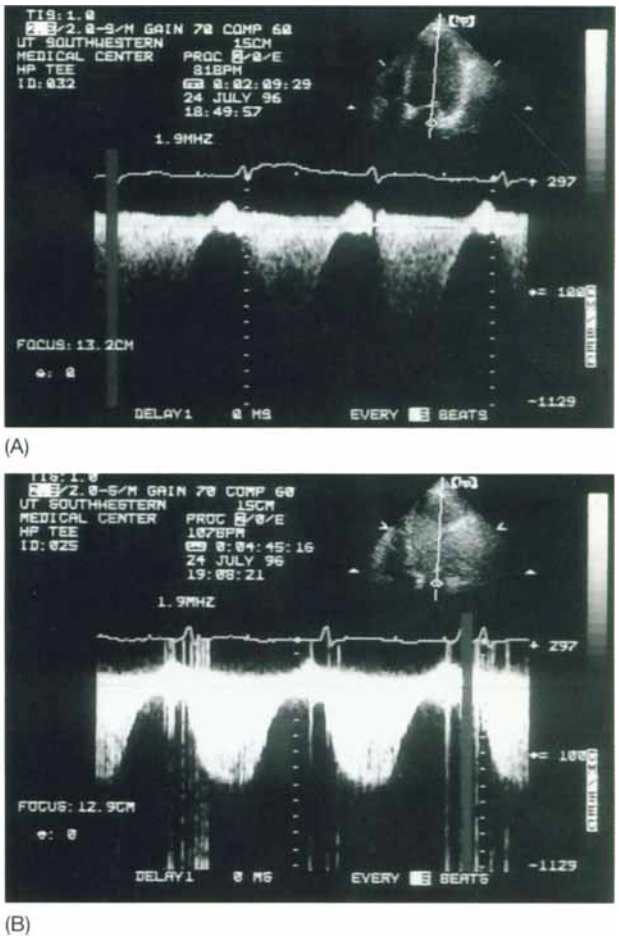

FIG. 5 Enhancement of spectral and color Doppler signals. (A) Continuous wave Doppler spectrum from a patient with mitral regurgitation. The outline of the velocity profile is indistinct. (B) After perflenapent emulsion (EchoGen®), the mitral regurgitation velocity is clearly seen.

icits (Fig. 6). The size and location of a perfusion defect may allow the physician to better assess the need for thrombolytic therapy or primary angioplasty in patients presenting with acute myocardial ischemia.[10] Moreover, resolution of a perfusion defect after thrombolytic therapy would indicate successful reperfusion; failure of the perfusion defect to resolve may predict the need for salvage angioplasty.[10]

Finally, in both cardiology and radiology, the duration of enhancement afforded by perflenapent emulsion may allow the physician to interrogate anatomy in multiple views and enable bilateral examination. The significant microbubble persistence of perflenapent emulsion within the vasculature enables adequate interrogation during the postcontrast examination as well.

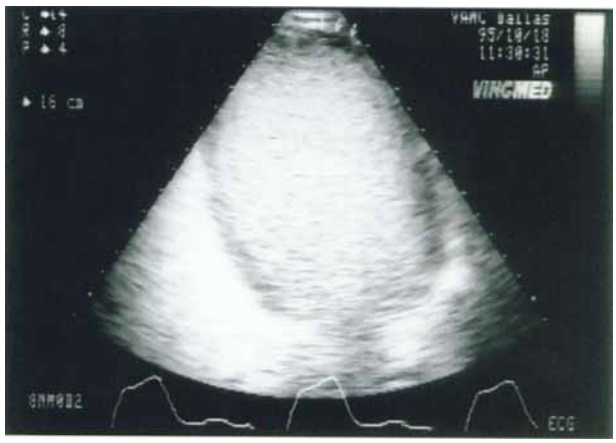

FIG. 6 Imaging myocardial perfusion deficits. After injection of perflenapent emulsion (EchoGen®), this patient developed enhancement of the septal and lateral wall myocardium. A perfusion deficit was observed at the apex (arrows) which was confirmed by single-photon emission computed tomography thallium imaging.

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