Intravenous Optison® (FS069) Enhances Pulmonary Vein Flow Velocity Signals: A Multicenter Study

SAMER ELLAHHAM, M.D., EVA HAUSNEROVA, M.D.,* JOHN GOTTDIENER, M.D.*

Division of Cardiology, Washington Hospital Center; *Division of Cardiology, Georgetown University Medical Center, Washington, D.C., USA

Summary

Background: Pulmonary vein spectral Doppler signals to characterize ventricular diastolic and systolic function, though often difficult to obtain, can be enhanced using contrast agents.

Hypothesis: The objective of this study was to determine the efficacy of the intravenous contrast agent Optison® for enhancement of Doppler signals in patients with poor signals on two-dimensional echocardiographic examinations.

Methods: Enhancement of pulmonary venous flow was evaluated in 191 patients at 0.2, 0.5, 3.0, and 5.0 ml per injection.

Results: Greatest contrast enhancement for right and left pulmonary veins was observed at the highest doses. At 0.5 ml, conversion from inadequate to adequate was observed in right and left pulmonary veins in 48.0 and 79.3% of patients, respectively, while any degree of improvement was 54.4 and 65.8%, respectively. The adverse event rate (6.5%) was similar to a first-generation agent.

Conclusion: The results demonstrate that Optison is a safe and effective contrast agent for improving visualization of pulmonary Doppler signals, especially the left pulmonary vein.

Key words: Optison®, ultrasound contrast, Doppler signals, echocardiography, velocity flow

Introduction

Using Doppler echocardiography, the velocity and direction of cardiac blood flow can be determined.¹ Doppler is useful for the analysis of diastolic function, especially that involving the pulmonary veins. A significant problem is that the pulmonary vein spectral waveform is often poorly visualized without the use of contrast agents. With the use of contrast agents, backscatter from within the intracardiac cavities is intensified.² Contrast agents have been shown to improve the Doppler signal in patients with mitral regurgitation, tricuspid regurgitation, and aortic stenosis, and allow for the analysis of valvular irregularities and pulmonary hypertension.^{3,4}

Optison® (Mallinckrodt, Inc., St. Louis, Mo., USA) is an ultrasound contrast agent for echocardiographic imaging, approved by the FDA for left ventricular opacification and endocardial border delineation.⁵ Optison is a second-generation contrast agent based on Alunex (sonicated human albumin) (Molecular Biosystems, Inc., San Diego, Calif., USA) and consists of human albumin sonicated in the presence of octafluoropropane. A 3.0 ml vial of Optison contains $5.0\text{--}8.0 \times 10^8$ microspheres/ml with a mean size of $2.0\text{--}4.5 \mu\text{m}$ (93% < $10 \mu\text{m}$). The duration of the contrast effect for gray-scale of Optison is 2–5 min while that of Alunex is < 1 min.⁵ In addition, Optison has been demonstrated to enhance myocardial opacification with echocardiography.^{6–9}

Address for reprints:

Samer Ellahham, M.D.
Washington Hospital Center
Division of Cardiology
Room # 1103
110 Irving St., NW
Washington, D.C. 20010, USA

Received: April 15, 1999

Accepted: June 9, 1999

Methods

Study Design

The design and methods used in this study were determined by the multicenter clinical trial that compared the safety and efficacy of Optison to Albutex and that is published in full elsewhere.⁵ As a component of the clinical trials, the effect of Optison on the spectral Doppler signals from the left and right pulmonary veins was analyzed. Briefly, 203 patients (161 men) > 18 years of age were enrolled in two identical Phase 3 trials at 14 US centers (see Appendix). All studies performed were in accordance with the Declaration of Helsinki. The participating institutions' human subject review committees approved the study. Signed informed consent was obtained from each patient, and women of child bearing potential were only enrolled if they tested negative for pregnancy within 24 h prior to contrast administration. Technically difficult visualization of the left ventricular endocardium was required for enrollment and was defined as the inability to evaluate two or more endocardial segments of the left ventricle of the six standard segments from the apical four-chamber view. Doppler signal quality from the pulmonary veins was not used as entry criterion.

A subset of patients (23%) had chronic pulmonary disease, and 17% had cardiomyopathy with a depressed left ventricular ejection fraction (between 20 and 40%). Baseline echocardiograms were performed, and four doses of Optison were administered intravenously to each patient in increasing volumes of 0.2, 0.5, 3.0, and 5.0 ml each (cumulative dose of 8.7 ml). Safety was evaluated throughout the study and for at least 48 h following administration of Optison.

Enhancement of Doppler Signal

Doppler signals were only obtained after all two-dimensional imaging data had been collected for each dose, which was between 2 to 5 min after injection of Optison depending on dose volume. When collecting the Doppler signal, standard laboratory settings, chosen locally, were used to obtain the most optimal noncontrast signal and were left unchanged when the signal was collected after injection of Optison. The order of pulmonary vein sampling was determined by the sonographer performing the study. Doppler signal was scored visually at a core laboratory (Georgetown University Medical Center) using a six-point grading scale. A core lab representative, blinded to all clinical information, acquired the most clearly visualized noncontrast and contrast pulmonary vein signals. A blinded reader (EH) then graded these randomized noncontrast and contrast signals. The grading scale was as follows: 1 (optimal), where there were multiple completely visible Doppler envelopes with identifiable acceleration, peak, and deceleration phases; 2 (good), where there was one completely visible Doppler envelope with identifiable acceleration, peak, and deceleration phases; 3 (adequate), where there was incomplete acceleration or deceleration but a clearly identifiable peak on one or more complexes; 4 (poor), where there

was some signal, but no complex had clearly definable peak or acceleration/deceleration phases; 5 (absent), where there was no pulmonary vein signal occurring anywhere on the record; and 6 (not clinically measurable), where the visual quality of the Doppler signal was not adequate for diagnostic interpretation. After the primary reading was performed, those images that read as optimal, good, and adequate were consolidated into the score of "adequate," while those read as poor, absent, and not clinically measurable were deemed "inadequate."

Doppler signal enhancement scores were analyzed using McNemar's test. For each patient, Optison scores were compared with baseline scores and judged as better, the same, or worse.

The proportion of patients improving from noncontrast scores of not clinically measurable, absent, or poor, to post-contrast scores of adequate, good, or optimal was calculated for each Optison dose volume. Chi-square tests were used to test for differences in these proportions among the doses for each pulmonary vein. No comparison was made between right and left pulmonary veins. A *p* value of ≤ 0.05 was considered significant.

Results

Of the 203 patients enrolled in the trial, 191 were included in this analysis of Doppler enhancement. These included 80% men with an age range of 21 to 83 years. Of these patients, 37% had either chronic pulmonary disease and/or cardiomyopathy. The number of patients with inadequate baseline signals (collapsed grades of "poor," "absent," "not clinically measurable") varied depending on the pulmonary vein sampled and on the timing of the assessment (prior to 0.2 ml, 0.5 ml, 3.0 ml, and 5.0 ml Optison dosing). The right pulmonary vein was inadequate in 48 to 50 patients, while the left pulmonary vein was inadequate in 78 to 84 patients depending on the timing of interrogation pre-Optison. At all doses tested, enhanced contrast was seen for the right and left pulmonary veins (Table I and Figs. 1 and 2). As the dose of Optison was increased, greater contrast enhancement was observed. At the

TABLE I Conversion from inadequate to adequate Doppler signals

Optison (ml)	Right pulmonary vein	Left pulmonary vein
0.2	21/48 (43.8%)	64/84 (76.2%)
0.5	24/50 (48.0%)	65/82 (79.3%)
3.0	34/50 (68.0%)	68/84 (81.0%)
5.0	34/49 (69.4%)	72/78 (92.3%)
P value ^a	0.014	0.030

^aP value for equality of proportion.

Inadequate = collapsed grades of 4, 5, 6 (poor, absent, not clinically measurable, respectively).

Adequate = collapsed grades of 1, 2, 3 (optimal, good, adequate, respectively).

FIG. 1 Right pulmonary vein signals. Before contrast, very little signal can be discerned, which is of no clinical value (Grade 4).

FIG. 2 Right pulmonary vein signals. After Optison, there is now clear delineation of the waveform with peak velocity, acceleration, and deceleration (Grade 1).

lowest dose of 0.2 ml, conversion from inadequate to adequate Doppler signals in the right and left pulmonary veins was observed in 43.8 and 76.2% of patients, respectively. With 0.5 ml, which is most commonly used in the clinic, conversion of the signal of the right and left pulmonary veins was observed in 48.0 and 79.3% of patients, respectively. At the highest dose of 5.0 ml, conversion was observed in 69.4% ($p = 0.014$) of patients for visualization of the right pulmonary vein and in 92.3% ($p = 0.030$) for the left pulmonary vein (Table I).

At the 0.2 ml dose, improvements by at least one grade over baseline in the right and left pulmonary veins were seen in 50.9 and 61.75% of patients, respectively (Table II). For the clinically relevant dose of 0.5 ml, Doppler signal enhancement in the right pulmonary vein was observed in 54.4% of patients and in the left pulmonary vein in 65.8% of patients. Improvement over baseline in the right and left pulmonary veins was greatest with the highest dose of 5.0 ml and was observed in 73.7 and 72.9% of patients, respectively (Table II).

In Table III, the improvement from baseline to postcontrast scores is shown at the 0.5 ml dose for the right and left pulmonary veins. The majority of patients with poor visualization of the right and left pulmonary veins displayed a substantial increase in their Doppler score after administration of Optison (Table III).

TABLE II Percent of patients with improvement over baseline by at least one grade for Doppler signal enhancement

Optison (ml)	Right pulmonary vein	Left pulmonary vein
0.2	28/55 (50.9%)	74/120 (61.7%)
0.5	31/57 (54.4%)	79/120 (65.8%)
3.0	38/58 (65.5%)	80/124 (64.5%)
5.0	42/57 (73.7%)	86/118 (72.9%)
P value ^a	0.015	0.092

^aP value for equality of proportion.

Only 3 of 57 patients showed a worsening of Doppler score for the right pulmonary vein, while 7 of 120 showed a worsening of the left pulmonary vein signal after Optison at the 0.5 ml dose.

During the study, 6.5% of patients were reported to have experienced adverse events attributed to the administration of Optison. The most frequent adverse events were transient alterations in taste (2.5% of patients), headaches (2.0% of patients), and warm sensation/flushing (2.0% of patients).

Discussion

The use of contrast agents to enhance echocardiographic images has been explored since the late 1960s.^{10, 11} Optison is an FDA-approved, second-generation contrast agent and represents the latest advance in the evolution and refinement of contrast agents.⁵ Preclinical and clinical trials have demonstrated that, during routine echocardiography, Optison is a contrast agent superior to Albunex for left ventricular endocardial delineation.^{5, 12} The results from this study demonstrate the utility of Optison for enhancing the Doppler signals arising from the left and right pulmonary veins.

The use of Doppler echocardiography to examine both systolic and diastolic function of the heart has steadily increased. Advances in echocardiographic imaging devices have resulted in very sophisticated and detailed Doppler measurements of cardiac function. Our data suggest that the use of Optison will allow further refinement of the Doppler technique for the non-invasive examination of the heart in detail. Since pulmonary vein Doppler signals are among the most clinically challenging to obtain, it is reasonable to assume that the results reported here may be applicable to other clinical situations where contrast could be useful, such as aortic stenosis, valvular gradients, and estimation of pulmonary artery pressures, by interrogation of the tricuspid regurgitation envelope.

TABLE III Change in scores for the right and left pulmonary veins at 0.5 ml Optison

Baseline scores		Final scores					
		1	2	3	4	5	6
1	R	2 (100%)	0	0	0	0	0
	L	17 (85%)	2 (10%)	0	1 (5%)	0	0
2	R	0	0	0	0	0	0
	L	7 (63%)	2 (18%)	1 (9%)	1 (9%)	0	0
3	R	1 (20%)	1 (20%)	1 (20%)	2 (40%)	0	0
	L	4 (57%)	1 (14%)	0	2 (28%)	0	0
4	R	11 (25%)	3 (7%)	8 (18%)	20 (46%)	1 (2%)	0
	L	45 (60%)	4 (5.4%)	10 (13%)	15 (20%)	0	0
5	R	0	0	1 (20%)	4 (80%)	0	0
	L	5 (71%)	0	0	1 (14%)	0	0
6	R	1 (50%)	0	0	1 (50%)	0	0
	L	0	0	0	1 (100%)	0	0

Final Scores = 1 (optimal), 2 (good), 3 (adequate), 4 (poor), 5 (absent), 6 (not clinically measurable).

Abbreviations: R = right pulmonary vein, L = left pulmonary vein.

The use of sonicated albumin has also been shown to improve Doppler signals in patients undergoing transesophageal echocardiography. A recent study of 200 patients who underwent transesophageal Doppler echocardiography demonstrated that sonicated albumin increased the optimal visualization of pulmonary venous flow in 99% of patients compared with a precontrast optimal visualization of 77%.¹³

A significant issue for transthoracic echocardiography is that up to one-third of patients may have inadequate pulmonary vein imaging.^{14,15} Inadequate visualization of pulmonary venous flow has generated interest in improving the Doppler signal by the use of contrast agents. In one study, Alunex significantly improved the Doppler signal collected from patients with aortic stenosis.¹⁶ Sonicated albumin microbubbles have also been shown to enhance Doppler echocardiographic imaging of the left atrial appendage.¹⁷ Sonicated albumin was also responsible for producing enhanced Doppler signals during transthoracic echocardiography that approached the quality of the signals obtained with transesophageal echocardiography. The results in this study demonstrate that the use of Optison enhances Doppler signals from the same injection used for left ventricular opacification. Such pulmonary vein spectral enhancement may result in improved assessment of left ventricular diastolic function and quantitation of mitral regurgitation. Further studies will be required to confirm this.

There were some aspects of the study design that limited the number of Doppler images analyzed. Not all patients enrolled in the trial underwent Doppler analysis. The protocol was conducted in 1995, at a time when pulmonary vein imaging was

performed less frequently. Investigators were allowed to delete pulmonary vein imaging if initial noncontrast imaging failed to obtain recognizable waveforms. This study design excluded patients who would have been graded "6." It is likely that a substantial proportion of these patients would have demonstrated improvement of one or more grades in quality after Optison had they been imaged. Dosing of Optison was not randomized. It is possible that a cumulative dosing effect influenced results. However, were that to have been the case, one would have expected a decreasing number of "inadequate" baseline signals with successive doses; this was not the case (Table I). Furthermore, the results emphasized the second injection (0.5 ml) and deemphasized later injections where cumulative dose effect, if present, would be more prominent.

Conclusion

The data generated from this clinical investigation suggest that the Doppler technique for the noninvasive examination of the heart can be refined further with the administration of Optison. Enhanced Doppler signals were observed for the right and left pulmonary veins after injection of Optison. The conversion of inadequate to adequate Doppler signals of the right and left pulmonary veins occurred in 48.0 and 79.3% of the patients, respectively, at a 0.5 ml dose of Optison. The results from this study demonstrate that Optison is a safe and effective contrast agent for improving visualization of pulmonary Doppler signals.

Appendix

List of Investigators

Core Lab: Echocardiography Laboratory, Georgetown University Medical Center

Principal investigator: John Gottdiener, M.D., Co-investigator: Eva Hausnerova, M.D.

FS-3000		
No. of Patients	Center No.	Investigator
26	1	Jorge Cheirif, M.D. Ochsner Heart and Vascular Institute, New Orleans, La.
22	4	Douglas Segar, M.D. Krannert Institute of Cardiology, Indianapolis, Ind.
15	3	Steven B. Feinstein, M.D. The University of Illinois at Chicago, Chicago, Ill.
14	7	David Bach, M.D. University of Michigan Medical Center, Ann Arbor, Mich.
11	6	Linda J. Crouse, M.D. Mid America Cardiology Associates, Kansas City, Mo.
8	2	Miguel Zabalgaitia, M.D. The University of Texas, Health Science Center at San Antonio, San Antonio, Tex.
5	5	Charles Pollick, M.B., Ch.B The Heart Institute, Good Samaritan Hospital, Los Angeles, Calif.
FS-3500		
30	3	Jerald Cohen, M.D. Veteran's Administration Medical Center, E. Orange, N.J.
20	2	Linda D. Gillam, M.D. Hartford Hospital, Hartford, Conn.
15	4	Candace Dick, M.D. Hennepin County Medical Center, Minneapolis, Minn.
12	1	Michael Picard, M.D. Massachusetts General Hospital, Boston, Mass.
11	6	Samer Ellahham, M.D. Washington Hospital Center, Washington, D.C.
7	5	Gary D. Plotnick, M.D. University of Maryland Hospital, Baltimore, Md.
7	7	John Dent, M.D. University of Virginia Medical Center, Charlottesville, Va.

References

- Franklin DL, Schlegel W, Rushmer RF: Blood flow measured by Doppler frequency shift of backscatter ultrasound. *Science* 1961; 134:564-570
- von Bibra H, Becher H, Firschke C, Schlieff R, Emslander HP, Schomig A: Enhancement of mitral regurgitation and normal left atrial color Doppler flow signals with peripheral venous injections of a saccharide-based agent. *J Am Coll Cardiol* 1993;22:521-528
- Himelman RB, Stulbarg MS, Lee E, Kuecherer HF, Schiller NB: Non-invasive evaluation of pulmonary artery systolic pressure during dynamic exercise by saline-enhanced Doppler echocardiography. *Am Heart J* 1990;119:685-688
- Nakatani S, Imanishi T, Terasawa A, Beppu S, Nagata S, Miyatake K: Clinical application of transpulmonary contrast-enhanced Doppler technique in the assessment of severity of aortic stenosis. *J Am Coll Cardiol* 1992;20(4):973-975
- Cohen J, Cheirif J, Segar DS, Gillam LD, Gottdiener JS, Hausnerova E, Bruns DE: Improved left ventricular endocardial border delineation and opacification with OPTISON® (FS069), a new echocardiographic contrast agent: Results of a phase III multicenter trial. *J Am Coll Cardiol* 1998;32:746-752
- Firschke C, Lindner JR, Wei K, Goodman NC, Skyba DM, Kaul S: Myocardial perfusion imaging in the setting of coronary artery stenosis and acute myocardial infarction using venous injection of a second-generation echocardiographic contrast agent. *Circulation* 1997;96:959-967
- Kaul S, Senior R, Dittich H, Raval U, Khattar R, Lahiri A: Detection of coronary artery disease using myocardial contrast echocardiography: Comparison with ^{99m}Tc-sestamibi single photon emission computed tomography. *Circulation* 1997;96:785-792
- Kaul S: Myocardial contrast echocardiography: 15 years of research and development. *Circulation* 1997;96:3745-3760
- Dittich HC, Bales GL, Hunt RM, McFerran BA, Kuvelas T, Widder KJ, Greener Y: Myocardial perfusion by intravenously administered novel ultrasound contrast agents in canines. *J Am Soc Echo* 1994;7:S16
- Gramiak R, Shah PM: Echocardiography of the aortic root. *Invest Radiol* 1968;3:356-366
- Gramiak R, Shah PM, Kramer DH: Ultrasound cardiography: Contrast studies in anatomy and function. *Radiology* 1969;92:939-948
- Meza M, Greener Y, Hunt R, Perry B, Revall S, Barbee W, Murgo JP, Cheirif J: Myocardial contrast echocardiography: Reliable, safe, and efficacious myocardial perfusion assessment after intravenous injections of a new echocardiographic contrast agent. *Am Heart J* 1996;132:871-881
- Izumi C, Yoshida K, Akasaka T, Hozumi T, Miyake S, Yoshikawa J: Improved visualization of pulmonary venous flow Doppler signal by intravenous injection of sonicated albumin. *Am J Cardiol* 1996;78:598-600
- Williams MJ, McClements BM, Picard MH: Improvement of transthoracic pulmonary venous flow Doppler signal with intravenous injection of sonicated albumin. *J Am Coll Cardiol* 1995;26:1741-1746
- Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KR, Seward JB: Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 1994;69:212-224
- Padula L, Fram D, Kieman F, Chen C, Gillam L: Intravenous Alunex dramatically improves the Doppler evaluation of aortic stenosis. *J Am Coll Cardiol* 1996;27(2 suppl A): 77A
- Kato H, Nakanishi M, Maekawa N, Ohnishi T, Yamamoto M: Evaluation of left atrial appendage stasis in patients with atrial fibrillation using transesophageal echocardiography with an intravenous albumin-contrast agent. *Am J Cardiol* 1996;78:365-369