

Safety of echocardiographic contrast in hospitalized patients with pulmonary hypertension: a multi-center study[†]

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Aims

Echocardiographic contrast (EC) improves the diagnostic accuracy of suboptimal echocardiograms. In October 2007, the Food and Drug Administration (FDA) placed a black box warning on the label of the perflutren-based agents Definity and Optison, contraindicating their use in patients with pulmonary hypertension (PHT) and unstable cardiopulmonary status, after serious cardiopulmonary reactions occurred in temporal relation to EC administration. In 2008 and 2011, the FDA revised the black box warning allowing their use in this same population. However, limited data exist regarding the safety profile of these agents in patients with PHT.

Methods and results

Consecutive hospitalized patients with PHT who were referred for echocardiographic evaluation, but required the use of EC, were included. All our patients received the EC agent Definity. We evaluated these patients for serious adverse events (respiratory decompensation, hypotension, syncope, convulsions, arrhythmias, anaphylactic reactions, or death) occurring within 24 h of EC administration. The study group included 1513 patients (age 69 ± 14 years, 55% males, BMI 33 ± 9 kg/m²), of which 911 (60%) had mild PHT, 515 (34%) had moderate PHT, and 87 (6%) had severe PHT. The mean pulmonary artery systolic pressures (PASP) in the groups with mild, moderate, and severe PHT were 41 ± 4 (range 35–49) mmHg, 55 ± 5 (range 50–69) mmHg, and 78 ± 9 (range 70–122) mmHg, respectively. The incidence of adverse events in all subgroups was rare (0.002%) and they were not attributed to EC because of temporal and clinical considerations.

Conclusion

The use of the EC agent Definity is safe in hospitalized patients with PHT.

Keywords

Perflutren • Echo contrast • Definity • Safety • Pulmonary hypertension

Introduction

The use of echocardiographic contrast (EC) is indicated in patients with technically limited echocardiograms to improve diagnostic accuracy.^{1–5} Patients with obesity, chronic lung disease, and critical illnesses, with or without mechanical ventilation support, are usually the most difficult to image patients and are also more

likely to have pulmonary hypertension (PHT). This group benefits the most from the use of EC, which in this setting has a significant impact on cardiac diagnosis, patient management, resource utilization, and cost-effectiveness, often eliminating the need for more invasive and expensive diagnostic tests.^{6–9}

In October 2007, the Food and Drug Administration (FDA) placed a black box warning on the label of the perflutren-based

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agents Definity (Lantheus Medical Imaging, Billerica, MA, USA) and Optison (GE Healthcare, Princeton, NJ, USA), contraindicating their use in patients with unstable cardiopulmonary status and PHT, after serious cardiopulmonary reactions, including deaths, occurred in relation to EC administration.¹⁰ Although temporally related, there was no evidence of causality as numerous studies involving both EC agents have subsequently shown. Multiple single- and multi-center studies involving over 4 million patients found no difference in mortality between patients undergoing contrast echocardiograms compared with those not receiving EC. In fact, a 24% decrease in mortality was shown in one study.^{11,12} Similarly, the safety of EC has also been demonstrated in patients undergoing stress testing.¹³ Recent data from the post-approval prospective and multi-centre open-label CaRES (Contrast Echocardiography Registry for Safety Surveillance) safety registry are consistent with previous studies. In 1053 patients receiving Definity in routine clinical practice, who were monitored for 30 min following EC administration, no serious adverse events were noted.¹⁴ Consequently, based on a review of available data as well as strong advocacy from physicians and ultrasound societies, in July 2008 the FDA revised the black box warning on the label of EC agents, removing their contraindication in patients with unstable cardiopulmonary status but mandating monitoring of vital signs, electrocardiography, and cutaneous oxygen saturation for 30 min in these patients as well as in those with PHT.¹⁵ Additionally, in October 2011 the FDA approved further important changes to the US product label for Definity, removing the need for monitoring post-administration altogether.¹⁶ However, at this time there is still concern about the safety of EC agents in patients with PHT as the information supporting their safety is limited. Therefore, we conducted this study to determine the safety of EC administration in a large cohort of patients with PHT in the hospital setting.

Methods

Patient population

We conducted a multi-centre retrospective analysis of consecutive hospitalized patients who were referred for echocardiographic studies by their treating physicians due to various clinical indications, were found to have PHT during the echocardiographic evaluation, and required the use of EC. Patients who received EC during transthoracic and stress echocardiograms were included in the study. Outpatients were excluded from the present study as an accurate assessment of adverse events is not feasible in such patients when analysed retrospectively. The patients who constituted the study group were selected by searching the echo databases of the following tertiary care university-affiliated institutions located in New York City area: St. Lukés-Roosevelt Hospital Center, during the period of January 2001 to January 2011; North Shore University Hospital, during the period of October 2003 to December 2010; and Long Island Jewish Medical Center, during the period of October 2003 to June 2010. The starting dates for the selection process coincide with the time EC use was initiated in the respective institutions. The study was approved by the institutional review boards from all the participating institutions.

Echocardiographic evaluation protocols

Transthoracic echocardiographic protocol

Transthoracic echocardiograms were performed following a standard protocol.¹⁷ The echocardiographic images were obtained from the parasternal, apical, subcostal, and suprasternal windows, using commercially available ultrasound systems [ACUSON Sequoia 512 (Siemens Medical Solutions, Mountain View, CA, USA), Vivid 7 & Vivid 9 (GE Healthcare, Princeton, NJ), and iE33 (Philips Ultrasound, Bothell, WA, USA)].

The left ventricular ejection fraction (LVEF) and segmental wall motion analysis were visually estimated by an experienced echocardiographer. Left ventricular wall motion assessment was performed using a 16-segment model as recommended by the American Society of Echocardiography.¹⁸ Right ventricular (RV) size and function were determined qualitatively from the parasternal long-axis, parasternal short-axis, apical four-chamber, and subcostal views. The RV size and the right atrial (RA) size were classified as normal vs. dilated. The wall motion of the RV was classified as normal vs. abnormal.

Stress echocardiography protocol

Patients had stress echocardiograms with either dobutamine or exercise. Both stress testing modalities were performed according to a previously described protocol and standard endpoints.¹⁹ Cardiac rhythm was monitored throughout the stress echocardiographic protocol, and 12-lead electrocardiograms and blood pressure measurements were obtained at baseline, at each level of stress, and during the recovery phase. A complete transthoracic echocardiogram was performed prior to each stress echocardiogram.

Calculation of pulmonary artery systolic pressure

Pulmonary artery systolic pressure (PASP) can be determined non-invasively using standard echocardiographic techniques. PASP is equivalent to RV systolic pressure (RVSP) in the absence of pulmonary outflow obstruction. RVSP was estimated by measuring the tricuspid valve regurgitation velocity (TRV), which was applied to the modified Bernoulli equation and added to an estimate of the RA pressure: $PASP = 4 \times (TRV)^2 + RA \text{ pressure (mmHg)}$.²⁰

The RA pressure was estimated based on the inferior vena cava (IVC) diameter and its response to respiration, measured from a subcostal long-axis view, at 1–2 cm from the junction with the RA. For a small IVC (<1.5 cm) collapsing during inspiration, an RA pressure in the range of 0 and 5 mmHg was assigned; for a normal size IVC (1.5–2.5 cm) collapsing >50% during inspiration, a value in the range of 5 and 10 mmHg was assigned; for a normal size IVC collapsing <50% during inspiration, a value in the range of 10 and 15 mmHg was assigned, and for a dilated IVC (>2.5 cm) collapsing <50% during inspiration, an RA pressure in the range of 15 and 20 mmHg was assigned.²¹

PASP was determined in all the patients prior to the administration of the EC agent, and no measurements of PASP were performed after EC administration, with the exception of those patients where EC was indicated for Doppler signal enhancement. Based on PASP estimation, the study cohort was divided in three groups: mild PHT (35–49 mmHg), moderate PHT (50–69 mmHg), and severe PHT (≥ 70 mmHg).

Contrast-enhanced echocardiographic studies

All patients in our study received the contrast agent Definity. There was no significant use of Optison in the participating institutions during the study period. Therefore, patients receiving Optison were excluded

from our analyses. EC was administered for left ventricular opacification and Doppler signal enhancement, according to the American Society of Echocardiography guidelines.¹ For transthoracic echocardiograms, Definity was used as follows: 1.3 mL of activated Definity was diluted in 8.7 mL of normal saline (total solution of 10 mL), and administered intravenously in 1–2 mL boluses as needed for image enhancement. During pharmacological stress echocardiograms, Definity was administered as a 1–2 mL bolus at the baseline study and subsequently as 1–2 mL boluses for low-dose, peak, and recovery stages. During exercise stress echocardiograms, Definity was administered as a 1–2 mL bolus at the baseline study and subsequently as a 1–2 mL bolus administered 30 s prior to exercise termination. The most frequently administered doses were: 1–2 mL for transthoracic echocardiograms, 4–8 mL for pharmacological stress echocardiograms, and 2–4 mL for exercise stress echocardiograms. The total dose of diluted Definity never exceeded 10 mL in our patients. The use of EC for Doppler signal enhancement followed the same protocol described for transthoracic echocardiograms. The contrast images were obtained using harmonic imaging and the low mechanical index (≤ 0.8).

Patient follow-up and study endpoints

Patient medical records as well as individual records from our echocardiography laboratories and echo databases were reviewed. Our echocardiography laboratory databases are electronic and the data are entered by a physician. Any adverse event occurring during any echocardiographic study in our laboratories is immediately reported to the physician, who is responsible for evaluating, treating the patient, and ultimately entering the adverse event into the patient's record and into the database. Any complication is also reported immediately to the Definity drug safety hotline and a full record of any adverse events occurring during the study period was retrieved directly from the manufacturing company. We compiled patient demographics, co-morbidities, echocardiographic results, and serious adverse events taking place up to 24 h from the contrast echocardiographic study. The endpoints of this study were respiratory decompensation, hypotension, arrhythmias, syncope, convulsions, anaphylactic reactions, or death at the time of the examination and within 24 h after EC administration.

Respiratory decompensation was defined as the acute onset of respiratory distress resulting in hypoxaemia ($\text{SpO}_2 < 90\%$ or $\text{PaO}_2 < 60$ mmHg) and requiring supplemental oxygen. Hypotension was defined as a fall in systolic blood pressure < 90 mmHg or a reduction ≥ 20 mmHg from the baseline. The arrhythmic events of interest included sustained and non-sustained ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, sinus pauses, and sinoatrial and atrioventricular conduction blocks (second and third degree). Syncope was defined as a transient loss of consciousness with abrupt onset and offset. Convulsions were defined as generalized tonic-clonic seizures in the presence of a diagnostically positive electroencephalogram and/or determined by a full neurological evaluation. Anaphylactic reaction was defined as a serious allergic reaction of rapid onset resulting in dermatological, mucosal, respiratory, or haemodynamic compromise.

Statistical analysis

Data were summarized using standard statistical descriptors such as means, standard deviations, frequencies, and percentages. Stress echocardiographic studies, which included a complete transthoracic evaluation within their standard protocol, were counted as one study. Patients who had additional echocardiograms in subsequent visits were included in the study and counted as separate patients (ratio

of echocardiographic studies to the number of patients of 1.06). Comparisons between study groups were performed using one-way analysis of variance for continuous variables and Pearson's χ^2 test for categorical variables. A *P*-value < 0.05 was considered significant. All analyses were performed using STATA software, version 12 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the study population

A total of 1513 consecutive inpatients (mean age 69 ± 14 years, 55% males, BMI 33 ± 9 kg/m²) with PHT, who underwent echocardiographic evaluation with the use of EC were identified. Indications for echocardiographic evaluation were heart failure (25%), acute coronary syndrome (13%), chest pain (9%), dyspnoea (9%), arrhythmia (13%), syncope (12%), valvular heart disease (2%), cardiac source of embolism (6%), pulmonary embolism (2%), haemodynamic assessment (3%), endocarditis (3%), and other (3%). Transthoracic contrast echocardiograms were performed in 1257 (83%) patients, whereas 256 (17%) patients had stress contrast echocardiograms (dobutamine stress echo representing 12% of the total studies). Stress-induced ischaemia was observed in 36 (14%) patients undergoing stress echocardiographic evaluation. The indications for EC use were the following: LV opacification and endocardial border delineation (99.3%), and Doppler signal enhancement (0.7%).

Within the study group, 1235 (82%) patients were located in regular inpatient wards, whereas the remaining 278 (18%) patients underwent bedside studies in intensive care units. Eighty-four per cent of the patients were closely monitored with telemetry, including patients in telemetry wards (66%) and intensive care units.

There were 911 (60%) patients with mild PHT, 515 (34%) patients with moderate PHT, and 87 (6%) patients with severe PHT. Baseline patient characteristics are shown in the Table 1. Among clinical characteristics, patients in the study group were predominantly obese and had a high prevalence of cardiovascular risk factors. Furthermore, there was a high percentage of patients with known cardiovascular diseases and chronic obstructive pulmonary disease (COPD). Among echocardiographic characteristics, a higher proportion of patients with increased RA and RV size, and impaired RV and LV function was observed with increasing severity of PHT, with the highest proportion of right-sided abnormalities noted in the severe PHT group.

Adverse events

In all patients, follow-up was obtained for up to 24 h after EC administration. EC was well tolerated in all patients, and no serious adverse events occurred immediately after administration of the contrast agent or during the echocardiographic evaluation. Follow-up revealed that none of the study endpoints attributable to EC occurred within 24 h of contrast administration. However, rare serious events did occur in temporal relation to the administration of EC, but after careful evaluation were deemed as likely unrelated to the use of EC. One patient with mild PHT who underwent a dobutamine stress echo had an episode of non-sustained

Table 1 Baseline characteristics

	Mild PHT (n = 911)	Moderate PHT (n = 515)	Severe PHT (n = 87)	Total (n = 1513)	P-value
Clinical characteristics					
Age, years ^a	68 ± 14	70 ± 14	70 ± 13	69 ± 14	<0.01
Gender, male	500 (55)	285 (55)	44 (51)	829 (55)	0.71
Body mass index, kg/m ^{2b}	32 ± 9	33 ± 10	35 ± 12	33 ± 9	0.05
Hypertension	645 (71)	379 (74)	57 (66)	1081 (71)	0.24
Diabetes ^b	374 (41)	238 (46)	47 (54)	659 (44)	0.02
Dyslipidaemia	567 (62)	325 (63)	54 (62)	946 (62)	0.94
CAD ^a	422 (46)	292 (57)	45 (52)	759 (50)	<0.01
Previous CABG	189 (21)	123 (24)	22 (25)	334 (22)	0.30
Cardiomyopathy ^c	375 (41)	285 (55)	47 (54)	707 (47)	<0.01
Atrial fibrillation	226 (25)	149 (29)	27 (31)	402 (27)	0.15
Valvular heart disease	58 (6)	37 (7)	6 (7)	101 (7)	0.83
COPD ^c	189 (21)	173 (34)	35 (40)	397 (26)	<0.01
Asthma	69 (8)	45 (9)	8 (9)	122 (8)	0.68
Tobacco use ^b	416 (46)	261 (51)	52 (60)	729 (48)	0.02
Pulmonary embolism ^b	37 (4)	26 (5)	9 (10)	72 (5)	0.03
ARDS ^c	7 (0.8)	10 (2)	6 (7)	23 (1.5)	<0.01
Echocardiographic characteristics					
PASP, mmHg	41 ± 4	55 ± 5	78 ± 9	48 ± 11	<0.01
Increased RA size	188 (21)	214 (42)	63 (72)	465 (31)	<0.01
Increased RV size	106 (12)	148 (29)	54 (62)	308 (20)	<0.01
Abnormal RV function	103 (11)	145 (28)	44 (51)	292 (19)	<0.01
LVEF	50 ± 16	45 ± 18	43 ± 20	48 ± 17	<0.01
Resting LV wall motion abnormalities	337 (37)	255 (50)	40 (46)	632 (42)	<0.01

CAD, coronary artery disease; CABG, coronary artery bypass grafting.

Values are expressed as mean ± SD or n (%). A P-value <0.05 is considered significant.

^aSignificant difference between mild and moderate PHT.

^bSignificant difference between mild and severe PHT.

^cSignificant difference between mild and moderate PHT; and mild and severe PHT.

ventricular tachycardia during the peak dose of dobutamine infusion. The resting echo showed an LVEF of 25% and PASP of 40 mmHg, whereas the stress echo revealed anterior wall ischaemia. Coronary angiography was consistent with an 80% mid-left anterior descending artery stenosis which was treated with coronary angioplasty and stent placement. This episode of non-sustained ventricular tachycardia was attributed to dobutamine-induced ischaemia by the supervising physician and thus did not preclude the use of the EC agent in the recovery stage of stress.

Another patient with mild PHT (PASP 39 mmHg) had non-sustained ventricular tachycardia 12 h after administration of EC. The patient had an LVEF of <35% and an extensive history of coronary artery disease, including coronary artery bypass graft surgery, and multiple percutaneous coronary interventions. He presented with syncope and the workup, including a stress test, was unrevealing. Interrogation of his defibrillator, which had been implanted for primary prevention of sudden cardiac death, revealed four episodes of supraventricular tachycardia in the days preceding the administration of EC and one episode of ventricular

tachycardia occurring 1 month prior to this hospitalization. His serum electrolytes (except magnesium which had not been drawn) were normal throughout his stay. A third patient had cardiac arrest ~4 h after administration of EC and ultimately expired despite intense resuscitative efforts. The patient was an 83-year-old female with mild PHT (PASP 39 mmHg) who presented with acute ischaemic stroke, heart failure, and non-ST elevation myocardial infarction. The patient was stabilized medically and treated with dual antiplatelet regimen and i.v. anticoagulation. Cardiac catheterization revealed triple vessel coronary artery disease and severe segmental LV systolic dysfunction with an LVEF of 30%. The patient was considered to be at high surgical risk and was treated medically. Prior to her discharge to the inpatient rehabilitation service, and 3 h and 40 min after undergoing a trans-thoracic echocardiogram with EC, the patient was noted on telemetry to be in complete heart block which immediately degenerated to ventricular fibrillation and then pulseless electrical activity. Resuscitation was unsuccessful and the patient expired. The latter two events were attributed to the presence of severe underlying cardiomyopathy with possible electrolyte abnormalities in the

second patient, and progression of underlying disease in the setting of advanced age, acute coronary, and cerebrovascular events, as well as severe ischaemic cardiomyopathy with non-revascularized anatomy in the last patient.

Discussion

Our study shows an extremely low rate of serious adverse events in only 3 of 1513 patients with PHT who received EC for clinical indications. Moreover, these events were not attributed to EC. Rather, they were attributed to the patient's severe underlying cardiac pathology.

While the package inserts for the commercially available EC agents were recommending caution in patients with chronic pulmonary vascular disorders even before issuance of the FDA black box warning, the events that followed escalated even further the concern regarding the safety of EC in patients with PHT and this issue still remains unresolved to this day. The pathophysiological substrate for this controversy stems from the fact that the gas octafluoropropane, a component of the perflutren lipid microspheres of Definity, is entirely eliminated by means of the lungs.^{22,23} In animal experiments, a spectrum of haemodynamic changes have been noted after administration of high doses of EC, ranging from increases in mean pulmonary artery pressures without clinical significance, to induction of pulmonary oedema, haemodynamic collapse, and death.^{24–28} Patients with PHT have increased pulmonary vascular resistance and frequently inefficient gas exchange. Although the elimination of Definity is similar in healthy subjects (1.3 min) vs. subjects with COPD (1.9 min),²² animal studies suggest that, theoretically, the transit of microbubbles through the human pulmonary capillaries could adversely affect haemodynamics either by mechanical obstruction or more importantly by vasoactive mediator release with secondary vasoconstriction through activated macrophages. This could potentially result in worsening pulmonary artery pressures, hypoxaemia and ultimately circulatory collapse. Although these macrophages have not been found in the lungs of healthy subjects, they have been found in lungs of patients with acute respiratory distress syndrome (ARDS) and other serious pulmonary conditions.^{29,30}

Our study specifically addresses this concern in a large cohort of patients with PHT from a multi-institutional experience. The main finding of our study is that the use of the EC agent Definity in patients with PHT of any degree, undergoing echocardiographic evaluation under various clinical scenarios, is safe.

Previous studies involving large cohorts of patients have included only a small percentage of patients with PHT. While they have suggested that the use of EC is safe, they have not specifically targeted patients with PHT.^{11–13} Only recently, a single-centre retrospective study evaluated the safety of EC in patients with PHT undergoing stress echocardiography. The study included 1900 patients with PHT receiving EC, from which 414 patients had an RVSP ≥ 50 mmHg. The authors found no difference in event rates (death/myocardial infarction/significant arrhythmias) between patients undergoing stress testing with and without EC, at 72 h and 30 days.³¹ Shortly after, Lantheus Medical Imaging announced new data from a phase 4, multi-centre, open-label study of patients with normal (16 patients) and elevated PASP

(16 patients, 35 mmHg < PASP < 75 mmHg) undergoing right heart catheterization. The study demonstrated no clinically important or statistically significant pulmonary and systemic haemodynamic changes.³² Our study expands on this knowledge by documenting an extremely low rate of serious adverse events (0.002%) in over 1500 patients with PHT. Forty per cent ($n = 602$) of our patients had a PASP ≥ 50 mmHg, whereas 6% ($n = 87$) of the patients had PASP ≥ 70 mmHg. Our study group included patients at high risk for cardiovascular and pulmonary events. As in the latter study, serious adverse events rarely occurred during the follow-up period; however, these events were likely related to the different underlying pathological processes and no deaths or serious adverse events, including worsening of respiratory or haemodynamic status, attributable to the use of EC were observed. While the first adverse event reported, attributed to dobutamine-induced ischaemia, occurred early after the use of EC, the latter two events occurred hours after administration of EC, which is not consistent with the time frame of events associated with the black box warning or the haemodynamic effects observed in animal experiments that occurred within minutes of EC administration. The fact that the second patient had multiple other documented episodes of arrhythmias in the days preceding the administration of EC and that all three patients had only mild PHT further supports the notion that the adverse events presented are pseudo-complications rather than true events directly related to the use of EC.

It is noteworthy that our study included a high number of patients with significant pulmonary disorders, including 397 (26%) patients with COPD, 72 (5%) patients with pulmonary embolism, and 23 (1.5%) patients with ARDS. None of these patients experienced serious adverse events.

Study limitations

The main limitation of this study is its retrospective nature and the lack of comparison with a control group that did not receive contrast. However, the extremely low incidence of adverse events makes it very unlikely that we would find any meaningful difference with a control group of patients with comparable cardiac pathology.

Although we did not monitor vital signs or changes in PASP in all of these patients during EC administration, a substantial proportion were monitored in intensive care units (18%) and during stress testing (17%) and no immediate adverse effects on vital signs were noted. Furthermore, this held true in an additional 42 (2.8%) patients undergoing contrast studies between October 2007 and July 2008 who were closely monitored with vital signs, pulse oximetry, and electrocardiography for 30 min post-procedure as recommended by the American Society of Echocardiography expert panel at the time.

A minority of our patients (0.7%) received Definity for TR Doppler signal enhancement. Although this is currently not an FDA-approved indication, we do not believe this to have influenced our results. Excellent correlation between non-invasive and invasive PASP measurements has been observed in clinical studies using a variety of non-perflutren-based EC agents.^{33–34} We did not evaluate the safety of EC used for myocardial perfusion echocardiography in the setting of PHT. As this imaging modality is

not FDA approved and is not part of routine clinical practice at this time, such patients were not available for inclusion in our study.

We believe the inclusion in our study of a large number of inpatients, from a multi-centre perspective, to be a major strength. The majority of patients were closely monitored and no patients were lost to follow-up. The wide availability of detailed inpatient records allowed for rigorous assessment of clinical status and acuity. In addition, the use of well-defined study endpoints that are readily identifiable in the hospital setting made underestimation of adverse events less likely in our study population.

Conclusion

Our study indicates that the use of the perflutren-based EC agent Definity is safe in hospitalized patients with PHT.

Conflict of interest: Dr F.A.C. is a speaker and is receiving grant support from Lantheus Medical Imaging.

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