Original Article

The Safety Profile of Perflutren Microsphere Contrast Echocardiography During Rest and Stress Imaging: Results from an Australian Multicentre Cohort

David G. Platts, FRACP [a,b,*], Sushil A. Luis, FRACP [a,b], Damian Roper, FRACP [a,b], Darryl Burstow, FRACP [a,b], Tony Call, B Ex Sci [c], Anthony Forshaw, B Ex Sci [c] and Roess Pascoe, FRACP [c]

[a] *Echocardiography Department, The Prince Charles Hospital, Australia*
[b] *School of Medicine, University of Queensland, Australia*
[c] *Hearts 1st, Greenslopes Private Hospital, Australia*

Background: **Contrast enhanced echocardiography (CEE) is utilised when sub-optimal image quality results in non-diagnostic echocardiograms. However, there have been numerous safety notices issued by regulatory authorities regarding rare but potentially serious adverse reactions (AR). This multi-centre, retrospective analysis was performed to assess the short-term safety of CEE in a broad range of indications.**

Methods: **All CEE performed over 58 months at three institutions were assessed for AR within 30 min.**

Results: **A total of 5956 CEE were performed in 5576 patients. A total of 4903 were stress CEE and 1053 resting CCE. Bolus administration in 5719, infusion in 237 cases; 89.9% of CCE were outpatients. Commonest CEE indication was functional stress testing (82.3%). There were 16 AR related to CEE (0.27%). All AR were mild, transient and all patients made a full recovery. No cases of serious anaphylaxis or death within 30 min of contrast administration. Comparing those with and without an AR, there were no significant differences in age, gender, BMI, LVEF, patient location, exam type or RVSP. There was a slightly increased likelihood of an AR during infusion versus bolus dosing ($p = 0.02$).**

Conclusion: **CEE is a safe investigation in a broad range of indications and clinical scenarios. AR are very rare, mild and transient.**

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Keywords. Contrast echocardiography; Left ventricular opacification; Exercise stress echocardiography; Dobutamine stress echocardiography; Safety

Introduction

Transthoracic echocardiography (TTE) is a safe, non-invasive bedside imaging technique that provides comprehensive information regarding cardiac structure and function. It is the most frequently used cardiac imaging modality. However, in up to 25% of cases suboptimal images are obtained [1–4]. This may be due to body habitus, lung disease or a difficult scanning environment, such as in the critical care complex where lighting, patient position and mechanical ventilation can all hinder acquisition of diagnostic TTE images. The administration of an echocardiographic contrast agent, when coupled with contrast specific imaging modalities, offers the ability to salvage and convert these non-diagnostic scans into diagnostic echocardiograms [5–11].

Although these agents have been in clinical use for over a decade, in 2007 the American Food and Drug Administration (FDA) and European Medicines Agency (EMEA) issued a "boxed warning" regarding their safety profile [12,13]. Whilst this warning has subsequently been downgraded on two separate occasions, there still remains a perception these agents may have a significant adverse event profile, which could unduly influence recommendations for their use. This retrospective analysis was performed to assess the short term safety of the perflutren microsphere contrast agent Definity® (Lantheus Medical Imaging, North Billerica, MA, USA) during both resting

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* Corresponding author at: Echocardiography Department, The Prince Charles Hospital, Rode Rd., Chermside, Brisbane 4032, Queensland, Australia. Tel.: +61 07 3139 4000; fax: +61 07 3139 4426.
E-mail addresses: david_platts@health.qld.gov.au, dgplatts@hotmail.com (D.G. Platts).

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and stress echocardiography, at three different institutions.

Material and Methods

A retrospective analysis of all contrast echocardiograms using Definity® at three institutions in Queensland, Australia (Greenslopes Private Hospital, The Prince Charles Hospital (TPCH) and Caboolture Hospital) was performed. A database search of all reports written for contrast echocardiograms was undertaken and the necessary information derived from these reports. Contrast use was based upon conventional indications to enhance image quality or where the supervising cardiologist determined that contrast administration would improve their confidence in image interpretation. Contrast was administered either as a diluted bolus or an infusion. Bolus dosing was performed by diluting one activated ampoule of Definity® contrast with 10–30 mL of normal saline and slowly injecting 0.5–1.0 mL aliquots. Infusion dosing was performed by diluting one activated ampoule of Definity® contrast to 50 mL with normal saline and infusing at a rate between 150 and 300 mL/h, to optimise image quality.

Resting contrast echocardiograms were performed in the standard manner with contrast specific, low mechanical index imaging techniques during Definity® administration. Dobutamine stress echocardiograms (DSE) were performed in a conventional manner with incremental increases in dobutamine every 3 min (from 5 mcg/kg/min to 40 mcg/kg/min infusion rates) and intravenous atropine if required, to achieve a target heart rate of 85% of maximum predicted for age. Definity® was administered at each stage where echocardiographic imaging was required. For contrast exercise stress echocardiograms (ESE), Definity® was administered at baseline and just prior to image acquisition at peak stress.

Conventional patient demographics were collected as well as the following parameters: method of contrast administration (diluted bolus or infusion), type of echocardiogram (rest or stress), indication for contrast imaging, patient location (in-patient or outpatient), presence of any adverse event, severity of adverse event, impact of adverse event upon test continuation, left ventricular ejection fraction (LVEF) and right ventricular systolic pressure (RVSP). During stress echocardiography (where the chosen stressor could also induce an adverse reaction), the supervising clinician reported whether the AR was thought due to contrast or the method of stress. Additionally, during the course of this analysis, the requirement for formal monitoring in patients following contrast administration varied. However, all patients were under medical supervision for at least 30 min after initiation of contrast administration.

Continuous variables were expressed as a mean, ±1 standard deviation and range. Categorical variables were expressed as a frequency and percentage proportion. Comparison between two groups (adverse event versus no adverse event) was performed using the two sample student's *t*-test for continuous variables and chi-square tests for categorical variables. A p value of <0.05 was considered as statistically significant. All statistical analyses were performed using MedCalc® version 12.3 (Mariakerke, Belgium). Approval for publication of this article was obtained from the Research, Ethics and Governance Unit at The Prince Charles Hospital.

Table 1. *Baseline Patient and Echocardiographic Characteristics for All Contrast Echocardiograms.*

	Mean + SD
Gender	
Males	3545 (59.5%)
Females	2411 (40.5%)
Age (years)	61.5 ± 13.4 (range 15–99)
Body mass index (kg/m^2)	29.4 ± 6.3
LVEF (%)	58.3 ± 10.6 (range 4–85)
RVSP (mmHg)[a]	36.0 ± 8.9 (range 27–100)
Patient location	
Out-patient	5354 (89.9%)
In-patient	602 (10.1%)
Study type	
Resting transthoracic echocardiogram	1053 (17.7%)
Dobutamine stress echocardiogram	747(12.5%)
Exercise stress echocardiogram	4156 (69.8%)
Study indication	
Functional stress testing	4903 (82.3%)
Resting ventricular function	709 (11.9%)
Ventricular thrombus evaluation	231 (3.9%)
Ventricular morphology/mass	94 (1.6%)
Other	19 (0.3%)
Contrast administration	
Diluted bolus	5719 (96%)
Infusion	237 (4%)

LVEF = left ventricular ejection fraction and RVSP = right ventricular systolic pressure.
[a] RVSP was obtained in 1844 (31%) contrast echocardiograms performed.

Results

A total of 5956 contrast echocardiograms were performed in 5576 patients between August 2007 and May 2012. All patients received Definity® contrast as no alternative contrast agent was commercially available in Australia. A total of 5354 contrast cases (89.9%) were out-patients and 602 (10.1%) were performed as an in-patient basis. A total of 211 inpatients (35%) were in the critical care complex (153 in the coronary care complex and 58 in the intensive care unit). Table 1 lists the patient demographics and echocardiographic characteristics for all contrast echocardiograms.