Original Article

Contrast Echocardiography in Australian Clinical Practice

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Background: **The second-generation contrast agent Definity® (a perflutren microsphere) became available in Australia in mid-2007. We describe the introduction of contrast echocardiography into a high-volume quaternary teaching hospital, performing over 16,000 echocardiograms per year. Workflow protocols were developed for patient selection, contrast administration, and image acquisition and analysis.**

Methods: **Data were prospectively collected for all contrast cases. Endocardial definition scores were derived by three independent observers before and after contrast administration, and statistically compared.**

Results: **161 patients received contrast in the first 12 months of the contrast program. There was statistically significant improvement in endocardial definition scores after contrast administration ($p = 0.0001$), and reduction in inter-observer variability of wall motion assessment. A number of clinically significant findings (pseudoaneurysm, non-compaction, thrombus) were detected on contrast echo that were not apparent on standard 2D imaging. Adverse events were rare (0.6%) with no life-threatening events.**

Conclusions: **The introduction of a second-generation contrast agent into clinical workflow in a hospital echocardiography department resulted in a statistically significant improvement in endocardial definition, and safely provided diagnostic imaging in cases which were otherwise non-diagnostic. Inter-observer variability was reduced, and diagnostic yield increased. These results reflect previously published data, and indicate that contrast echocardiography is feasible in Australian clinical practice.**

(Heart, Lung and Circulation 2010;19:385–394)

Keywords. Contrast echocardiography, Mechanical index, Left ventricular opacification, Myocardial Contrast Echocardiography (MCE)

Introduction

Contrast echocardiography using second-generation microbubble contrast agents has been used in clinical echocardiographic practice for several years in many centres outside Australia. Echo contrast agents dramatically improve endocardial definition in both resting echocardiography and stress echocardiography [1–5]. The improvement in the blood-myocardial interface also renders contrast echocardiography very useful in evaluating ventricular morphology. Research applications of contrast microbubbles include myocardial perfusion echocardiography, targeted delivery of gene therapy and three-dimensional echocardiography [6–9].

Received 12 December 2008; received in revised form 20 January 2010; accepted 1 February 2010

Abbreviations: LVEF, left ventricular ejection fraction; LVO, left ventricular opacification; CMR, cardiovascular magnetic resonance; MCE, myocardial contrast echocardiography.

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Until recently, only a first generation agent was available in Australia (Levovist®, Schering), most often used during trans-septal alcohol ablation for hypertrophic cardiomyopathy. A second-generation contrast agent (Definity®, Lantheus Medical Imaging) was introduced for clinical use in Australia for the first time in mid 2007. Definity® is a suspension of microbubbles composed of perflutren tri-lipid spheres with an inert octafluoropropane gaseous core. Activated contrast microbubbles are the size of red blood cells with a similar intravascular rheology, and act as biologically inert blood pool tracers. The contrast agent is injected into a peripheral venous cannula, either as intermittent boluses or as a constant infusion, and imaged with contrast-specific echocardiographic imaging techniques (see below). This second-generation contrast agent has been approved by the Australian Therapeutic Goods Administration for use in both resting and stress echocardiography to improve endocardial definition in those patients with sub-optimal image quality [10].

This paper reports the initial clinical experience of introducing contrast echocardiography to a high-volume

1443-9506/04/$36.00
doi:10.1016/j.hlc.2010.02.001

Table 1. *Indications for Contrast Echocardiography.*

1. Sub-optimal endocardial definition in *2 or more* LV segments as per ASE guidelines. This is both for resting echocardiography and stress echocardiography.
2. To further delineate ventricular structure/morphology: a. Pseudoaneurysm b. Apical hypertrophic cardiomyopathy c. Ventricular non-compaction
3. To further delineate a ventricular mass: a. Intra-cardiac thrombus b. Intra-cardiac tumour
4. Inability to obtain a clear and complete maximal velocity from Doppler spectral profiles.

quaternary teaching hospital, performing over 16,000 echocardiograms per year. We outline the method of introduction of this new technology into the imaging department, the results obtained both for resting and dobutamine stress echocardiography and suggest clinical protocols for its use in the daily practice of clinical echocardiography.

Contrast echocardiography was introduced into the Prince Charles Hospital Echocardiography Department in August 2007. Working protocols were developed for (1) patient selection for contrast imaging, (2) contrast preparation, (3) contrast administration, (4) contrast agent imaging and (5) method of image interpretation. Two sonographers were specifically trained in contrast imaging, and one consultant with overseas expertise in contrast echocardiography (DGP) was responsible for supervising the contrast examinations.

Aim and Hypothesis

Addition of a microsphere contrast echocardiography protocol to a busy Australian teaching hospital would provide improved endocardial definition and reduce unevaluable studies in a safe and efficient manner.

Endpoints: Endocardial definition on a 16-segment basis, the percentage (%) of evaluable segments and the percentage fully evaluable studies. A study was considered fully evaluable if all 16 segments could be confidently evaluated by three independent expert readers.

Patient Selection for Contrast Imaging

A working protocol was implemented to minimise impact of performing contrast echocardiography on the workflow through the laboratory.

Following imaging via conventional echocardiography, conventional guidelines were applied to assess for the need for contrast echocardiography (Table 1). Contrast administration was reserved for use in cases where improved image quality would result in a change in management, or have a significant incremental benefit in the diagnosis of the patient (Table 1).

Method of Contrast Preparation

Perflutren microsphere contrast is presented in a glass vial and requires storage in a refrigerator (at around 4 °C). Prior to administration, it has to be activated via agitation into a suspension of microbubbles. In its inactivated form, it appears as a clear liquid (the lipid shell) with a clear gas above it (the octafluoropropane gaseous core).

The contrast is activated by placing the vial in a device called a Vialmix^{TM}. This is a modified dental amalgam mixer that rapidly agitates the contrast vial for 45 s at 2400 revolutions per minute. Following activation, the contrast appears as a homogeneous milky white substance with an undiluted volume of 1.3 ml.

Method of Contrast Administration

Microsphere contrast is diluted into 10 ml of normal saline and administered into a peripheral intravenous cannula as a slow bolus. The initial dose is a 1.0 ml bolus, given over approximately 2 s. Signal persistence in the left ventricular cavity is usually present for several minutes after a single bolus. Once the contrast concentration falls below an acceptable level, follow up boluses of 0.5–1.0 ml were administered. Care was taken to avoid over-administration of contrast by intermittent bolus, as this would result in artefact in the left ventricular cavity and significant basal attenuation. There was a practical learning curve for Fellows and staff to adjust their technique of intermittent bolus administration, which was in the order of 5–10 studies.

Contrast infusions were occasionally employed during dobutamine stress echocardiograms. The contrast was diluted in 50 ml of normal saline and was administered at a rate sufficient to evenly and constantly opacify the left ventricular cavity. The recommended infusion rate is 4.0 (starting) to 10.0 (maximum) ml/min, using the above dilution schedule and adjusted to provide a consistent level of left ventricular opacification [10]. However we found that the intermittent bolus technique was simpler and easier in clinical practice. Perfusion imaging (myocardial contrast echocardiography) may require the more constant opacification provided by infusions. However contrast agents are not currently approved for assessment of perfusion, so our practice was to continue with the intermittent bolus technique.

Method of Contrast Agent Imaging

Imaging of contrast agents with conventional 2D ultrasound results in bubble destruction due to the high ultrasound power (mechanical index, or "MI" of approximately 1.4). Contrast-specific imaging modalities have been developed which exploit the non-linear oscillation properties of microbubbles when exposed to low MI ultrasound (MI approximately 0.1) [2]. Contrast-specific imaging results in nullification of the myocardial signal, rendering this black, and enhancement of the contrast signal, rendering this white; i.e. the inverse appearance to a standard echo examination (see Figs. 1 and 2). Two forms of contrast imaging were utilised in this study: Power Modulation (PM) and Power Pulse Inversion Imaging (PPI).