

# Use of Contrast Agents with Echocardiography in Patients with Suboptimal Echocardiography

An Evidence-Based Analysis

*Presented to the Ontario Health Technology  
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# Executive Summary

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## Objective

The objective of this report is to assess the ability of microbubble contrast agents to enhance the visualization of cardiac structures in patients with suboptimal echocardiography results.

## Contrast Echocardiography

The most common use of contrast echocardiography is the enhancement of the endocardial border. Left ventricular (LV) opacification with contrast echocardiography has the potential to improve the definition of the LV border. The aim of contrast echocardiography is to provide better quantification of LV volume and assessment of LV wall motion analysis than echocardiography alone.

Some patients, however, are more likely to exhibit poor echocardiograms than others. These patients include critically ill patients on ventilators or with lung problems, patients who've had recent chest operations, and obese patients. Echocardiography studies performed in the intensive care unit (ICU) are frequently inadequate or suboptimal because of the difficulties in positioning patients properly, poor lighting, chest tubes and bandages.

Contrast agents could potentially be used in 5% to 10% of resting echocardiography exams and in an estimated 30% of stress echocardiography tests due to suboptimal echocardiograms. The American Society of Echocardiography guidelines stated that 75% to 90% of suboptimal echocardiography results can yield interpretable results with the use of contrast agents.

## Evidence-Based Analysis Methods

### Research Question

Do contrast agents improve the visualization of the cardiac structures in patients exhibiting suboptimal echocardiograms?

### Literature Search

A literature searches was performed on June 22, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published since 1950. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria; full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

### *Inclusion Criteria*

- Systematic reviews, meta-analyses, randomized controlled trials, observational studies
- Minimum sample size of 20 enrolled patients
- The contrast agent used in the study must be licensed by Health Canada (at least Notice of Compliance)
- Patient population must include patients with suboptimal echocardiography results
- Compares echocardiography without contrast to echocardiography with contrast
- English
- Human

### ***Exclusion Criteria***

- Non-systematic reviews, case reports
- Grey literature (e.g. conference abstracts)

### ***Outcomes of Interest***

- Change in visualization with and without contrast agent

## **Summary of Findings**

Based on the results of this review:

- Five studies consistently demonstrated that the addition of contrast to echocardiography improves heart visualization in patients with previously uninterpretable or suboptimal echocardiography results.
- Suboptimal echocardiography was consistently defined as >2 contiguous segments not seen in non-contrast images.
- The additional cost of using contrast agents in Ontario would range from approximately \$5M to \$30M annually.

# Background

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## Contrast Echocardiography

The addition of contrast agents to echocardiography has been available since the technology was first introduced in the 1960s. The challenge for these agents is that the air bubbles caused by agitation are unreliable, unstable, and could possibly lead to severe adverse events, primarily embolism. In the 1980s, the concept of encapsulating the air bubbles in a protective shell was developed. These shell-encapsulated air bubbles have since become referred to as microbubbles or microspheres. The shells preserve the gas within the microsphere and increase the duration of opacification.

The first commercially available microsphere contrast agent was Albunex, which received approval by the Food and Drug Administration in the United States in 1994. (1) This original microsphere contrast agent was limited by a rapid loss of gas volume, which caused a concomitant decline in ultrasound signal. (1) Although the agent worked well in the right chambers of the heart, it dissolved when passing through the pulmonary capillaries and was thus unable to provide contrast for the left side of the heart.

Modern microsphere technology comprises a unique class of contrast agents other than dyes, chemical compounds or radioisotopes. Microsphere contrast agents have been developed in conjunction with updated ultrasound imaging techniques to maximize their capabilities. Microspheres are now typically just 4 to 5µm in diameter and able to pass through the microcirculation. (2)

The clinical applications of contrast echocardiography have been expanded since the early days of contrast enhancement. It is widely cited that contrast echocardiography can be used to identify Doppler signal enhancement, evaluation of non-compaction cardiomyopathy, thrombus detection, assessment of global and regional wall motion, and to enhance the endocardial border. (2)

### *Endocardial Border Enhancement*

Today, the most common use for contrast echocardiography is to enhance the endocardial border. Left ventricular (LV) opacification with contrast echocardiography has the potential to improve the definition of the LV border. Contrast echocardiography may be able to provide better quantification of LV volume and assessment of LV wall motion analysis than echocardiography alone. (2) In critically ill patients, for instance, LV opacification is used for the assessment of LV contractility and ejection fraction (personal communication, August 2009).

### *Myocardial Perfusion Assessment*

The newest area of development in the research of contrast echocardiography is myocardial perfusion assessment, also known as myocardial contrast echocardiography. As myocardial ischemia and infarction affect both perfusion and contractility (wall motion), contrast echocardiography could, theoretically, be an ideal non-invasive imaging test that could assess both perfusion and contractility simultaneously in real time. (2)

Perfusion requires that the echocardiograph is set to a high mechanical index (MI), which is a standardized measure of peak acoustic intensity. At a high MI, the microbubbles burst or are destroyed, thus new microspheres replenish the myocardium. Perfusion is assessed by measuring how quickly the microspheres are replenished within the myocardium. Thus, if the microspheres are replenished in the myocardium within 5 to 7 cardiac cycles (about 5 seconds), the myocardium is considered normal. If the microspheres are not replenished within 5 to 7 cycles, the myocardium is said to exhibit decreased perfusion. (2-5)

Myocardial perfusion assessment with contrast echocardiography is still considered mostly a research technique and is not routinely used in most echocardiography laboratories (personal communication, December 2009).

### ***Suboptimal Echocardiography***

There are some patients who are more likely to generate poor echocardiograms than others. Such patients include the critically ill, those on ventilators or with lung conditions, patients who've undergone recent chest operations, and the obese (personal communication, August 2009). (6) Echocardiography studies performed in the intensive care unit (ICU) are frequently inadequate or suboptimal because of the difficulties in positioning patients properly, poor lighting, chest tubes and bandages. (7)

Contrast agents have the potential to be used in 5% to 10% of resting echocardiograms and in approximately 30% of stress echocardiograms due to suboptimal echocardiograms. (8;9) Stress can be either induced pharmacologically (dobutamine, dipyridamole, adenosine) or with exercise. Generally, contrast agents are used more in pharmaceutical stress echocardiograms than in exercise stress echocardiograms. (2) The American Society of Echocardiography guidelines stated that 75% to 90% of suboptimal echocardiography results yield interpretable results with the use of contrast agents. (10)

### **Regulatory Status**

There is only one contrast agent for echocardiography fully licensed by Health Canada, though several others have received a Notice of Compliance approval. The Notice indicates that the agent has been approved for its safety and effectiveness, but the marketing and labelling of the packaging has not been approved for distribution in Canada. For the purposes of this review, any study using a contrast agent with at least a Notice of Compliance from Health Canada was included in the review.

The contrast agent licensed by Health Canada is indicated for “contrast-enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders) and function (regional wall motion) in adult patients with suboptimal echocardiograms. *The safety and efficacy of [the contrast agent] with exercise stress or pharmacologic stress testing (e.g., IV dipyridamole) have not been established.*” (Product Monograph for Definity, September 22, 2008)

### **Guidelines on the Use of Contrast Agents with Echocardiography**

The American Society of Echocardiography published a consensus statement in 2008 on the use of contrast agents in echocardiography. (10) They recommended using contrast agents in the following situations:

- In patients presenting for rest echocardiography with reduced image quality
  - To enable improved endocardial visualization when  $\geq 2$  contiguous segments are not seen on non-contrast images
- In patients presenting for stress echocardiography with reduced image quality
  - To obtain diagnostic assessment of wall motion and thickening at rest and stress
- In all patients presenting for rest echocardiography for the assessment of LV systolic function
- To confirm or exclude the following LV structural abnormalities:
  - Apical variant of hypertrophic cardiomyopathy
  - Ventricular non-compaction
  - Apical thrombus
  - Complications of MI (e.g., LV aneurysm, pseudoaneurysm, myocardial rupture)



- To assist in detection and classification of intracardiac masses
- For use in the intensive care unit when standard echocardiography is inadequate
- To enhance images to assess diastolic and/or valvular function
- To increase confidence in interpretations

In 2009, the European Association of Echocardiography also made recommendations regarding the use of contrast agents in echocardiography. (9) They made similar recommendations to the American Society of Echocardiography, primarily using contrast in patients at rest or stress with suboptimal standard echocardiography images (when  $\geq 2$  contiguous segments are not seen on non-contrast images)

The Canadian Cardiovascular Society and the Canadian Society of Echocardiography published a position paper in 2007 regarding the use of contrast echocardiography. (11) They concluded that the addition of contrast echocardiography can limit the use of cardiac imaging technologies that are not as readily available as echocardiography.

# Evidence-Based Analysis

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## Objective of Analysis

The objective of this report is to assess the ability of microbubble contrast agents to enhance the visualization of cardiac structures in patients exhibiting suboptimal echocardiography results.

## Research Question

Do contrast agents improve the visualization of the cardiac structures in patients with suboptimal echocardiograms?

## Methods

### Literature Search

A literature searches was performed on June 22, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published since 1950. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria; full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. The complete search strategy is detailed in Appendix 1.

### *Inclusion Criteria*

- Systematic reviews, meta-analyses, randomized controlled trials, observational studies
- Minimum sample size of 20 enrolled patients
- The contrast agent used in the study must be licensed by Health Canada (at least Notice of Compliance)
- Patient population must include patients with suboptimal echocardiography results
- Compares echocardiography without contrast to echocardiography with contrast
- English
- Human

### *Exclusion Criteria*

- Non-systematic reviews, case reports
- Grey literature (e.g., conference abstracts)

### *Outcomes of Interest*

- Change in visualization with and without contrast agent

**Table 1: Quality of evidence of included studies**

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	3
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modelling	4d	1
Case series presented at international conference	4(g)	0
	<b>Total</b>	<b>5</b>

\* RCT refers to randomized controlled trial.

† g indicates grey literature.

## Quality of Evidence

The quality of the evidence was analysed for overall quality by GRADE Working Group Criteria. (12) The GRADE developers have specifically developed strategies for assessing the overall quality of diagnostic tests using GRADE. (12) Table 2 describes GRADE for the assessment of left ventricular function using contrast agents in patients with suboptimal echocardiography results.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

- High** Further research is very unlikely to change confidence in the estimate of effect.
- Moderate** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- Low** Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- Very Low** Any estimate of effect is very uncertain

**Table 2. GRADE quality of evidence: assessment of left ventricular function using contrast agents in patients with suboptimal echocardiography results**

Factor	Explanation	GRADE
<b>Risk of Bias</b>		
Study design	RCT, prospective and retrospective studies	High
Limitations	Various study designs, no consistency in presentation/description of results	Reduced by one level to Moderate
<b>Indirectness</b>		
Outcomes	Varied across studies	Moderate
Patient populations, diagnostic test, comparison test, and indirect comparisons	All studies included patients with suboptimal echocardiography results that were being assessed for left ventricular function	Unchanged
Important inconsistency in study results	No inconsistency	Unchanged
Imprecise evidence	Sufficient consistent evidence	Unchanged
Publication bias	No publication bias suspected	Unchanged
<b>Overall Quality of Evidence</b>		<b>Moderate</b>

## Results of the Evidence-Based Analysis

Five studies were identified that investigated the use of microbubble contrast agents in patients undergoing echocardiography to assess LV function. Four of the studies examined patients at rest, while a study by Dolan et al. (13) examined patients at stress. All of the studies included patients with suboptimal echocardiograms, in most cases defining suboptimal as  $\geq 2$  contiguous segments not visualized. This definition of suboptimal echocardiography is consistent with both the American and European echocardiography guidelines. (9;10) Other characteristics of the studies are described in Table 3.

Unfortunately, the studies identified all presented their results differently, thus it was not possible to pool their results for meta-analysis. Nonetheless, the results of the all of the studies consistently demonstrated that the addition of contrast to standard echocardiography improved visualization of the heart.

**Table 3. Characteristics of studies investigating the role of contrast agents in patients with suboptimal echocardiography results**

Study	Type of study	Patient population	Mean age (% male)	Rest or stress	Contrast agent
Kurt et al, 2009 (14)	Prospective	-632 pts with suboptimal echo	64 SD 14 (63%)	Rest	Definity
Corsi et al, 2006 (15)	Prospective	-16 pts with suboptimal echo -8 controls	Not reported	Rest	Definity
Makaryus et al, 2005 (7)*	Retrospective	-213 pts in ICU (29% received contrast due to suboptimal echo results)	68 SD 15 (54%)	Rest	Definity or Optison
Dolan et al, 2001 (13)	Prospective	-117 pts with suboptimal echo -112 controls	64 SD 11 (55%)	Stress (dobutamine)	Optison
Kitzman et al, 2000 (16)	RCT	-211 pts with suboptimal echo	56 SD 16 (66%)	Rest	Definity

Note: LV, left ventricular; RCT, randomized controlled trial; SD, standard deviation

\* In the study by Makaryus et al the majority of patients (65%) underwent echocardiography to assess left ventricular function, the remaining patients received echocardiography to assess other cardiac issues.

The largest study identified was published by Kurt et al. (14) in 2009. They prospectively performed 4,362 echocardiograms during the study period, and identified that 632 were “technically difficult” or suboptimal (14.5%). They stratified their results by the type and location of the patient using the following subgroups: inpatients (non-intensive care), medical intensive care unit patients, surgical intensive care unit patients, and outpatients. The majority of suboptimal echocardiograms were in patients in the intensive care unit (21.1%) compared to only 5.8% of echocardiograms in outpatients.

The results of the Kurt et al study reported that after contrast administration, 89.9% of the echocardiography studies were considered “adequate” for interpretation. (Table 4) Based on Kurt et al.’s results, it appears that patients in surgical intensive care units benefit from contrast administration, but to a lesser degree than other subgroups. It is important to note, however, that contrast administration still resulted in a significant improvement in all subgroups.

**Table 4: Subgroup results reported after contrast echocardiography from Kurt et al (14).**

Contrast Echocardiography Result	Inpatients (non-ICU)	Medical ICU	Surgical ICU	Outpatient	Total
Adequate	90.1%	96.2%	77.4%	96.6%	89.9%
Technically difficult / uninterpretable	9.9%	3.8%	22.6%	3.4%	10.1%

Note: ICU, intensive care unit

The study by Corsi et al. (15) included 24 patients who were undergoing cardiac MRI to assess LV function. Sixteen of these patients had suboptimal echo, and the other 8 patients were included to act as control patients because their results were adequately visualized on echocardiography without contrast. They found that in patients with prior uninterpretable or suboptimal echocardiography results, the results for contrast echocardiography correlated well with cardiac MRI ( $r=0.76$ ).

The retrospective study by Makaryus et al (7) studied 213 consecutive patients in the ICU who underwent echocardiography. The majority of the patients (65%) were undergoing echocardiography to assess left ventricular size and function. Of the 213 patients, 62 patients (29%) required contrast agents due to suboptimal visualization of the cardiac structures. After contrast administration in patients with suboptimal results, 91% of patients had interpretable images on echocardiography.

In 2001, Dolan et al (13) reported the results of a non-random study comparing diagnostic accuracy in patients receiving contrast due to previously suboptimal echocardiograms (n=117) to patients with interpretable non-contrast echocardiography (n=112). The reference standard for establishing a true diagnosis of coronary artery disease was coronary angiography. All patients underwent stress echocardiography using dobutamine. The authors reported sensitivity and specificity for the stress contrast echocardiography group as 78% and 73%, respectively, and 71% and 82%, respectively for the stress echocardiography without contrast group. These differences in sensitivity and specificity are not statistically significant. Thus, the results of this study also conclude that in patients with suboptimal echocardiograms, contrast administration makes the images comparable to interpretable non-contrast echocardiograms.

The RCT by Kitzman et al. (16) randomized 211 patients with suboptimal echocardiograms to undergo contrast echocardiography with a microbubble contrast agent or placebo (saline). At baseline, 47% of segments were visible without contrast in the contrast group, and 50% of segments were visible in the saline group at baseline. In the contrast group, after the contrast injection, 81% of segments were visible compared to 49% within the saline placebo ( $P < .01$ ). Thus, saline had no impact on increasing the visualization of the endocardial segments (50% at baseline vs. 49% post injection). The contrast agent improved visualization from 47% at baseline to 81% post-injection of contrast agent.

## **Cost of Contrast Agents**

There is only one microbubble contrast agent which is licensed by Health Canada to be marketed in Canada. This contrast agent costs ~\$170 per vial and each vial is single use (each patient requires one vial of contrast agent). The total cost of the contrast echocardiography is, therefore, ~\$170 plus the cost of a standard echocardiogram (~\$382). According to a clinical expert, additional professional fees to be used with patients receiving contrast are unnecessary as the addition of contrast enhances the visualization of the cardiac structures, obviating the need for additional skill requirements to interpret these images (personal communication, January 2010).

In fiscal year 2007/08 in Ontario, approximately 600,000 echocardiograms were performed (includes both rest and stress). It is unclear what proportion of the echocardiograms performed are done at rest and how many are done at stress. The average cost of an echocardiogram is \$382 for a total estimated provincial expenditure of \$229M annually on echocardiograms. Table 5 lists various scenarios regarding the additional costs of adding contrast agents. As mentioned previously, approximately 5% to 10% of resting echocardiograms and 30% of stress echocardiograms are suboptimal and may benefit from contrast administration. It is important to note that by using the contrast agent, subsequent imaging tests may be avoided.

**Table 5. Scenarios for the cost of contrast agents depending on the proportion of stress versus rest echocardiograms performed in the province**

Scenario	# of patients requiring contrast	Annual cost of contrast agents
100% rest ECHO	30,000 (rest)	\$5.1M
75% rest ECHO, 25% stress ECHO	22,500 (rest) + 45,000 (stress)	\$11.5M
50% rest ECHO, 50% stress ECHO	15,000 (rest) + 90,000 (stress)	\$17.9M
25% rest ECHO, 75% stress ECHO	7,500 (rest) + 135,000 (stress)	\$24.2M
100% stress ECHO	180,000 (stress)	\$30.6M

Assumptions:

- 600,000 echocardiograms annually
- 5% of rest echocardiograms require contrast agent
- 30% of stress echocardiograms require contrast agent
- Contrast costs \$170/per patient

## Conclusions

Based on the results of five studies, the addition of contrast to echocardiography improves the visualization of the heart in patients with previously uninterpretable or suboptimal echocardiography results.

The additional cost of using contrast agents in Ontario would range from approximately \$5M to \$30M annually.

# Appendix 1

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## Literature Search Strategy

Search date: June 18, 2009

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to June Week 2 2009>

- 1 exp Ventricular Dysfunction, Left/ (14322)
- 2 (left adj2 ventric\* adj2 (dysfunction\* or failure or insufficienc\*)).ti,ab. (12423)
- 3 exp Heart Failure/ or exp Myocardial Infarction/ (181961)
- 4 ((myocardi\* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).ti,ab. (84862)
- 5 heart attack.mp. (2167)
- 6 ((myocardi\* or heart or cardiac) adj2 infarct\*).ti,ab. (113525)
- 7 or/1-6 (257911)
- 8 exp Contrast Media/ (69972)
- 9 (contrast adj (enhancement or dye\* or medium\* or agent\* or media or material\*)).ti,ab. (37005)
- 10 exp Microbubbles/ (926)
- 11 exp microspheres/ (17710)
- 12 (microsphere\* or microbubble\*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (27675)
- 13 exp Fluorocarbons/ (5813)
- 14 (fluorocarbon\* or perflutren or perfluoropropane or octafluoropropane or aerosomes).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7752)
- 15 (Luminity or albnex or Cardiosphere or definity or Optison or levovist or SonoVue or imagify).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1514)
- 16 or/8-15 (117239)
- 17 7 and 16 (3287)
- 18 limit 17 to (english language and humans) (1592)
- 19 limit 18 to (case reports or comment or editorial or letter) (235)
- 20 18 not 19 (1357)

Database: EMBASE <1980 to 2009 Week 24>

- 1 exp Heart Failure/ or exp Heart Infarction/ (224790)
- 2 (left adj2 ventric\* adj2 (dysfunction\* or failure or insufficienc\*)).ti,ab. (11388)
- 3 ((myocardi\* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).ti,ab. (73359)
- 4 ((myocardi\* or heart or cardiac) adj2 infarct\*).ti,ab. (88382)
- 5 heart attack.mp. (1584)
- 6 or/1-5 (256589)
- 7 exp Contrast Medium/ (55404)
- 8 exp contrast enhancement/ (35101)
- 9 (contrast adj (enhancement or dye\* or medium\* or agent\* or media or material\*)).ti,ab. (30042)
- 10 exp Microbubble/ (803)
- 11 exp Microsphere/ (9644)
- 12 (microsphere\* or microbubble\*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (20092)
- 13 exp Perflutren/ (423)
- 14 (fluorocarbon\* or perflutren or perfluoropropane or octafluoropropane or aerosomes).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4069)
- 15 (Cardiosphere or definity or Optison or levovist or SonoVue or imagify or luminity or albnex).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2614)
- 16 or/7-15 (105550)
- 17 6 and 16 (4812)
- 18 limit 17 to (human and english language) (2776)
- 19 limit 18 to (editorial or letter or note) (210)
- 20 Case Report/ (1040274)
- 21 18 not (19 or 20) (2083)



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