Contrast echocardiography in critical care: echoes of the future? A review of the role of microsphere contrast echocardiography

David G Platts and John F Fraser

Abstract

Echocardiography is an important diagnostic modality in the critical care setting. It is a safe, non-invasive bedside investigation that provides important cardiac structural, functional and haemodynamic information. However, in up to 25% of scans, the images are non-diagnostic, which can have a significant impact on patient diagnosis and management. Contrast echocardiography, using contrast microspheres coupled with contrast-specific ultrasound imaging modalities, overcomes many of the limitations that cause suboptimal echocardiograms in the critical care environment. These microspheres are haemodynamically inert and have the same intravascular rheology as red blood cells. By using the differential oscillating properties of myocardium and microspheres, contrast echocardiography can enhance the blood pool–myocardial interface, thus improving endocardial definition. Consequently, this technique can be used to improve the accuracy, feasibility and reproducibility of transthoracic echocardiography. The technique is well accepted and indicated for improving the image quality in suboptimal scans, and for the assessment of global and regional left ventricular (LV) function and LV ejection fraction. It also has a significant role to play in enhancing LV morphology (for conditions such as apical hypertrophic cardiomyopathy, pseudoaneurysm and non-compaction), assessing intracardiac masses and evaluating LV thrombus. Contrast echocardiography is of benefit in various clinical settings, particularly the critical care setting. Here it can salvage a non-diagnostic transthoracic echocardiogram, thus avoiding an alternative, more invasive investigation, while remaining a truly bedside, non-invasive investigative procedure. Future applications for contrast echocardiography could include use as a perfusion modality, enhancement of three-dimensional echocardiography, and targeted delivery of gene therapy.

Contrast-enhanced TTE (CE) is a safe and non-invasive imaging technique that can overcome these limitations, even in unstable patients who cannot be moved from the intensive care unit.
ICU. This review provides staff in the critical care setting with information about contrast imaging modalities, agents available, indications, contraindications, safety, and future applications of the technique.

**Contrast agents**

The term “contrast echocardiography” can refer to several forms of echocardiography, but this review focuses on microsphere contrast echocardiography. Contrast echocardiography can also refer to the simple administration of agitated saline to assess for right-to-left shunts. In this technique, normal saline is agitated and injected into a peripheral venous cannula during conventional TTE imaging. These agitated saline bubbles are typically 50–90 μm in diameter and have a very short half-life. This basic technique is useful to determine whether there is an intrapulmonary or intracardiac right-to-left shunt.

Microsphere contrast echocardiography (MCE) is a different entity and utilises microbubbles during contrast-specific echocardiographic imaging modalities to enhance the blood pool and improve the blood–myocardial interface. After administration into a peripheral venous cannula, the contrast microspheres pass through the right heart, enter the pulmonary circulation and flow to the left heart, thereby increasing ultrasound backscatter of the blood pool. The following section will explain the ultrasound principles involved in this technique.

The different ultrasound contrast agents currently available or under development are all based on a similar structural principle: they have an outer shell and inner gaseous core. It is the composition of these two components that makes each agent unique, both in its response to ultrasound waves and in its clinical utility. The microbubbles need to be sufficiently elastic to resonate in response to ultrasound, but sufficiently robust to survive passage through the giving sets and the pulmonary circulation.

Echocardiographic contrast agents can be classified as first-generation, second-generation or third-generation (novel/custom-made bubbles). The first-generation bubbles had a basic structure, with air as their gaseous core. First-generation agents included sonicated albumin (Albunex) and Levovist. Second-generation agents have a more complex structure, with a high-molecular-weight gaseous core. Currently available second-generation agents are Optison (GE Healthcare, Amersham, UK), Sonovue (Bracco Diagnostics, Milan, Italy) and Definity (Lantheus Medical Imaging, Billerica, Mass, USA). Novel (third-generation) contrast agents are custom-made for a particular purpose, either for therapy or for a particular type of imaging.

Definity (perflutren microspheres) is the second-generation agent approved for use and marketed in Australia. Definity microspheres have a mean diameter of 3 μm and consist of a gaseous core and a lipid shell. The gaseous core is a high-molecular-weight gas called octafluoropropane (MW=188). This biologically inert gas is encapsulated in a trilipid shell. In the unactivated form (left panel image in Figure 1), it consists of the clear liquid lipid shell below and the gaseous core above. It requires activation in a VialMix (Lantheus Medical Imaging, Billerica, Mass, USA) device (Figure 2), which agitates the ampoule at 4530 ± 100 oscillations per minute for 45 seconds. This generates a solution of perflutren microsphere bubbles, which have an opaque, milky white appearance (right panel image in Figure 1). Activation produces 1.3 mL of contrast agent with the following properties:

- Microsphere concentration 1.2 × 10^10/mL;
- Microsphere mean diameter 3 μm;
- Size distribution 98% < 10 μm;
- Maximum diameter 20 μm;
- pH 5.8–7.0.

**Pharmacokinetics**

After Definity has been administered, it provides 3–5 minutes of contrast signal persistence before the bubbles lose their structure and hence no longer produce ultrasound backscat-
ter. The octafluoropropane gas is not metabolised and is excreted unchanged in the lungs. The mean half-life is 1.3 minutes in healthy subjects and 1.9 minutes in people with chronic airflow limitation. The lipid shell is metabolised by the usual process of fatty acid metabolism.

Other contrast agents

Two other commercially available contrast agents are available outside Australia, Optison and SonoVue. Optison has an octafluoropropane gaseous core and a 1% human albumin shell. It requires no preparation other than hand agitation and dilution with normal saline. SonoVue has a gaseous core of sulfur hexafluoride ($SF_6$) and a phospholipid shell. The agent is reconstituted with 5 mL of normal saline and hand agitated for 20 seconds.

Additional agents are undergoing research and development, with a view to using them as possible perfusion agents or for targeted delivery of gene therapy.

Contrast-specific imaging

Contrast imaging employs techniques that are specific to microbubble imaging. Imaging of these bubbles with conventional modes results in excessive bubble destruction and non-diagnostic images. Figure 3A shows a contrast image obtained with conventional TTE imaging, and Figure 3B is the same view with contrast-specific imaging activated. As demonstrated, a high transmit power (typically with a mechanical index [MI] above 1.0 during conventional imaging) destroys microbubbles. Thus, low-transmit power imaging modalities had to be developed.

Contrast agent microbubbles have a greater harmonic signal than tissue. However, in early experimentation with these agents, the presence of tissue harmonics confounded the issue and reduced the discrimination between the contrast agent and tissue. This resulted in the need to develop specific techniques to maximise the contrast signal while minimising the tissue signal (or enhancing the contrast-to-tissue signal ratio). These are multipulse, real-time imaging techniques based on three important concepts that are key to microbubble imaging:

- Mechanical index;
- Oscillation properties of tissue and microbubbles:
  - Tissue with linear oscillation;
  - Microbubbles with non-linear oscillation; and
- Effect of microbubble size.

The MI is a measure of the acoustic output power of the ultrasound system. It is an indicator of the non-thermal bioeffect of ultrasound waves. It can also be defined as a measure of the negative acoustic pressure within the ultrasound field. The MI is quoted as a single, unitless number. In conventional, two-dimensional echocardiographic scanning, it is typically around 1.4.6 However, the MI during contrast-specific imaging is significantly lower, in the order of 0.1–0.3.

In low-MI imaging, myocardial tissue and contrast microbubbles have significantly different backscattering properties. By exploiting this difference, contrast imaging modes can enhance the contrast signal while suppressing the myocardial signal, with the net result of enhancing the endocardial border. At low MI, tissue (myocardium) acts as a linear reflector (or backscatterer) of ultrasound energy. As such, if $P$ level of energy (MI) is directed at the myocardium, then $T$ amplitude response will be received. Furthermore, if $2P$ of energy is then directed at the myocardium, then $2T$ (double the initial response) will be returned.

However, contrast agents behave significantly differently to tissue in a low-output power ultrasound field. At low MI, contrast microbubbles demonstrate a non-linear oscillation response to exposure to an ultrasound wave. They expand more than they contract and there is a difference in the phase of the response. The higher the transmit...
power, the greater the difference in expansion and contraction of the microbubbles and hence the greater the non-linearity of the signal response (Figure 4).

Each of the ultrasound vendors has its own specific form of contrast-specific imaging, using modulation of either ultrasound amplitude or phase or both. Power modulation imaging using a Philips iE33 scanner (Philips Ultrasound Systems, Andover, Mass, USA) is one such example. It is a multipulse technique that sends two pulses down each scan line. The two transmit pulses are of different amplitude, one at full amplitude and one at half amplitude. The processor transiently stores the received signals. The returning signal from the full-strength pulse is labelled T, and the other signal (originating from the half-strength pulse) is labelled ½T. The processor generates a final signal by doubling the half-strength signal (½T) and then subtracting this from the returning signal from the full-strength pulse (T). Doubling a half-strength signal and subtracting this from a full-strength signal from a myocardial image results in cancellation of these signals, as tissue is a linear reflector. That is, the echoes received from the full- and half-amplitude pulses are just scaled copies of one another. The net result is that the myocardium is suppressed and essentially appears black in the absence of any contrast signal. However, as contrast microbubbles are non-linear reflectors, the returning signals are not scaled images of each other; they are slightly out of phase and are not scaled copies of each other. Doubling the transmit power will result in a greater than doubled received echo amplitude. Thus, when the doubled half-amplitude signal is subtracted from the full-amplitude signal, they do not cancel out. The net result is that a contrast signal is generated.

The final image generated depends on whether the signal is coming from linear, non-oscillating tissue or non-linear, oscillating contrast microbubbles. Figure 5A shows the best possible image obtained using tissue harmonic imaging in a supine, ventilated patient in the ICU. Figure 5B shows the same view in the same patient after administration of a contrast agent during contrast-specific imaging. Note the significantly improved endocardial definition and anterolateral papillary muscle.

Microbubble size is also a crucial factor in contrast imaging. For an intravenous agent to reach the coronary circulation, it has to be small enough to pass through the pulmonary circulation. That is, the microbubbles essentially have to be the same size as red blood cells. The bubble size determines their resonant frequency. The backscattering property of a bubble is proportional to the 6th power of its radius. Hence, the largest bubble that will cross the pulmonary circulation will result in a superior acoustic signal. Fortunately, contrast agents that have a size enabling them to cross the pulmonary circulation also resonate at a frequency that is used in conventional medical imaging (1.5–7 MHz).
Contrast agent preparation and administration
The Definity contrast agent is presented in a glass vial and requires storage in a refrigerator (at around 4°C). Before administration, it is activated by agitation, using the VialMix device, into a suspension of microbubbles. After preparation, the solution is withdrawn from the ampoule (using a venting needle) and diluted with normal saline to either 10 mL (for bolus dosing) or 50 mL (for an infusion).

Contrast indications and clinical applications
Limitations of TTE, particularly in the critical care setting, can result in suboptimal cardiac imaging. The use of contrast agents has proved beneficial by improving the definition of the endocardial border in suboptimal studies. This form of contrast imaging, called LV opacification (LVO), results in improved assessment of LV structure and function. It is an accurate and reproducible technique, both for resting and stress echocardiography.8-20 LVO imaging has also been assessed in the critical care setting, where it has been shown to be safe, feasible and comparable to transoesophageal echocardiographic assessment of LV regional and global function.1,2,21-25

In light of the extensive data supporting the use of contrast to improve LVO, regulatory authorities (such as the United States Food and Drug Administration [FDA], European Medicines Agency and the Australian Therapeutic Goods Administration) have approved its use in situations where conventional TTE is suboptimal or non-diagnostic. Both the American Society of Echocardiography and the European Association of Echocardiography have recently issued position papers and consensus statements regarding the clinical application of CE.6,26 The following are accepted indications for the use of contrast to improve the diagnostic yield of echocardiography:

- To improve assessment of LV structure and function when two or more continuous segments are not seen on unenhanced imaging (both for resting and stress echocardiography);

![Figure 6. Ventricular trabeculation](image)
A: Best possible image obtained using conventional tissue harmonic imaging.
B: The same view with contrast-specific imaging. Note the prominent trabeculation in the left ventricular lateral wall.

![Figure 7. Apical four-chamber images: left ventricular (LV) thrombus](image)
A: Conventional imaging.
B: The same view with contrast-specific imaging, clearly delineating the LV apical thrombus that was not detected with conventional imaging (arrow).
To improve assessment, confidence and reproducibility of LV volumes and ejection fraction (EF); and

To improve assessment of LV morphology in the following situations in which unenhanced imaging is non-diagnostic:
- LV non-compaction (non-compaction cardiomyopathy);
- Apical hypertrophic cardiomyopathy;
- LV thrombus;
- LV pseudoaneurysm formation.

Figure 6A represents the best possible image obtained with conventional, tissue harmonic imaging. Figure 6B is the same image with contrast-specific imaging. Note the prominent trabeculation in the LV lateral wall.

There are other clinical uses of CE in which contrast enhancement has been found to be beneficial but where the evidence base is weaker. These indications include:
- Assessment of cardiac masses;27-34
- Enhancement of spectral Doppler signals;20,35
- Assessment of aortic dissection; 36-38 and
- Assessment of femoral artery pseudoaneurysm.39

Figure 7A shows an unenhanced apical four-chamber view to assess for LV thrombus. Figure 7B represents the same view with contrast-specific imaging, clearly delineating the LV apical thrombus that was not detected with conventional imaging.

Figure 8A shows an unenhanced apical four-chamber TTE image. Figure 8B is a contrast-enhanced apical four-chamber TTE image demonstrating an LV pseudoaneurysm (as measured). Figure 8C shows the corresponding view with a cardiac magnetic resonance image, confirming the pseudoaneurysm.

**Application of contrast LVO in critical care**

Echocardiography is integral to the assessment and management of patients in the critical care setting. It provides a rapid, safe, non-invasive, complete and accurate assessment of cardiac structure and function. One of the other key benefits of TTE is that it is a bedside test within the critical care complex. There is no need to move or transfer a patient for this investigation. It can be performed on critically ill patients with a wide range of complex conditions. Its use in critical care is endorsed within societal guidelines on appropriateness criteria.40 Due to the complex problems of patients in critical care, they have the most to gain from accurate and reliable assessment of cardiac structure and function. However, they can also present the greatest challenge in obtaining diagnostic TTE images. If TTE does not provide satisfactory diagnostic information on cardiac structure or function, TOE or a right heart catheter may be required to obtain the necessary information.

Although accurate, these investigations are limited by being invasive, time-consuming, costly and more uncomfortable for the patient. In a non-ventilated patient, TOE will also require sedation. In critically ill patients with limited cardiopulmonary reserve, this sedation could precipitate the need for intubation and ventilation. CE has the ability to improve diagnostic accuracy of suboptimal unenhanced TTE, and hence to avoid the need for these other investigations.

However, the incremental benefit of administering a contrast agent with TTE can be dependent on the indication. Contrast enhancement is not beneficial for assessing valvular structure or function (except for spectral Doppler enhancement). For example, echocardiographic assessment for infective endocarditis is not enhanced by using contrast. For these indications, TOE is still required to obtain the necessary information.

In a prospective study of 70 unselected patients in an ICU, Reilly and colleagues assessed LV wall motion and LVEF using standard TTE (SE), harmonic TTE (HE) and CE.1
was a significantly higher mean number of uninterpretable segments using SE and HE compared with CE (5.4 v 4.4 v 1.1, respectively; \( P < 0.001 \) for HE v CE). The LVEF was uninterpretable in significantly more cases with unenhanced imaging (23% for SE, 13% for HE and 0% for CE; \( P = 0.002 \) for CE v HE; \( P < 0.001 \) for CE v SE). Scoring confidence for LV wall motion was also significantly better with CE than with unenhanced imaging (56% for SE, 62% for HE and 91% for CE; \( P = 0.47 \) for SE v HE; \( P < 0.001 \) for HE v CE). This study highlights how frequently conventional TTE is non-diagnostic in the critical care setting and shows that contrast enhancement can result in increased image quality and confidence in assessment of LVEF.

Figure 9A shows an unenhanced apical four-chamber TTE image, revealing that the apical echo density is due to extensive LV apical trabeculation (arrows), a common mimicker of apical thrombus in unenhanced imaging.

In an important study, Yong and colleagues assessed the accuracy and cost-effectiveness of CE in technically difficult studies in the ICU.\(^{21}\) Fundamental TTE (FE), HE and CE were performed in 32 patients with poor images and compared with TOE. Adequate or good endocardial definition was obtained in 13% of segments using FE, 34% with HE and 87% with CE (\( P < 0.001 \)). There was no significant difference between CE and TOE (87% v 90%; \( P = \text{ns} \)). LVEF was interpretable in 31% of cases with FE, 50% with HE and 91% with CE. LVEF calculated using CE correlated best with TOE (\( r = 0.91 \)). Additionally, the study sought to assess the cost-effectiveness of CE. Compared with TOE, CE was cost-effective in assessing regional and global LV systolic function, with cost savings of 3% and 17%, respectively. Similar results, showing a benefit of contrast-enhanced imaging in the critical care setting, have been demonstrated by Cohen et al,\(^{41}\) Makaryus et al,\(^{22}\) Kornbluth et al,\(^{2}\) Daniel et al,\(^{3}\) Nguyen et al\(^{42}\) and Costa et al.\(^{23}\)

The impact and outcome of improved image quality (a key component of assessing the benefit of a new form of imaging) was addressed in a recent study by Kurt et al.\(^{24}\) In this study, 632 patients with suboptimal TTE images were prospectively enrolled and administered a contrast agent. Image quality and the impact on clinical management were assessed before and after administration of the contrast agent. The mean numbers of LV segments seen before and after contrast imaging were 11.6 \( \pm \) 3.3 and 16.8 \( \pm \) 1.1, respectively (\( P < 0.001 \)). Additionally, the number of TTE studies that were uninterpretable was reduced from 11.7% pre-contrast to 0.3% post-contrast (\( P < 0.001 \)). Contrast was also beneficial in LV thrombus assessment. Before contrast was added, there were 35 suspected and three definite thrombi. After addition of contrast, only 1 patient remained with a suspected thrombus and another five had confirmed thrombi (\( P < 0.001 \)). The cost-effectiveness of CE was also assessed in this study. With respect to the cost of diagnostic procedures alone, CE resulted in a saving of $122 per patient (and this did not take into account other potential cost benefits of altering or correct-
the medical ICU having a potential further diagnostic procedure avoided. With respect to patient management, the results of CE altered medical treatment in 67 cases (10.6%). Again, when patients in the critical care setting were assessed, the impact on patient treatment was even greater, with 25.5% in the surgical ICU and 8.9% in the medical ICU having an alteration in medical therapy based on CE results. Together, a total of 225 patients (35.6%) had an alteration in diagnostic procedure or treatment based on CE results. The greatest impact was in the critical care setting, with changes of 62.7% and 41.9% for surgical and medical ICU patients, respectively. As expected, the likelihood of contrast imaging altering management was related to the number of segments poorly visualised on TTE. In patients with more than 12 segments poorly visualised, contrast imaging had an impact on management in 93.6%. For those with 2–6 segments poorly visualised, contrast imaging results influenced management in 14.2% (P < 0.001).

Figure 10 shows a CE image of a large LV apical thrombus in a patient with cardiogenic shock due to coronary artery disease. The patient was being supported with venoarterial extracorporeal membrane oxygenation (ECMO).

**Contrast agent safety and contraindications**

Echocardiography using contrast agents is a safe procedure. Quoted adverse reactions are headache (2%), back pain or flushing (1%) (both of which resolve as soon as administration of contrast agent is stopped), and a 1 in 10 000 risk of anaphylaxis. Contraindications to the use of Definity are known or suspected right-to-left cardiac shunts, hypersensitivity to perflutren, and direct intra-arterial injection. Extensive data indicate that Definity has an excellent safety profile and that there is no increased morbidity or mortality associated with its use. After administration, there is no change in pulmonary or systemic haemodynamics, ventricular function, gas exchange or myocardial blood flow, and no increase in major adverse cardiac events or mortality. Contrast microspheres act as biologically inert, pure blood flow tracers and are not taken up by cells or metabolised by mitochondria.

However, in October 2007, the FDA issued a “black box” warning for contrast agents, following four deaths within half an hour of patients receiving contrast agents. To put this in context, contrast agents had been in clinical use for over 10 years and had been used in over two million cases. Extensive evaluation of this decision resulted in the conclusion that these cases reflected a “pseudo-complication”, where there was a temporal but not causal association with the deaths. After further extensive work and analysis of these cases, in May 2008, the FDA significantly down-graded its concerns. This related to both contraindications to administration and requirements for monitoring after dosing. The current recommendation of the FDA is that if a patient has an unstable cardiopulmonary condition or pulmonary hypertension (severity not stated), the patient should be monitored (vital signs, electrocardiogram, oxygen saturations) for 30 minutes after administration of a contrast agent.

Although the FDA has stated that closer monitoring of patients with pulmonary hypertension is required, there are no data to guide the clinician as to what pulmonary pressure precludes administration of a contrast agent. The level has not been stipulated by the FDA. To help resolve this issue, Abdelmoneim and colleagues have recently reported on a large retrospective trial assessing the effect of contrast agent administration in patients with pulmonary hypertension. The authors assessed 26 774 patients undergoing stress echocardiography. Right ventricular systolic pressure (RVSP) was calculated in 16 434 patients, of whom 6164 received a contrast agent and 10 270 did not. RVSP cut-off points were ≥ 35 mmHg, ≥ 50 mmHg and ≥ 60 mmHg. Endpoints were short-term (≤ 72 hours and ≤ 30 days) and long-term (4.3 years) death and myocardial infarction. The patients who received contrast agents were older and more likely to have a positive stress echo result. Despite this, there was no significant difference in short- or long-term events between patients who received a contrast agent and those who did not.

In another landmark study, Exuzides and colleagues evaluated mortality among critically ill patients undergoing echocardiography with and without contrast. In this
retrospective review, 2900 patients with critical illness who received CE were compared with 11 600 patients with critical illness who did not. Propensity score matching was used to control for differences between the two groups (with each contrast patient being matched to four control patients). There were 167 deaths in the study (38/2900 in the contrast group and 129/11600 in the non-contrast group). Comparing patients who received CE with those who did not, there was no increase in mortality on the same day (odds ratio [OR], 1.18 [95% CI, 0.82–1.17]; \(P = 0.37\)) or on the next day (OR, 1.22 [95% CI, 0.91–1.64]; \(P = 0.178\)). Subgroup analysis also revealed that there was no same-day or next-day mortality difference between mechanically ventilated and non-ventilated critically ill patients.

In summary, CE is a safe and effective technique, even in critically ill patients, for whom its benefits greatly outweigh any potential risks. While it is important to understand the technique’s limitations and safety profile, harm can also be done by withholding a valid technique and thus making an incorrect diagnosis due to suboptimal imaging.

As for any clinical situation, the decision whether to use a particular investigation (in this case, CE) in critically ill patients is based on the balance of risk to benefit on a case-by-case basis. The ability to obtain an accurate cardiac assessment using a non-invasive bedside test should be sought in the critical care setting.

### Contrast artefacts and limitations

CE can salvage a non-diagnostic unenhanced transthoracic echocardiogram. However, like all forms of imaging, it has limitations and potential artefacts. As with any ultrasound investigation, obtaining a satisfactory contrast image relies on the interaction between the agent and ultrasound. If there is significant distortion of chest anatomy that prevents adequate exposure of the heart to ultrasound, the addition of contrast will not necessarily result in an improved or diagnostic image. Contrast artefacts that can limit image quality include basal attenuation, contrast swirling, low concentration and blooming. Attenuation of the far field can occur, as contrast agent in the apical region can act as a concentration and blooming. Attenuation of the far field diagnostic image. Contrast artefacts that can limit image of contrast will not necessarily result in an improved or adequate exposure of the heart to ultrasound, the addition there is significant distortion of chest anatomy that prevents mechanically ventilated and non-ventilated critically ill patients.

Contrast echocardiography in patients receiving cardiac mechanical support

Contrast microspheres are hydrodynamically labile structures and are prone to destruction from mechanical forces. Even injection into a side port is not recommended, as the shear forces and turbulent flow result in a degree of bubble destruction before any clinically useful imaging. Patients receiving cardiac mechanical support, such as those using a ventricular assist device or undergoing ECMO treatment, are usually difficult to image with conventional TTE. These patients could benefit from CE. However, there is a paucity of data on the feasibility and safety of CE in this clinical setting, and further research is required in this area.

Increased bubble destruction (due to transit through the ventricular assist device or ECMO chamber), coupled with natural attrition, would be expected to result in reduced signal persistence and hence reduced diagnostic imaging time with each bolus dose.

In a case report describing CE use in a patient supported on venoarterial ECMO, diagnostic images were obtained with contrast imaging, but with the anticipated reduction in signal persistence after each bolus dose. Figure 11A and Figure 11B show an apical four-chamber view before and after contrast enhancement, respectively.

### Future applications

Contrast echocardiography is a well accepted and approved modality for LVO. However, there are additional potential applications for CE, including the assessment of organ perfusion (eg, cardiac and renal perfusion) and the targeted delivery of gene therapy. Despite an increasing body of supportive evidence, no agent is currently approved for use in the perfusion setting. The use of contrast imaging to assess cardiac perfusion is referred to as myocardial contrast echocardiography. Contrast microbubbles have many properties that make them potentially attractive as perfusion agents: they are haemodynamically inert, uniformly distributed throughout the blood pool, do not rely on diffusion or extraction from the circulation for effect, remain entirely within the blood pool, and have the same intravascular rheology as red blood cells. Consequently, they have the potential to act as pure blood flow tracers. There are numerous clinical scenarios in which MCE may potentially be useful, including detection of acute coronary syndromes,
detection of chronic coronary artery disease and assessment of myocardial viability. By using specific perfusion modalities (such as flash destruction, replenishment and low-MI imaging), MCE could potentially be used to determine myocardial blood volume and myocardial blood flow.6,56,57

The ability to assess patients for myocardial viability would hold particular promise in the critical care setting. Myocardial viability is a crucial component in patients with coronary artery disease who are being considered for revascularisation, be it percutaneously or surgically.58,59 However, for a critically ill patient in the ICU, the options for myocardial viability assessment are essentially non-existent. Conventional viability assessment using cardiac magnetic resonance imaging, nuclear imaging techniques or dobutamine stress echocardiography are not practically feasible, particularly in the setting of mechanical support of any type. There is evidence to support the use of MCE for viability assessment,60-69 although it has not been evaluated in the critical care setting. A bedside test of myocardial viability could have significant potential in this setting.

Conclusion
Echocardiography is a fundamental investigation used to manage patients in the critical care setting. The information it provides has a significant impact on treatment strategies, but suboptimal image quality can often limit the accuracy or confidence in the data obtained. Non-diagnostic TTE images may be obtained in up to 25% of patients in the critical care setting. However, with the advent of contrast microspheres and contrast-specific imaging modalities, there is now a method available to convert these non-diagnostic images into accurate and clinically useful scans. Contrast-enhanced TTE can provide an accurate, safe and rapid assessment of LV structure, function and morphology. It can also help in cardiac mass evaluation, vascular imaging and spectral Doppler enhancement. Research is ongoing regarding its role as a myocardial perfusion agent, and potential future applications within this field include targeted delivery of gene therapy, myocardial perfusion imaging and contrast-enhanced three-dimensional echocardiography.

A recent consensus statement issued by the American Society of Echocardiography26 states that “the availability of contrast imaging in the ICU enhances overall efficiency, diagnostic accuracy and cost-effective patient management and has no incremental risk for death compared with non contrast echocardiography”. For patients in the critical care setting with non-diagnostic TTE results, CE should now be at the forefront of a diagnostic algorithm.

Author details
David G Platts, Senior Staff Specialist1,3
John F Fraser, Eminent Staff Specialist2,3
1 Department of Echocardiography, Prince Charles Hospital, Brisbane, QLD, Australia.
2 Department of Critical Care Medicine, Prince Charles Hospital, Brisbane, QLD, Australia.
3 Critical Care Research Group, Prince Charles Hospital, Brisbane, QLD, Australia.
Correspondence: david_platts@health.qld.gov.au

References
2 Kornbluth M, Liang DH, Brown P, et al. Contrast echocardiography is superior to tissue harmonics for assessment of left ventricular
25 Platt D, Fraser JF, Mullany D, Burstow D. Left ventricular endocardial definition enhancement using perfluor microsphere contrast echocardiography during peripheral venoarterial extracorporeal membranous oxygenation. Echocardiography 2010; 27: E112-4.
28 Foster E, Gerber IL. Masses of the heart; perfusing the “good” from the bad. J Am Coll Cardiol 2004; 43: 1420-2.


49 Grayburn PA. Product safety compromises patient safety (an unjustified black box warning on ultrasound contrast agents by the Food and Drug Administration). Am J Cardiol 2008; 101: 892-3.


