Contrast echocardiography in Canada: Canadian Cardiovascular Society/ Canadian Society of Echocardiography position paper

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As an adjunct to transthoracic, transesophageal and stress echocardiography, contrast echocardiography (CE) improves the diagnostic accuracy of technically suboptimal studies when used in conjunction with harmonic imaging.

Intravenous ultrasound contrast agents are indicated for left ventricular (LV) opacification and improvement of LV endocardial border delineation in patients with suboptimal acoustic windows. Demonstrated benefits of CE include improvement in the accuracy of LV measurements, regional wall motion assessment, evaluation of noncompaction cardiomyopathy, thrombus detection, Doppler signal enhancement and conjunctive use with stress echocardiography. Studies have shown the value of CE in the assessment and quantification of myocardial perfusion, and recent clinical trials have suggested a role for contrast perfusion imaging in the stratification of patients with suspected coronary artery disease.

While it adds some time and cost to the echocardiographic study, CE frequently obviates the need for additional specialized, expensive and less accessible cardiac investigations, and allows for prompt and optimal subsequent patient management. Despite its proven advantages, CE is presently underused in Canada, and this situation will, unfortunately, not improve until several barriers to its use are overcome. Resolving these important hurdles is vital to the future of CE and to its eventual implementation into clinical practice of promising contrast-based diagnostic and therapeutic applications, including the assessment of perfusion by myocardial CE.

Key Words: *Contrast; Echocardiography; Imaging; Perfusion*

Échocardiographie de contraste au Canada : Énoncé de position de la Société canadienne de cardiologie / Société canadienne d'échocardiographie

À titre de mesure d'appoint aux échocardiographies transthoraciques, trans-œsophagiennes et de stress, l'échocardiographie de contraste (ÉC) améliore la précision diagnostique des examens suboptimaux sur le plan technique lorsqu'elle est utilisée en conjonction avec une imagerie harmonique.

Les agents de contraste intraveineux sont indiqués avec l'ÉC pour opacifier le ventricule gauche et améliorer la visibilité du rebord endocardique VG chez les patients qui présentent des fenêtres acoustiques suboptimales. Les avantages avérés de l'ÉC sont notamment qu'elle améliore la précision des mesures VG, l'évaluation du mouvement pariétal régional, l'évaluation de la cardiomyopathie sans compaction, le dépistage des thrombi, l'amplification du signal Doppler et l'utilisation concomitante de l'échocardiographie de stress. Les études ont montré l'utilité de l'ÉC dans l'évaluation et la quantification de la perfusion myocardique et selon de récents essais cliniques, l'imagerie de perfusion avec agent de contraste pourrait faciliter la stratification des patients chez qui on soupçonne une coronaropathie.

Si elle prend plus de temps et coûte plus cher, l'échocardiographie de contraste permet par contre souvent d'éviter le recours à d'autres épreuves cardiaques spécialisées qui se révèlent coûteuses et moins accessibles, d'où un traitement plus rapide et optimum des patients. Malgré ses avantages éprouvés, l'ÉC est actuellement sous-utilisée au Canada et cette situation risque fort malheureusement de ne pas s'améliorer tant que certains obstacles à son utilisation ne seront pas surmontés. Et il faudra aplanir ces importantes difficultés si l'on veut assurer l'avenir de l'ÉC comme outil d'évaluation de la perfusion myocardique et assister éventuellement à son utilisation à grande échelle dans la pratique clinique, comme n'importe quelle autre technique diagnostique et thérapeutique prometteuse à base d'agents de contraste.

Intravenous ultrasound contrast agents are indicated for left ventricular opacification (LVO) and improvement of LV endocardial border delineation in patients with suboptimal acoustic windows. Benefits of contrast echocardiography (CE) have been demonstrated for accuracy of LV measurements (1), regional wall motion assessment (2), evaluation of noncompaction cardiomyopathy (3), thrombus detection (4), Doppler signal enhancement (5) and conjunctive use with stress echocardiography (6). Studies have shown the value of CE in the assessment and quantification of myocardial perfusion (7,8), and recent clinical trials have suggested a role for contrast perfusion imaging in the stratification of patients with suspected coronary artery disease (CAD) (9,10).

While the injection of a contrast agent often improves study diagnostic quality, the use of CE in Canada is still quite limited. Time constraints, financial concerns, and a lack of equipment and expertise are some of the many challenges that have prevented more widespread use of CE in the past, underscoring the importance of developing criteria for the appropriate use of this simple and useful technique. The present document reviews the basic principles and clinical applications of CE and provides the Canadian cardiology community

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TABLE 1
Echocardiographic contrast agents

Name	Shell composition	Gas	Manufacturer
Albunex/Infoson	Albumin	Air	Mallinckrodt, USA
Optison	Albumin	Air/PFC	Mallinckrodt, USA
Levovist	Galactose/palmitate	Air	Schering/Berlex, USA
BY 963	Lipid	Air	Byk-Gulden Konstanz, Germany
PESDA	Albumin	Air/PFC	Dr Tom Porter, USA
Sonazoid	Lipid	Air/PFC	Nycomed, Norway
Definity*	Lipid	Air/PFC	Bristol-Myers Squibb, USA
Imagent	Surfactant/powder	Air/PFC	Alliance/Schering, USA
SonoVue	Surfactant/powder	Air/SF6	Bracco†, Italy
EchoGen	Surfactant	PFC	Sonus, USA
CARDIOsphere‡	Bilayer	Nitrogen	POINT Biomedical, USA
AI-700§	Polymer	Air/PFC	Acusphere, USA

**In clinical use in Canada; †Formerly known as Bracco Diagnostics Inc; ‡Undergoing phase III testing; §Undergoing phase II testing. PESDA Perfluorocarbon (PFC)-exposed sonicated dextrose albumin; SF6 Sulphur hexafluoride*

with some guidance for the implementation of CE in local echocardiography laboratories based on the best available scientific evidence.

BASIC PRINCIPLES

Enhancement of the acoustic signal of blood during echocardiography was first described in 1968 (11), when it was noted that saline injected into the aortic root produced strong echoes within the aortic lumen. This contrast effect was attributed to the accidental introduction of small air bubbles into the bloodstream with fluid injections. These air bubbles strikingly increase the backscatter because of their high impedance to ultrasound propagation compared with blood. However, air bubbles present in agitated saline administered intravenously do not cross the pulmonary circulation because the larger bubbles are trapped by the microcirculation, while microbubbles small enough to pass through the pulmonary capillary bed (smaller than 8 μm) collapse within a few seconds before reaching the left heart cavities due to surface tension, surrounding pressure and gas diffusion from bubbles into the blood (12,13). Early applications of CE were therefore limited to using agitated saline to detect intracardiac and intrapulmonary shunts, confirm needle placement during pericardiocentesis, and enhance right-sided Doppler signals and two-dimensional images. Agitated saline CE is still widely used in these clinical settings in the modern-day echocardiography laboratory.

To overcome the instability of air-filled microbubbles, and to allow them to cross the pulmonary capillary bed and reach the left heart, two main strategies were initially adopted. Substances with surfactant-like properties to reduce surface tension (14), as well as a protein shell to encapsulate the bubbles and limit outward gas diffusion, were included in some formulations (15). More recently, high-molecular-weight gases (mainly fluorocarbons) with low solubility in blood have been used to yield microbubbles with greater stability than the first generation, air-filled agents (16). These newer agents also encapsulate the gas within lipid shells to further enhance microbubble stability in the circulation (Table 1).

Harmonic imaging

Harmonic imaging, which is available on most ultrasound systems currently in clinical use, was first developed specifically for CE (17). The intent of harmonic imaging was to take advantage of the unique physical properties of contrast microbubbles exposed to an ultrasound field. When bubbles are insonated, they oscillate within the acoustic field, going through rapid successions of compression and expansion. The amplitude of the bubble volume change is maximal at a specific frequency, termed resonant frequency. The resulting backscattered signal therefore includes frequencies that are multiples (harmonics) of the incident (fundamental) frequency. In standard harmonic imaging, only the second harmonic echoes are displayed and the remaining frequencies are filtered out (18). It was then observed that cardiac tissues, such as the endocardium-blood pool boundary, also generate harmonic signals, while many artifacts do not. The use of second harmonic imaging, therefore, results in substantial improvement in two-dimensional image quality, even in the absence of any contrast injection.

Mechanical index

The mechanical index (MI) is an estimate of the ultrasound output power and is defined as the peak negative acoustic pressure at the focus of the ultrasound beam, divided by the square root of the incident frequency (19). MI is user-adjustable and its value appears onscreen on most commercially available ultrasound systems. Many echocardiographic platforms offer different contrast presets with an MI optimized for LVO and perfusion imaging.

At a high MI, microbubbles are susceptible to destruction by insonation. Therefore, a lower MI is desired during contrast imaging to prolong the effect of the agent and optimize the enhancement of the blood-myocardium interface. However, the ability to generate strong acoustic signals by microbubble destruction has implications for myocardial CE (MCE). Early attempts to assess perfusion using high MI harmonic imaging failed because microbubbles were continually destroyed while entering the myocardial microvasculature on insonation at the high frame rates used in continuous imaging. Intermittent imaging was introduced to overcome this problem. Imaging with this modality is performed at very low frame rates, triggered according to the electrocardiogram. This allows the replenishment of microbubble contrast agent into the myocardium in between destructive imaging frames, and enables the qualitative and quantitative (investigational) assessment of myocardial perfusion. With intermittent imaging, delayed and incomplete replenishment implies reduced myocardial perfusion.

Newer imaging techniques

Other than harmonic imaging, specific modalities have been developed to selectively enhance the microbubble signal, and abolish background noise and tissue signal. These techniques use low acoustic power to minimize microbubble destruction and prolong the contrast effect, and also maximize the microbubble signal intensity to noise ratio. Such ultralow MI (0.1 to 0.2) technologies are referred to as real-time perfusion imaging because they allow assessment of tissue perfusion

during real-time continuous imaging. These newer contrast imaging techniques specifically take advantage of the nonlinear response of microbubbles to an ultrasound field. A unique ultrasound signature from the contrast backscattered signal is generated by the asymmetrical oscillations of microbubbles, which can expand more than they can be compressed. By sending sequences of ultrasound pulses of alternating phase and/or intensity, the system suppresses the linear backscattered echoes from tissue. On the contrary, the successive nonlinear signals received from microbubbles do not cancel out when added, and are selectively amplified and displayed. These modalities are very sensitive for detecting contrast signal while virtually eliminating the surrounding tissue echoes. Real-time perfusion imaging limits microbubble disruption by the use of a low MI and avoids the need for intermittent triggered imaging. Therefore, wall motion can be assessed in real time without interruption of image acquisition (16). The great potential of these approaches is their ability to acquire cardiac systolic function and myocardial perfusion information simultaneously.

LV FUNCTION ASSESSMENT

Accurate determination of LV ejection fraction (LVEF) is important in the clinical management of patients with cardiovascular disease. For example, LVEF predicts the risk of adverse outcomes in patients with congestive heart failure, as well as those postmyocardial infarction and following revascularization (20-24). Several techniques have been used for the determination of LV volumes and LVEF, among them, echocardiography, cineventriculography, radionuclide-ventriculography and magnetic resonance imaging (MRI). Although echocardiography is the most frequently used modality in clinical practice, it has gained little acceptance in clinical trials, because prior studies have indicated that conventional noncontrast echocardiography may have significant variability compared with accepted gold standards, with resultant low interobserver agreement, and moderate reproducibility and accuracy to define LVEF. The main reasons for the compromise in reproducibility and accuracy, aside from geometric assumptions, lie with the inadequate discrimination of the endocardial border. CE provides better endocardial border delineation than nonenhanced echocardiography (2,15,25,26).

CE has been demonstrated to significantly improve agreement in the measurements of LV volumes and LVEF using current reference standards, including cineventriculography, radionuclide ventriculography, electron beam computed tomography and MRI (1,27-30). The enhanced accuracy of CE has been demonstrated in several single-centre and multicentre studies, with significant reductions in intra- and interobserver variability when contrast is used in the assessment of ventricular function, volumes and EF (1,27,28-30). The interobserver variability for CE has been demonstrated to reach the same level as that for MRI (1). Ultrasound technologies, including the automatic quantification of LV structure and function using a variety of edge detection and blood pool algorithms, have been greatly facilitated and improved with echocardiographic contrast agents, and have been shown to correlate well with current reference standards (31,32).

LVO and stress echocardiography

The diagnosis and stratification of significant CAD by stress echocardiography depends on the identification of regional wall motion deterioration with exercise or pharmacological stimulation. This qualitative analysis of segmental contractility is limited by inadequate image quality. Therefore, optimal endocardial delineation of all LV segments at rest and during stress is of utmost importance to maximize diagnostic accuracy and improve interobserver agreement (33). Image acquisition at peak stress inherently carries additional challenges over baseline recording. Image degradation commonly takes place from rest to maximal stress because of the limited time to scan in different incidences in the contexts of patient discomfort, tachycardia, hyperventilation, increased cardiac translation, and sometimes significant ischemia, which have to be addressed simultaneously.

Stress echocardiography in conjunction with LVO has been studied mostly with dobutamine testing (6,26,34-37). In several trials, contrast use consistently improved endocardial depiction and confidence of interpretation during stress echocardiography. However, the diagnostic accuracy of stress echocardiography with LVO compared with noncontrast harmonic imaging stress echocardiography has not been well studied. Some investigators have provided indirect evidence suggesting superior stress echocardiography performance in the detection of CAD with contrast. For example, LVO, during dobutamine stress echocardiography in patients with suboptimal acoustic windows, has shown sensitivity and specificity similar to noncontrast examinations in subjects with adequate images (34). In the largest trial of stress echocardiography with contrast (6), 300 consecutive outpatients underwent dobutamine testing using both noncontrast harmonic imaging and LVO. Although the subjects were not selected on the basis of having a poor acoustic window, contrast use improved image quality and confidence of interpretation both at rest and at peak stress. Moreover, LVO prevented the deterioration in image quality and confidence of interpretation from baseline to maximal stress that was observed with noncontrast images. Nevertheless, the most important benefits were observed in the subset of patients with suboptimal images, and the general consensus supports the use of LVO during stress echocardiography in selected patients.

MYOCARDIAL PERFUSION

The advent of newer myocardial contrast agents that safely traverse the pulmonary circulation has permitted the intravenous administration of contrast to assess not only LV wall motion, but also the myocardial microcirculation. These agents remain entirely within the vascular space, have similar rheology to red blood cells and are hemodynamically inert. During a constant intravenous infusion of microbubbles, a steady state is achieved within the capillary bed. The ultrasound signal returned from the bubbles within the myocardium at a steady state can be detected using modern ultrasound imaging modalities and is proportional to the number of intact capillaries or myocardial blood volume. Destruction of microbubbles using a high-energy pulse of ultrasound and observation of the subsequent replenishment of microbubbles into the microcirculation permits evaluation of myocardial tissue perfusion (38). Using these principles, techniques have been developed to quantify myocardial perfusion and have been validated experimentally by radiolabelled microspheres, and clinically against coronary Doppler flow wires and positron emission tomography imaging.

The excellent spatial resolution and the temporal ability of MCE to assess the rate of myocardial blood flow make it an ideal tool to evaluate the adequacy of myocardial perfusion.

MCE has been clinically shown to reliably identify the presence or absence of myocardial reperfusion following primary percutaneous coronary intervention (the 'no-reflow' phenomenon) (39), predict subsequent LV function post-MI (40), determine myocardial viability after ischemic injury (41), and assess infarct-related artery patency and the degree of collateral support to the infarcted territory (42). Multiple studies have also used MCE in conjunction with dobutamine or vasodilator (adenosine or dipyridamole) stress to detect CAD with a sensitivity and specificity comparable with that of nuclear techniques (43-45). Two studies have demonstrated the incremental prognostic value of MCE over routine clinical assessment in risk-stratifying patients who present to the emergency room with chest pain syndromes (46,47). Finally, Basic et al (48) recently demonstrated that MCE was able to accurately classify patients at risk for cardiac disease, and provided prognostic information comparable with validated nuclear imaging techniques.

Despite the safety (49) and potential utility of MCE, the initial enthusiasm over the use of MCE for perfusion imaging has not translated into routine clinical use, because several outstanding issues remain. It is important to note that MCE is a technically challenging modality, and requires an experienced operator and optimal acoustic windows to obtain accurate results. Interpretation of images to reliably differentiate perfusion defects from imaging artifacts is very user-dependent. An early multicentre study (50) of the use of MCE in routine practice by novice users demonstrated poor sensitivity compared with nuclear techniques for the detection of CAD. While phase III trials of a contrast agent proving the accuracy of MCE for the detection of CAD have been performed, most results are still unpublished, and currently, no contrast agent has been approved for use in perfusion imaging. Other unresolved issues include the optimal method of analysis – online qualitative versus offline quantitative analysis of perfusion studies, optimal imaging techniques for perfusion assessment, real-time versus intermittent imaging modalities and the optimal mode of contrast administration (constant infusion versus bolus). These shortcomings have limited the adoption of this technique for the assessment of myocardial perfusion. Currently, MCE should be considered an experimental technique, with clinical use limited to experienced centres alone. However, the development of newer contrast agents, continued refinements in ultrasound imaging modalities, optimization of online analysis, and successful completion of large, multicentre studies of MCE perfusion imaging demonstrating its diagnostic and prognostic use will be important steps in overcoming these issues.

PRESENT AND FUTURE CLINICAL APPLICATIONS

Currently, ultrasound contrast agents are approved for use in Canada to improve image quality in suboptimal echocardiograms by opacifying the LV cavity and improving endocardial border delineation. These ultrasound contrast agents have been proven to be safe and effective in numerous clinical studies (1-10), they are easy to use and they can be used with virtually all currently available echocardiographic systems. During transthoracic echocardiography, these agents have been shown in clinical trials to improve the qualitative assessment of global LV systolic function, to improve the accuracy LV volumes and LVEF quantification, to improve the accuracy and interobserver agreement for the assessment of resting regional wall motion, to reduce interobserver variability and enhance the reproducibility of stress echocardiography studies, to help define altered cardiac anatomy by improving the echocardiographic detection rates of myocardial rupture, pseudoaneurysms, intracardiac thrombi, aortic dissection, LV noncompaction and apical hypertrophic cardiomyopathy, and to enhance left-sided Doppler velocity signals in the assessment of intracardiac pressures and transvalvular gradients. Ultrasound contrast agents have also been used during transesophageal echocardiography in aortic dissection assessment and left atrial appendage thrombus detection.

Despite improvements in ultrasound imaging techniques, including the widespread availability of harmonic imaging, an estimated 10% of resting echocardiograms and 30% of stress echocardiograms remain diagnostically suboptimal. In these circumstances, the use of CE improves diagnostic accuracy and may contribute to a cost-effective pattern of care. This is achieved through the impact of the reduced downstream repetitive testing in patients with an initially nondiagnostic echocardiogram, a reduced rate of false-positive and false-negative echocardiograms as a result of improved image quality and increased laboratory efficiency in evaluation of labour-intensive, difficult-to-image patients. In a study involving multiple Canadian centres, Tardif et al (51) studied the impact of contrast stress echocardiography on resource use in the management of patients with suspected CAD, comparing it with standard stress nuclear perfusion imaging. The authors found that contrast stress echocardiography had a similar success rate to nuclear perfusion imaging in diagnosing CAD, but had a 28% lower cost, along with the potential for additional cost savings through the elimination of additional tests due to false-positive nuclear perfusion scans. Castello et al (52) showed that a 'sonographer-driven' CE protocol for LV assessment was feasible, decreased the decision time for contrast injection, and significantly improved LV global and regional wall motion visualization in technically difficult patients. Despite the overwhelming evidence of its benefit, CE remains highly underused in Canada. Barriers to the greater use of CE include the requirement of insertion of an intravenous access for contrast injection, lack of budget for the cost of the contrast agent, the need for additional scanning time, lack of physician experience with CE and the absence of physician reimbursement in most regions of the country.

The most promising future clinical application of CE is the noninvasive assessment of myocardial perfusion. Potential advantages of MCE over other available methods for assessment of perfusion, such as nuclear single-photon emission computed tomography and positron emission tomography techniques include the simultaneous assessment of perfusion and regional wall motion in real-time, with good spatial and temporal resolution; the ability to quantify myocardial blood flow and flow reserve; portability, allowing the performance of studies at the bedside, in the emergency room, coronary or intensive care unit and the operating room; and the use of a non-nephrotoxic, nonradioactive and safe contrast agent.

Finally, research continues into future novel and exciting diagnostic and therapeutic applications for CE. These include molecular imaging of pathophysiological molecular and cellular processes, such as thrombosis, endothelial dysfunction, inflammation (53) and angiogenesis (54), using contrast ultrasound and 'site-targeted' microbubbles, as well as the use

of ultrasound-mediated destruction of designer 'carrier' microbubble agents for the site-specific delivery of drugs, ligands and genes for therapeutic applications (55).

CONCLUSION

As an adjunct to transthoracic echocardiography, transesophageal echocardiography and stress echocardiography, CE, when used in conjunction with harmonic imaging, improves the diagnostic accuracy of technically suboptimal studies due to poor acoustic windows. While adding some time and cost to the echocardiographic study, CE frequently obviates the need for additional specialized, expensive and less accessible cardiac investigations, and allows for prompt and optimal subsequent patient management. Despite its proven advantages, CE is presently underused in Canada, and this situation will, unfortunately, not improve until several barriers to its use have been overcome. Resolving these important hurdles is vital to the future of CE and its eventual implementation into clinical practice of promising contrast-based diagnostic and therapeutic applications, including MCE.

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