Clinical Update

Clinical Use of Contrast Echocardiography with Microbubble-Based

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Contrast echocardiography is a technique that uses a peripheral intravenous injection of microbubble contrast agents to improve the echocardiographic signal. It is indicated for left ventricular opacification and to enhance the endocardial border delineation in patients with suboptimal echocardiographic images at rest and during stress. Technological advances and the use of commercially available contrast agents that provide more stability in the circulatory system have established the contrast echocardiography as a safe and efficient technique to assess myocardial perfusion. Clinical applications of myocardial contrast echocardiography include: evaluation of patients with suspected or known coronary artery disease; determination of area at risk and efficacy of reperfusion therapies in patients with acute myocardial infarction; assessment of post-infarction viability (identification of the no-reflow phenomenon); and viability in the setting of chronic coronary artery disease (identification of hibernating myocardium). Recent studies have demonstrated that myocardial perfusion analysis using real-time myocardial contrast echocardiography presents higher sensitivity and accuracy for the detection of coronary artery disease than the analysis of wall motion during stress echocardiography. As an additional benefit, quantification of regional myocardial flow and myocardial flow reserve using contrast echocardiography may also be able to estimate the severity of the coronary disease.

Introduction

Contrast echocardiography is a technique that uses peripheral intravenous injection of microbubble contrast agents to improve the echocardiographic signal. The primary mechanism by whichmicrobubbles injection can enhance cardiac structures is based on the introduction of multiple liquid-gas interfaces into the circulation which increases the ultrasound reflection and improves echocardiographic image quality[1,2]. The microbubbles currently used consist of a protein or lipid shell containing high molecular weight gases, the perfluorocarbons, that have sufficient stability to traverse the pulmonary barrier contrasting the left cardiac cavities and coronary circulation[3,4].

Current contrast echocardiography indications include left ventricular opacification and endocardial border delineation in patients with suboptimal echocardiography windows[2]. The recent development of microbubbles with greater persistence in the blood circulation as well as improved ultrasound techniques have made the analysis of myocardial perfusion possible, expanding the role of contrast echocardiography for the noninvasive assessment of coronary artery disease (CAD). Consequently, potential applications of contrast echocardiography include: assessment of myocardial ischemia in patients with chronic CAD through the detection of perfusion and coronary flow reserve abnormalities and the evaluation of patients with acute coronary syndromes by defining the acute myocardial infarction (AMI) risk area, the no-flow phenomenon after myocardial reperfusion and determining myocardial viability (Table 1).

Key words

Echocardiography; coronary arteriosclerosis; microbubbles.

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Table 1 - Potential diagnostic applications of myocardial contrast echocardiography

Known or suspected coronary artery disease
– Detection of coronary lesions
– Evaluation of collateral flow
Acute myocardial infarction
– Determination of the risk area during coronary occlusion
– Evaluation of the efficacy of reperfusion therapy
Evaluation of myocardial viability
– Detection of post myocardial infarction no-reflow areas
– Identification of hibernated myocardium in patients with chronic coronary disease

Even though the microbubbles improve endocardial border delineation, their major contribution to stress echocardiography is the ability to detect myocardial perfusion alterations. The development of contrast agents with smaller, more stable microbubbles and the technological advances such as transient response harmonic imaging and low mechanical index imaging have made it possible to evaluate myocardial perfusion[5-7]. Nevertheless, further multicenter studies are required to better standardize myocardial perfusion evaluation techniques and define the diagnostic accuracy for the detection of CAD detection.

Contrast echocardiography for left ventricular opacification

Echocardiographic contrast agents improve endocardial border delineation enabling a better assessment of global and segmental left ventricular contractile function, as well as more accurate measurements of ventricular volume and ejection fraction. Costa et al used contrast echocardiography on mechanically ventilated patients in intensive care units and reported that the use of these agents made it possible to correctly assess global left ventricular function in 77% of the nondiagnostic tests[8]. This technique has also been used successfully to define cardiovascular anatomical alterations[9] and can be useful for the identification of intracardiac masses such as tumors and/or thrombi (Figure 1) as well as the definition of right and left ventricular morphology in cases of hypertrophic cardiomyopathies and right ventricular dysplasia. Additionally, the detection of AMI complications by two-dimensional echocardiography, such as myocardial rupture and the formation of pseudoaneurysms, has been facilitated with the use of contrast agents as shown in Figure 2[10].

Contrast agents have also been demonstrated to improve endocardial delineation during pharmacologic stress echocardiography, particularly for wall motion evaluation at peak stress[11-13]. Contrast agents are indicated when at least two myocardial segments are not adequately visualized in any of the apical echocardiographic views at rest[2]. Mathias et al[13] studied 68 patients who underwent dobutamine stress echocardiography using second harmonic imaging and PESDA (Perfluorocarbon-Exposed Sonicated Dextrose and Albumin). In this study, 23 patients (34%) that had inadequate acoustic windows without the use of contrast agents, had their images salvaged using contrast agents. From the 2176 myocardial segments analyzed (1088 at rest and 1088 at the peak dobutamine infusion) adequate endocardial border

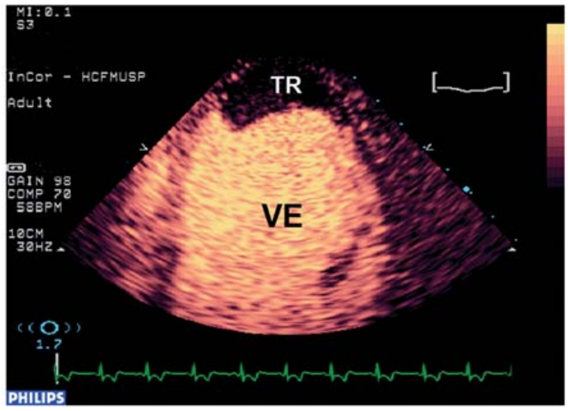

Fig. 1 - Contrast echocardiography in apical four chamber view demonstrating left ventricular apical thrombus. TR - thrombus, VE - left ventricle.

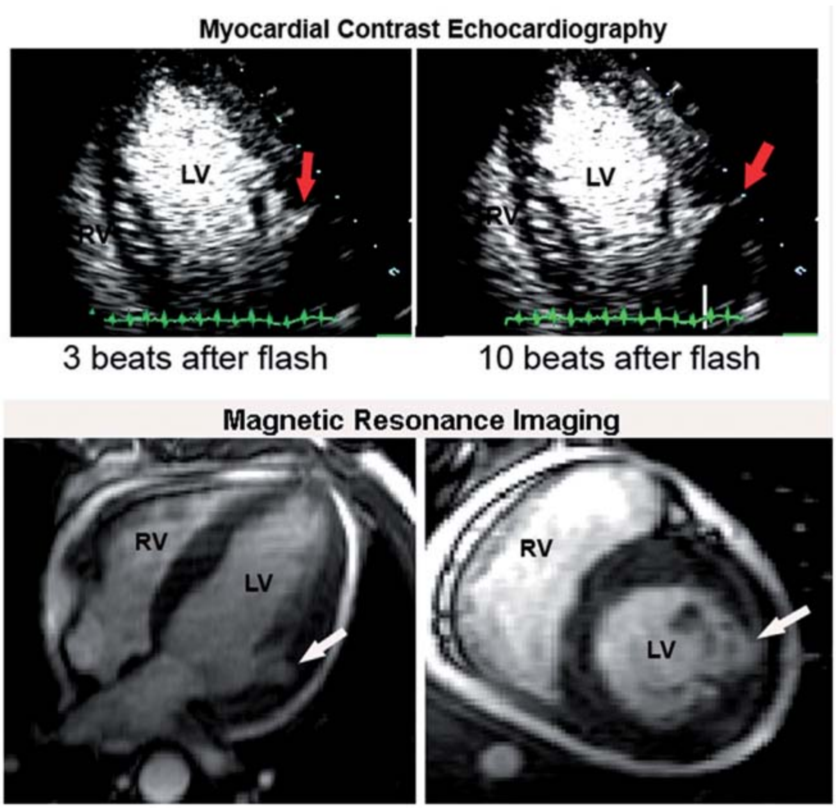

Fig. 2 - Contrast Echocardiography (upper panel) showing left ventricular opacification with contrast extrusion from the left ventricular cavity into the myocardium in the lateral wall, before reaching the pericardial space, suggesting an impending rupture (arrows). Magnetic resonance (lower panel) confirmed the echocardiogram findings of impending rupture of the left ventricular free wall. RV - right ventricle, LV - left ventricle. (Reproduced with permission. Trindade ML, et al. Left ventricular free wall impeding rupture in post-myocardial infarction period diagnosed by myocardial contrast echocardiography: case report. Cardiovasc Ultrasound 2006;Jan;4:7).

delineation increased from 81% of the segments analyzed without contrast to 95% using contrast agents. Therefore, it was demonstrated that the use of contrast agents during dobutamine stress echocardiography in association with second harmonic imaging increased the number of diagnostic tests and significantly improved endocardial border definition.

Contrast echocardiography to assess microvascular perfusion

Although coronary self-regulation mechanisms can maintain normal wall motion and myocardial perfusion at rest, a reduced coronary flow reserve can be identified by inducing abnormalities during physical or pharmacological stress in regions supplied by arteries with obstructive lesions.

Microbubbles concentration in the coronary microcirculation corresponds to the blood volume in the different myocardium regions and is the basis for perfusion assessment using the myocardial contrast echocardiography (MCE). Therefore, the relative perfusion differences between regions supplied by arteries without obstructions and those supplied by stenotic arteries can be detected by the MCE using different types of stressinducing agents such as positive inotropic agents and vasodilators (Figure 3) or exercise. Various clinical studies have demonstrated a positive correlation between regional myocardial perfusion defects detected by MCE using harmonic transient response imaging and those induced by different types of pharmacologic stress using myocardial scintigraphy and coronary angiography[7,14]. The recently developed MCE with real-time perfusion imaging is another echocardiography technique that uses a low mechanical index and is able to simultaneously assess wall motion and myocardial perfusion in real-time. Using this technique, mocardial perfusion defects may be detected before wall motion alterations during dobutamine stress test [15,16] in accordance with the pathophysiological sequence of events known as ischemic cascade[17].

In a study involving a large number of patients (n = 1,486), we evaluated the feasibility, safety and diagnostic accuracy of the dobutamine-atropine stress MCE in comparison to the conventional dobutamine stress echocardiography without contrast. (18) We demonstrated that adequate myocardial perfusion assessment can be obtained with contrast echocardiography without changing the incidence of adverse effects or cardiac arrhythmias when compared to the conventional protocol. The myocardial perfusion assessment increased the accuracy for detecting angiographically significant CAD in comparison to wall motion analysis (Table 2). The feasibility of myocardial perfusion analysis was 94% at rest and 95% at peak stress. The value of this technique was also demonstrated in the diabetic patients[6]. Elhendy et all studied 128 patients with diabetes mellitus who underwent MCE with real-time perfusion imaging and quantitative coronary angiography during a maximum interval of 30 days. The authors demonstrated that the detection of perfusion abnormalities had sensitivity of 89%, specificity of 52%, and accuracy of 81% to detect CAD.

Because of the good spatial resolution quality of echocardiographic images, it is possible to detect subendocardial perfusion defects (Figure 4). Reversible perfusion alterations were detected in two or more vascular regions in 44 of the 56 patients with multivessel CAD and in 8 of the 63 patients without multivessel CAD (sensitivity 68%, specificity 87%, and accuracy 79%). The authors concluded that the extent of perfusion alterations identified by MCE can identify multivessel CAD patients with moderate sensitivity and high specificity.

In another study, it was demonstrated that dobutamine-atropine stress echocardiography and MCE can be used to

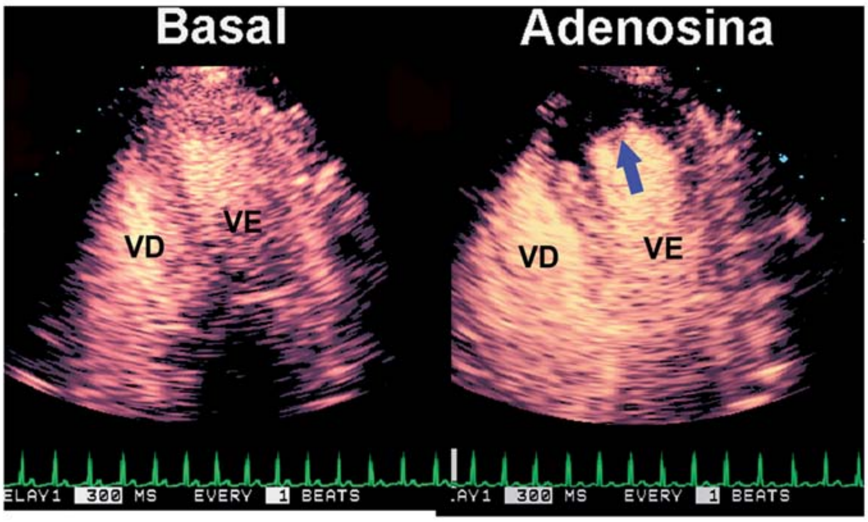

Fig. 3 - Myocardial contrast echocardiography showing homogenous myocardial perfusion at baseline (left) and a clear perfusion defect in the apical segment of the left ventricle during adenosine stress test (arrow on right) in a patient with a 90% lesion on the left anterior descending coronary artery. VD - right ventricle, VE - left ventricle.

assess patients that arrive at the emergency room with chest pain and suspected acute coronary syndrome[5]. Myocardial perfusion analysis is an accurate method to detect CAD and is an independent predictor of cardiac events.

The reperfusion dynamic of real-time myocardial contrast enables quantification of myocardial flow when the contrast agent is infused continuously. The myocardial flow can be quantified using mathematical models by estimating the plateau intensity and mean velocity of microcirculation refilling by the microbubbles[19]. The refilling time of the microbubbles in the myocardium can be measured by the increased acoustic intensity of each frame in the image sequence after the microbubbles destruction in the myocardium by a high energy ultra sonic pulse (flash). The use of specific computer programs to quantify myocardial contrast enables us to analyze the image sequences and quantify the regional myocardial flow, both at rest and after inducing cardiovascular stress resulting in determination of myocardial flow reserve. Recently, our group (20) studied the value of quantitative analysis of the myocardial perfusion to detect CAD during dobutamine-atropine and adenosine induced stress.

The authors demonstrated that the accuracy of myocardial flow velocity reserve obtained by the dobutamine-atropine stress real-time myocardial perfusion imaging was similar to that of adenosine stress test to detect CAD (accuracy of 80% for both drugs). Interestingly, the quantitative myocardial perfusion analysis during dobutamine-atropine stress test was significantly higher for CAD diagnosis in comparison to the 12 lead electrocardiogram, wall motion analysis and qualitative myocardial perfusion analysis.

Table 2 - Diagnostic parameters of myocardial perfusion (MP) and wall motion (WM) assessment using real-time myocardial contrast echocardiography to detect coronary artery disease.

	WM	MP
Sensitivity	115/180; 64% (57-71%)	173/180; 96% (93-99%)
Specificity	50/69; 72% (62-83%)	35/69; 51% (39-63%)
Positive predictive value	115/134; 86% (80-92%)	173/207; 84% (79-89%)
Negative predictive value	50/115; 43% (60-72%)	35/42; 83% (78-88%)
Accuracy	165/249; 66% (60-72%)	208/249; 84% (79-88%)

Results expressed as the number and % of patients with the respective 95% confidence intervals (Reproduced with permission. Tsutsui JM et al. Safety of dobutamine stress real-time myocardial contrast echocardiography. J Am Coll Cardiol 2005; 45:1235-42).

MCE in AMI patients

Echocardiography has various potential applications for AMI patients. During acute coronary occlusion, MCE permits the stratification of these patients by determining the extent of the area at risk for myocardial necrosis. The ultimate AMI size is determined by the duration of the coronary occlusion, the total area supplied by the infarct-related artery and the presence of collateral circulation[21]. MCE can determine the actual area at risk since the areas supplied by the collateral circulation can exhibit some degree of flow that maintains myocardial viability[22]. Therefore, MCE has been demonstrated useful to differentiate low risk patients (restricted area at risk or high degree of collateral flow) from those with a higher risk to present an extensive infarcted area if reperfusion is not established. MCE has also been demonstrated useful to evaluate the efficacy of reperfusion therapy and myocardial viability. It is known that the angiographic patency of the infracted-related artery does not necessarily reestablish adequate myocardial tissue perfusion. The absence of microvascular perfusion even though the patency of the epicardical coronary artery has been reestablished is called the no-reflow phenomenon[23]. This seems to be a marker of myocardical necrosis and has been consistently associated with a lower probability of functional recovery and worse prognosis[24-27].

Various studies have demonstrated the value of MCE to assess myocardial viability after AMI. Generally, MCE holds high sensitivity (62% to 90%) but low specificity (18% to 67%) to predict post AMI functional recovery,

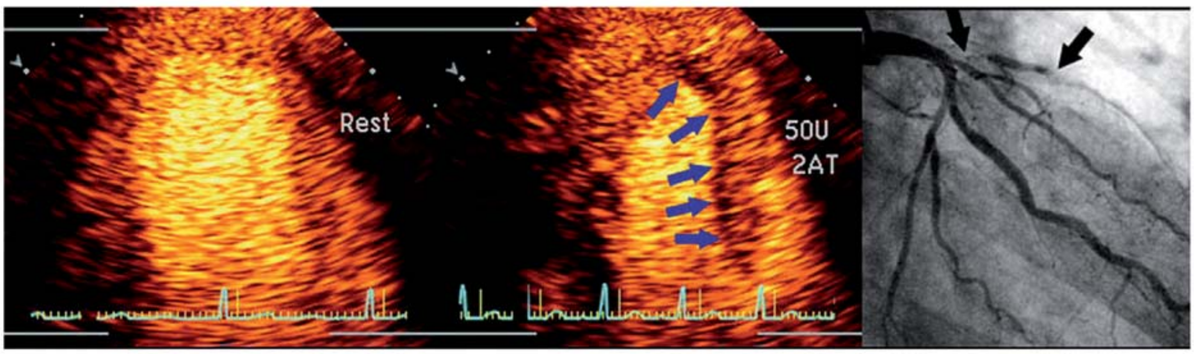

Fig. 4 - *Dobutamine stress real-time myocardial contrast perfusion echocardiography showing normal myocardial perfusion at rest (image on left) and subendocardium perfusion defect in the anterior septum at peak dobutamine stress (middle image). The coronary angiography demonstrated subocclusion of the left anterior descending coronary artery (Reproduced with permission. Elhendy A, et al. Noninvasive diagnosis of coronary artery disease in patients with diabetes by dobutamine stress real-time myocardial contrast perfusion imaging. Diabetes Care 2005 Jul; 28(7):1662-7).*

with high negative predictive value[28,29]. Senior et al[28] demonstrated that the sensitivity and negative predictive values of dobutamine stress echocardiography to assess functional recovery of akinetic segments three months after the AMI improved significantly when myocardial opacification was observed in myocardial segments that did not respond to an inotropic agent. For the detection of myocardial viability, the sensitivities of MCE, dobutamine stress echocardiography and combination of the two were 58%, 59%, and 79%, respectively ($p < 0.001$) and the specificities were 76%, 84%, and 69%, respectively ($p < 0.05$ compared to wall motion analysis). The combined analysis of perfusion and wall motion was an independent predictor of functional recovery, suggesting that MCE is a technique that should be used to optimize the assessment of viability after AMI. In addition to the prediction of functional recovery, the presence of no-reflow detected by MCE are related to higher incidence of acute complications after AMI. Caldas et al[29] evaluated 31 patients who had suffered their first anterior wall AMI and were submitted to thrombolytic therapy. The analysis of myocardial perfusion was performed with MCE using harmonic intermittent imaging. The authors demonstrated that determination of myocardial perfusion within 48 hours post infarction was an independent predictor for left ventricular remodelling in a six month follow-up period.

Identification of hibernated myocardium

Identifying hibernated myocardium in patients with chronic CAD is of utmost importance for adequate treatment of these patients, since coronary artery bypass surgery has been demonstrated to improve symptoms and decrease the risk for future events[30]. Many imaging modalities have proven to be accurate for the identification of hibernated myocardium, including magnetic resonance imaging, myocardial scintigraphy, dobutamine stress echocardiography and positron emission tomography. The assessment of myocardial viability by MCE is based on the fact that microvascular integrity is a prerequisite for maintenance of myocellular metabolism in the ischemic areas with viability. Some studies have demonstrated the value of MCE to identify hibernated myocardium and predict functional recovery after revascularization. Shimoni et al[31] recently described the importance of quantitative MCE to detect myocardial viability in comparison with dobutamine stress echocardiography and thallium-201 myocardial scintigraphy.

The accuracy of quantitative MCE perfusion analysis was higher than the qualitative analysis of myocardial perfusion. The measurement of myocardial blood flow was the best parameter to predict functional recovery within 3 to 4 months after surgical revascularization. In addition, the quantitative analysis of myocardial perfusion had similar accuracy and higher specificity than myocardial scintigraphy (Table 3). Although an increasing number of studies has demonstrated the importance of MCE to assess patients with CAD, it is important to emphasize that further multicenter studies are required to confirm these findings.

Final comments

Throughout the past few years, it has been demonstrated that contrast echocardiography using intravenous injection of microbubbles is an useful technique for the assessment of patients with suboptimal imaging as it enables a better evaluation of the cardiac anatomy. Microbubbles act as blood flow tracer, remaining within the intravascular space, and their distribution in the myocardium indicate the integrity of coronary microcirculation. MCE has proven to be safe and efficient to assess myocardial perfusion, and has incremental value over the analysis of wall motion for the wide spectrum of patients with acute and chronic coronary disease.

Table 3 - Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of myocardial contrast echocardiography (MCE), thallium-201 myocardial scintigraphy (Tl201) and dobutamine stress echocardiography (DSE) to predict functional recovery in patients with chronic ischemia.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MCE qualitative analysis				
Any presence of contrast	99	14	45	94
Homogenous contrast	81	49	53	78
MCE quantitative analysis				
MCI normalized ≥ 0.6	93*	53	61	90
MCI peak x β > 1.5	90	63*†	66*†	89
DSE				
Biphasic response	63‡	87‡	71‡	82
Any improvement	80	54	47	83
Tl201 ≥ 60%	92	45	52	89

*MCI - myocardial contrast intensity; β - refilling velocity. * $p < 0.05$ vs MCE qualitative analysis; † $p < 0.05$ vs Tl201; ‡ $p < 0.05$ vs MCE, Tl201 and DSE, any improvement. (Reproduced with permission. Shimoni et al. Identification of hibernating myocardium with quantitative intravenous myocardial contrast echocardiography: comparison with dobutamine echocardiography and thallium-201 scintigraphy. Circulation 2003;107:538-44).*

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