Review Article

Assessment of Myocardial Perfusion With Intravenous Myocardial Contrast Echocardiography Current State and Clinical Applications

Namsik Chung, MD, PhD
Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University College of Medicine, Seoul, Korea

(J Echocardiogr 2006; 4: 91-98)

Coronary angiography has been regarded as the gold standard to estimate the anatomic extent of disease involvement in coronary obstructive disease. However determination of the anatomic extent is not superior to myocardial perfusion imaging in predicting the outcome of the disease [1-3]. Hence accurate assessment of myocardial perfusion has been considered to be quite important in the functional diagnosis and stratification of both risk and therapy in this disease entity in addition to the anatomic information obtained from coronary angiography.

Myocardial contrast echocardiography (MCE) is a technique that uses microbubbles and simultaneously images LV wall motion and microcirculation of the myocardium consisting of small arteries, arterioles, capillaries and venules after administering echo-reflecting microbubbles.

Microbubbles remain entirely within the microvascular space, and their presence in any myocardium reflects the degree of microvascular perfusion within that region.

This new technology is rapidly evolving with simultaneous advances in both imaging machine technologies and manufacturing of stable intravenous microbubbles with the capability to transit pulmonary circulation.

New ultrasound contrast agents consist of microbubbles with a diameter less than 5 μm containing high molecular weight gas. The incorporation of higher molecular weight gases into lipid encapsulated microbubbles has prolonged their persistence in the circulation.

During recent years, many researchers have studied this topic in regards to the detection of inducible myocardial ischemia, assessment of no reflow, and myocardial viability. With this new technology, it is essential to delineate the spectrum of perfusion derangements in coronary artery disease (CAD) on routine echocardiographic examinations. However there are still many key issues that need to be overcome regarding technology to be applied, appropriate contrast agents to be administered, and mode of infusion.

Technologies to enhance nonlinear signals from microbubbles within the myocardium - From intermittent harmonic to real time perfusion imaging

Strong echocardiographic signal from the myocardium with conventional two-dimensional echocardiography prohibits discrimination of nonlinear signals of the microbubbles within the microvasculatures from signals of the myocardium. The fact that microbubbles respond differently to the ultrasound depending upon the degree of insonating acoustic power (mechanical index) has led to the development of harmonic and

Received October 17, 2006
Address for correspondence: Namsik Chung, MD, PhD
Department of Cardiology, Yonsei Cardiovascular Center, Yonsei University College of Medicine,
134 Shinchong-dong, Seodaemun-gu, Seoul 120-752, Korea.
Telephone: +82-2-2228-8291
Fax: +82-2-393-2041
E-mail: hamsikc@yumc.yonsei.ac.kr

intermittent triggered imaging technologies [4-6]. On top of these two technologies, there have been a number of refinements and modifications of imaging technologies to enhance nonlinear signals from the microbubbles and simultaneously reduce the linear signals from the tissue as much as possible. Power Doppler imaging exploits microbubble response to ultrasound and portrays contrast effect in Doppler mode [7-10]. In pulse inversion harmonic imaging, the transducer emits a normal sinusoidal wave shortly followed by emission of the same sinusoidal wave but in an inverted direction. When the returning signals are summed, signals from the linear tissue are cancelled but those from the nonlinear microbubbles are intensified yielding enhanced images from the microbubbles (Figure 1)[11]. Since these technologies utilize strong emitting signals from the bursting microbubbles when theys are insonated with high acoustic power, intermittent triggered imaging was the only possible method to visualize microvascular perfusion. Recently it has been possible to simultaneously visualize microvascular perfusion and LV wall motion using a new technology called real-time perfusion imaging [12]. Real-time contrast imaging techniques, such as power modulation, power pulse inversion, coherent imaging withlow mechanical index, are non-destructive. All three technologies are designed to enhance nonlinear signals from microbubbles and reduce linear ones from the myocardium, However this technology obviates the need for intermittent or triggered emission of pulses to obtain signals from the replenishing microbubbles. Flash imaging utilizes a burst of high mechanical index pulses to destroy microbubbles within the myocardium, followed by low mechanical index real-time MCE (Figure 2).

To assess myocardial perfusion accurately using these technologies, a thorough understanding of optimum machine settings, power output, and administration of microbubbles is crucial [13-15].

MCE in the detection of coronary artery stenosis

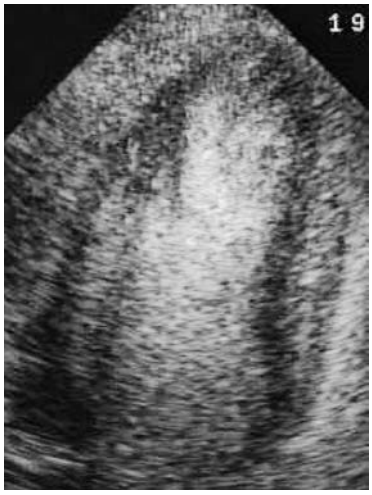
MCE can detect coronary stenosis by assessing changes in myocardial blood volume and myocardial blood flow.

Several studies have demonstrated the feasibility and accuracy of intravenous MCE in the detection of coronary stenosis employing pharmacologic or exercise stress tests.

Myocardial perfusion by harmonic power Doppler imaging was compared with simultaneously performed adenosine stress 99mTc-sestamibi SPECT in 123 patients with known or suspected CAD using adenosine as a pharmacological stressor [16]. The overall concordance between power Doppler imaging MCE and SPECT was 81% (83 of 103). The concordance for single-vessel disease was 68% and 93% for multi-vessel disease. Using intermittent triggered pulse inversion harmonic imaging, Chung et al also demonstrated a similar concordance rate between MCE and Tc99m sestamibi SPECT (86.9%) in 46 patients with chest pain and no history of prior myocardial infarction. The overall sensitivity and specificity of MCE and Tc99m sestamibi SPECT were 71 and 76% and 96 and 99% respectively [17].

With real-time imaging technology, it has been possible to generate a microbubble replenishment curve after microbubble destruction with high acoustic power ultrasound pulses followed by low acoustic power scanning. The peak videointensity (α) and the rate of replenishment of microbubbles (β) are calculated from the videointensity curve where the endsystolic frame is plotted against the pulsing interval [18]. In the stenosed myocardial bed, the rate of microbubble replenishment (β) is diminished. Therefore the ratio of β before and after vasodilator stress (flow reserve) is expected to detect the stenosed myocardial bed. Kaul and his colleagues demonstrated the usefulness of this new technology in the detection of coronary stenosis [19]. They compared the β ratio with SPECT images. The sensitivity and specificity of detecting coronary stenosis was 85 and 100% respectively.

On the basis of this quantitative analysis, Cho et al hypothesized that a delay in the replenishment of microbubbles assessed by visual endsystolic frame counting analysis can differentiate patients with coronary stenosis from normal subjects [20]. They sought to test the feasibility and accuracy of the visual analysis method in 45 patients with chest pain and no prior history of myocardial infarction who underwent adenosine stress real-time perfusion MCE. After the destruction of microbubbles with high acoustic power, the endsystolic frame was counted until the myocardium was homogeneously re-enhanced. All patients underwent QCA. Incomplete replenishment of microbub-



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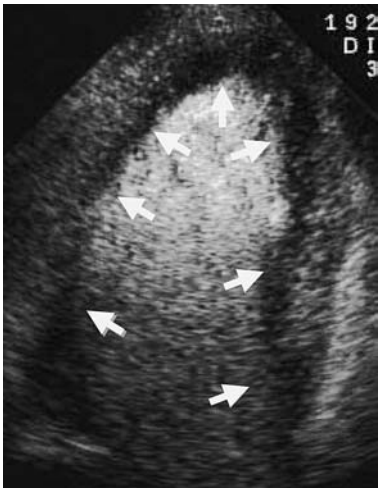

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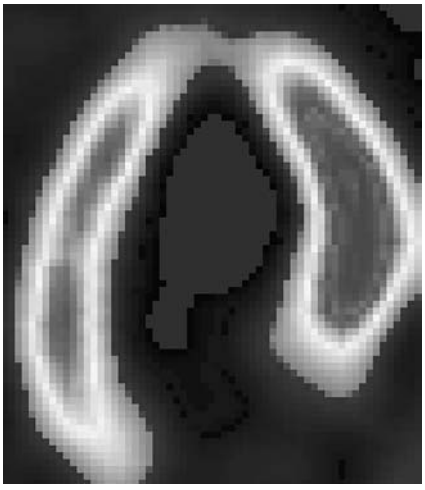

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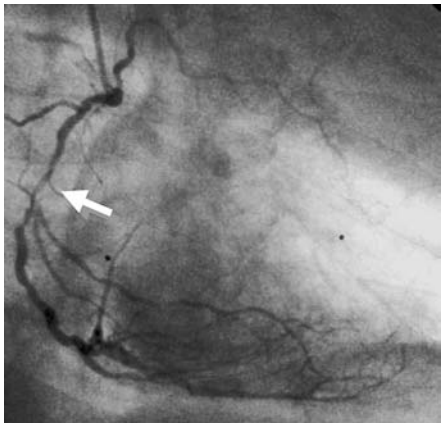

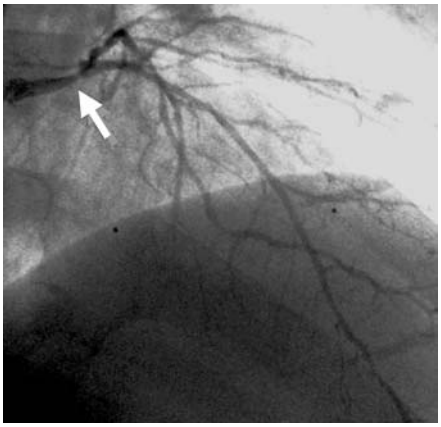

Fig. 1. Dipyridamole stress MCE using continuous intravenous infusion of PESDA shows multiple perfusion defects (arrows) in a patient with left main and right coronary artery stenosis. Note the simultaneously performed TC99m sestamibi SPECT images.

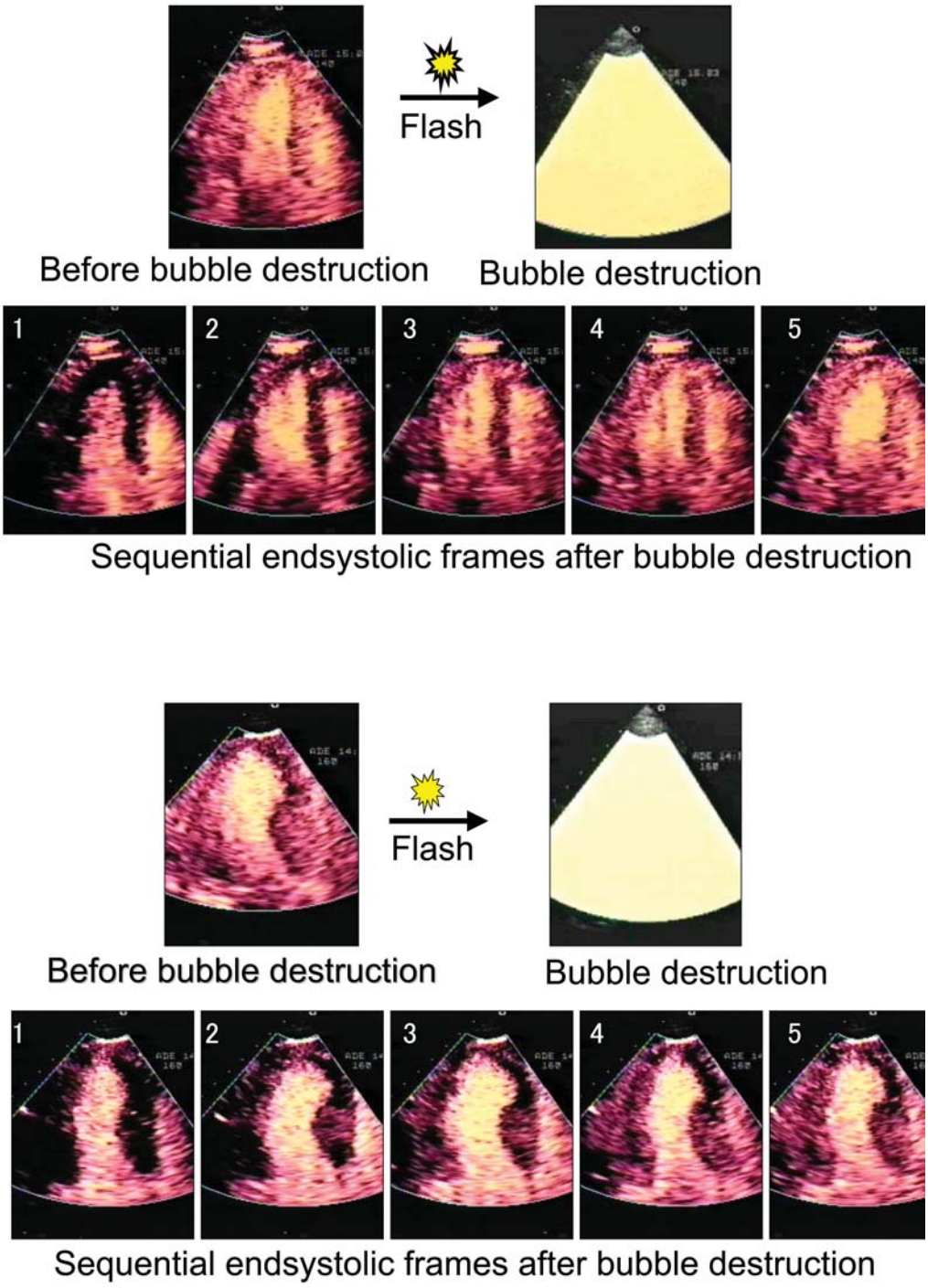

Fig. 2. After destruction by high acoustic power ultrasound pulses, gradual replenishment of microbubbles within the LV myocardial microvasculatures is displayed at sequential endsystolic fames. In a normal subject, homogeneous refilling of microbubbles is completed at the 5th endsystolic frame.
In a patient with left anterior descending artery (LAD) stenosis, incomplete refilling in the LAD territory is evident at the 5th endsystolic frame.

bles at 5th, 6th, 7th and 8th endsystolic frame predicted significant coronary stenosis (≥ 50%) with sensitivity of 90, 73, 72, 79% and specificity of 53, 64, 65, 68% respectively.

Porter and his colleagues demonstrated that simultaneous assessment of myocardial perfusion and LV wall motion with real time MCE imaging was superior to regional wall motion analysis only during dobutamine stress echocardiography [21]. In 117 patients, among whom 40 patients had QCA, a better agreement between MCE and QCA (83%) was observed than that between wall motion abnormality and QCA (72%). This study proves the additive value of myocardial perfusion assessment during dobutamine stress echocardiography.

Using exercise treadmill or supine bicycle stress test, the values of myocardial perfusion imaging with accelerated intermittent harmonic imaging was tested in one hundred patients by Shimoni and his colleagues [22]. Simultaneous radioisotope imaging was performed on all patients before and after exercise. Forty-four patients underwent QCA. The agreement was 76% between MCE and SPECT and 88% between MCE and wall motion abnormality. When compared with QCA as a gold standard, the sensitivity of MCE, SPECT, and wall motion analysis was about 75%, and the specificity was 100, 81, and 88% respectively. Simultaneous assessment of wall motion abnormality and MCE could achieve better sensitivity and specificity (86 and 88%) with an accuracy of 86%. Even though this study utilized low frame rate imaging, it clearly demonstrated the feasibility and usefulness of MCE in conjunction with wall motion analysis during stress echocardiography for better detection of coronary stenosis.

The detection of CAD at rest is a challenge. Wei et al [23] reported that changes in videointensity during systole and diastole can detect and quantify the degree of coronary stenosis at rest without stress intervention. They also reported that a significant increase in systolic videointensity was noted in coronary stenosis that resulted in a progressive increase in the systolic/diastolic videointensity ratio at higher degrees of stenosis. A systolic/diastolic myocardial arterial blood volume signal ratio of >0.34 provided a sensitivity and specificity of 80% and 71%, respectively, for the detection of > 75% coronary stenosis in 22 patients examined with Definity microbubbles, whereas a ratio of >0.43 provided a sensitivity and specificity of 89% and 74%, respectively, for the detection of > 75% stenosis in 22 patients examined with Imagent microbubbles [24].

Assessment of myocardial viability in acute ST elevation myocardial infarction

In patients with acute myocardial infarction (AMI), intact microvascular integrity assessed by intracoronary MCE has been proven to be very important in predicting the outcomes after recanalization with thrombolytic therapy or primary PTCA [25-27].

There are several reasons for low specificity of MCE to predict myocardial viability despite high sensitivity. These are reactive hyperemia, dynamic changes in the microcirculation post-AMI, and technical difficulties to distinguish microbubble signature from myocardium. The criteria of viability, i.e. recovery of wall motion abnormality, can contribute to low specificity of MCE since more than 20% of the subendocardium can make the segment akinetic despite the remaining portion of the myocardial segment being intact [28].

Recently, Lepper and his colleagues [29] investigated whether the extent of perfusion defects detected by intravenous MCE in patients with AMI treated by primary PTCA related to coronary flow reserve for assessment of myocardial reperfusion and was predictive for left ventricular recovery. Twenty-five patients with AMI underwent MCE with intermittent harmonic imaging before PTCA and after 24 hours. MCE before PTCA defined the risk region, and MCE at 24 hours, the no-reflow region. The ratio of the no-reflow and the risk region defined the ratio of the risk region. Coronary flow reserve (CFR) using a Doppler guide wire was assessed immediately after PTCA and 24 hours later. A smaller ratio of the risk region (≤ 50%) by MCE was associated with improvement of CFR from 1.67 ± 0.47 at baseline to 2.15 ± 0.53 at 24 hours and of regional wall motion improvement at 4 weeks (from 2.6 ± 0.5 to 1.9 ± 0.5). This study demonstrated that intravenous MCE can be used to define perfusion defects after AMI, correspond to evaluation of CFR, and has potential to identify patients likely to have improved LV function after AMI.

Main and his colleagues [30] demonstrated the usefulness of MCE using pulse inversion power Doppler technique in patients with a recent myocardial infarction. In 34 patients, perfusion by MCE predicted recovery of segmental wall function with a sensitivity of 77%, specificity of 83%, positive predictive value of 90%, and overall accuracy of 79%. They suggested 90% of perfused segments improved in wall motion while

the majority of non-perfused segments remained unchanged.

Balcells et al [31] demonstrated the optimal timing of performing MCE for the accurate prediction of myocardial viability 3-5 days after PCI. Almost all segments with good perfusion demonstrated wall motion recovery.

Swinburn et al reported that delayed enhancement with microbubbles in the infarcted area is an important marker of functional wall motion recovery regardless of the severity of residual stenosis of the infarct related artery [32].

Acute chest pain without ST-segment elevation

Currently, electrocardiographic changes may occur in less than one third of patients with acute coronary syndrome (ACS). Evaluation of regional wall motion abnormality may help in differentiating patients from acute ischemic chest pain. However, a change in ECG and regional LV wall motion occurs far later than the development of perfusion abnormalities in the ischemic cascade. Therefore, the ability to assess perfusion status in patients suspected of ACS is crucial in triaging therapeutic strategies in this patient group. Myocardial contrast echocardiography has great potential to improve diagnostic accuracy in this regard-because of its ability to assess regional wall motion abnormality and perfusion simultaneously. In Figure 3, multiple baseline perfusion defects are depicted within the myocardium in a patient with unstable angina. MCE may help differentiate patients with acute chest pain from atypical chest pain in the emergency setting.

Kaul et al [33] reported that MCE has incremental value for both diagnosis and short-term prognosis in patients presenting to the emergency department with chest pain and without ST-segment elevation.

Min P-K et al studied the value of MCE in predicting cardiac events in patients who presented with chest pain in the emergency room. From 101 patients without ST elevation, MCE was more sensitive than conventional two-dimensional echocardiography, and only the perfusion defect assessed by MCE was the strongest factor to predict cardiac events [34].

Limitations

The quality and accuracy of contrast perfusion imaging is influenced by a number of factors such as techniques and microbubbles being employed and anatomical as well as physiological factors of patients. Physical characteristics of each contrast agent, deter-

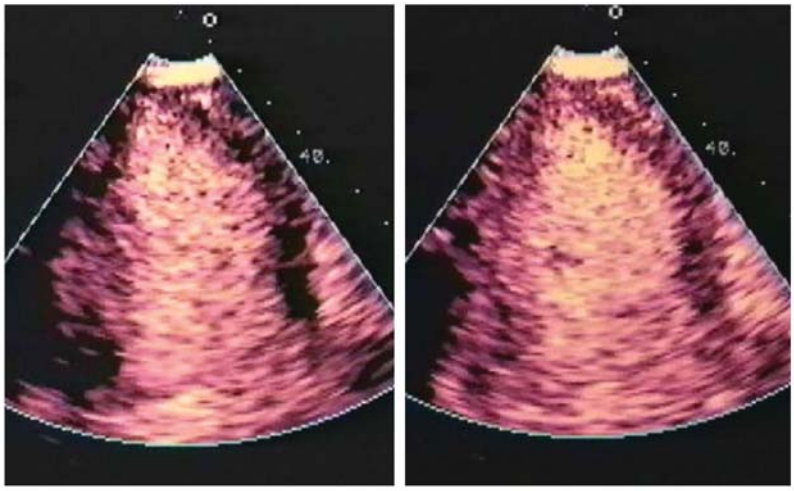

Fig. 3. Baseline apical long axis view of MCE in a patient with angina and severe left maincoronary artery stenosis. Severe filling defect of microbubbles within the whole LV myocardium is noted at the 6th end-systolic frame. Even at the 15th end-systolic frame, heterogeneous refilling is noted suggesting severe coronary perfusion abnormality.

mined by shell thickness and composition along with the amount and method of administration of microbubbles can determine the instantaneous amount of microbubbles reaching the myocardial microvasculature, which ultimately influences contrast enhancement. False positive or negative results can be obtained from improper techniques. For example, motion artifacts from the myocardium can mask perfusion defects in power Doppler harmonic imaging technique. Even though low mechanical index imaging is utilized, microbubble destruction at near field (especially at the apex on apical view imaging) is sometimes problematic as it can be misinterpreted as anatomical perfusion defects. Acoustic attenuation at far fields (basal walls at apical views) can mimic perfusion defects as well. Use of multiple acoustic windows, off-axis views, and locating the areas of interest at the center of the imaging scan may help avoid misinterpretation. Hence, thorough knowledge of microbubbles and instrumentation utilized is a prerequisite in performing myocardial contrast perfusion echocardiography to obtain the most accurate results.

Conclusion and Future direction

Intravenous MCE has been rapidly evolving since the introduction of stable high molecular-weight gas microbubbles and sophisticated machines to enhance nonlinear signals from the microbubbles. The feasibility and accuracy to diagnose perfusion abnormalities appear to be comparable with radionuclide SPECT imaging. Furthermore, the ability of intravenous MCE to discern viable myocardium in patients with AMI appears to be possible. MCE is attractive in terms of its versatility compared to other perfusion imaging modalities providing its ability to assess microvascular integrity and regional and global left ventricular wall function simultaneously.

After overcoming the technical limitations through continuous research and refinements, MCE shall be applied in routine clinical practice.

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