

# Myocardial Perfusion Imaging:

## *Current State of the Art*

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Contrast echocardiography has achieved major importance only in the last 5-6 years driven by a number of new developments. The new second- and third-generation ultrasound contrast agents are far more potent. Refined recording techniques aimed specifically at recording and detecting the contrast signal have been developed. Harmonics, power Doppler, a variety of echocardiographic-gated imaging, and most recently real-time contrast echo comprise this newer instrumentation. Instruments initially modified to detect tissue now have been modified to detect microbubbles. This combination of capabilities enables visualization of the left ventricular (LV) cavity and enhances Doppler signal as well as opacification of the myocardium to allow myocardial perfusion studies. In the future, these new microbubble agents will serve as targeted markers, for instance to

detect upregulation of endothelial adhesion cell molecules or to deliver drugs or therapies, such as thrombolytic agents or genes.

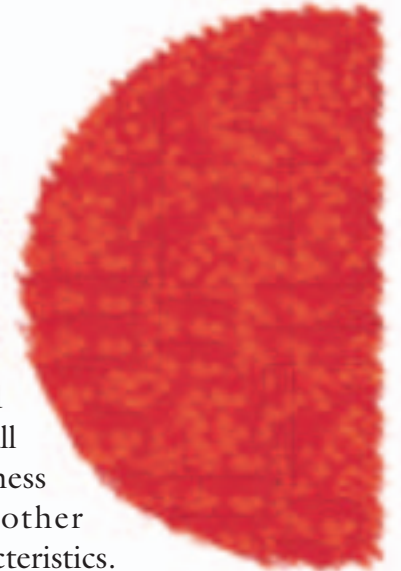
### CHARACTERISTICS OF NEW CONTRAST AGENTS

Microbubble persistence has been achieved by using high density, high molecular weight fluorocarbon gases that do not diffuse readily or rapidly saturate the blood if diffused. The new agents also employ shells, such as albumin, galactose, liposomes, or polymers to achieve microbubble persistence sufficient to pass through the lungs after an intravenous injection and opacify the cavity and myocardium of the left ventricle.

The second-generation agent, Optison, a fluorocarbon with an albumin shell, is the only approved new agent in the US. Many agents should be commercially available soon. Two agents entering clinical trials employ polymer shells, the same material as absorbable sutures,

can be very precisely honed for wall thickness and other characteristics.

Persistence, fragility, resonance, attenuation, and adhesion differences characterize the new microbubbles. Their unique shells (surface modifiers) and unique gases will alter their persistence and fragility. They will have various abilities to resonate in ultrasound fields to expand and contract, have various degrees of attenuation, and perhaps various degrees adhesion. To date all of the bubbles have been proven safe and easy to prepare. Opacification of the LV cavity and the myocardium after about 10 cardiac cycles can be achieved with these agents providing the opportunity to study myocardial perfusion. The goal is to ob-



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tain images that demonstrate a perfusion defect where the contrast signal is weak in the area of the infarct relative to the rest of the myocardium post-myocardial infarction.

## *Harmonics*

Harmonic capability is possible because bubbles resonate. When exposed to ultrasonic energy the bubbles expand and contract in a non-linear fashion creating a secondary, harmonic, frequency that is a multiple of the transmitted frequency. Therefore by recording the transmitted frequency the bubble signal can be amplified relative to the myocardium.

## *Gated Imaging*

ECG-gated imaging is used to minimize bubble exposure to ultrasonic energy so fewer bubbles are destroyed. Rather than expose bubbles to ultrasonic energy at 30 frames/second, they are exposed at one frame per one or four to five cardiac cycles. The greater time period between imaging pulses allows new blood with undestroyed microbubbles to fill the imaging field. Real-time im-

aging may minimize the importance of gated-imaging, though.

## *Power Doppler*

The power Doppler signal represents the correlation between two successive transmissions. Bubbles move between two successive transmissions, may be destroyed, or break into smaller bubbles with different reflection characteristics.

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*“Rather than expose bubbles to ultrasonic energy at 30 frames/second, they are exposed at one frame per one or four to five cardiac cycles.”*

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The power Doppler is able to detect these changes and therefore is very sensitive at imaging microbubbles.

## *Bubble Destruction*

Bubble destruction is one of the most important concepts in myocardial contrast echocardiography (MCE), as it provides the potential to quantify myocardial blood flow. Ohmori showed in studies performed at UCSD that bubbles were nearly all destroyed during continuous imaging (30 frames/second), whereas they were not

during triggered imaging (1 frame/second). In the interval between triggered pulses new blood with undestroyed microbubbles filled the tube and was imaged. He showed that very high flow rates of 30 cc/second can replenish the microbubbles between transmissions.

The ability to assess intensity as a measure of the velocity of blood flow is very important. Plotted data from Ohmori shows there is a close relation between flow rate and videointensity ( $r=0.95$ ). These data demonstrate that flow rate can be estimated using the ability to refill the imaging field between transmitted impulses.

Complete opacification is obtained with gating, whereas it is not with continuous mode, because at 1 frame/5 cardiac cycles, enough time is allowed for the entire myocardium to refill with microbubbles. Bubble destruction allows for clear visualization of blood vessels, for example the coronary artery, because the blood flow in the coronary artery has a much greater velocity than that of the microcirculation. New bubbles continuously entering the imaging field prominently define the vessel.

Bubble destruction can be used to distinguish which of the intensities in the myocardium is from bubbles and which is from underlying tissue. An image is taken after the myocardium is totally filled with microbubbles and then two rapid fire images are taken to insure all bubbles are destroyed. The difference between the myocardial signal when the bubbles are destroyed and when they are present represents bubbles rather than tissue. Experimental studies show that as the bubbles are destroyed the myocardial image becomes clearer. Clinically, all the microbubbles are destroyed, and then the length of time for the myocardium to refill is the function of myocardial flow rate, and is used as a parameter to recognize abnormal coronary blood flow.

### *Power Doppler*

The pulse-to-pulse change in contrast is great relative to tissue, giving power Doppler an advantage in imaging microbubbles. Power Doppler recording has a greater signal-to-noise threshold than gray scale; can employ an autocorrelation algorithm; is suitable for power display; has a quantitative potential for “event counts”; and enables image colorization. However, it is subject to motion artifacts and blooming.

### *Real-time imaging*

Real-time imaging is a major ad-

vance using several approaches, including beam coherence. Power pulse inversion is used widely in the US. Power modulation uses a very high mechanical energy pulse to destroy bubbles. These approaches use multiple pulses, because bubbles subjected to two successive but different (in phase, amplitude) pulses have a non-linear response, whereas tissue has a linear response. By removing the linear responders only the bubble signal remains, so low energy can be used for real-time imaging. Gray-scale image resolution is far superior in real-time, and both contraction and perfusion can be

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*“Real-time imaging is a major advance using several approaches...”*

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seen. In combination with intermittent high energy pulses real-time imaging enables looking at the rate of reperfusion; studying cyclic variation, potentially an important criteria for ischemia; and facilitates the use of myocardial contrast with stress echo.

## **MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY**

Despite the enormous potential for MCE, there are issues to be addressed. Attenuation is one of the largest challenges in MCE as thickening or shadowing could be

misread as a perfusion defect. Therefore most imaging to date uses the apical four-chamber view so the area of attenuation is the left atrium, not the myocardium.

Blood volume, microcirculatory flow velocity, and relative regional perfusion can be determined with MCE. Signal intensity is a function of blood volume as it is related to the number of microbubbles. Microcirculatory flow can be determined indirectly from the reflow rate and bubble destruction. Potentially, it will be possible to determine volumetric blood flow through blood volume and blood velocity. Relative regional perfusion has been the major endpoint of MCE to date, in the same fashion as radionuclide scans.

### *MCE in basic science*

Physiologic questions can be answered with basic science studies using MCE. For example, when Nozaki was at UCSD he used MCE to document gene transfer of fibroblast growth factor-5 with an adenoviral vector delivered directly to the coronaries that resulted in angiogenesis. The generation of coronary collaterals and repair of the perfusion defect could be documented with MCE after applying an ameroid constrictor that expands slowly over 10-14 days to occlude a coronary artery.

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## **Clinical applications of MCE in CAD**

MCE may be used to study clinical questions in patients with coronary artery disease (CAD). Potential applications of MCE include:

- Identify risk area of the infarct or ultimate infarct size in patients with occluded coronary arteries and acute myocardial infarction (MI)
- Determine reperfusion efficacy after thrombolytic therapy
- Identify no-reflow phenomenon when the epicardial vessel opened by PTCA or thrombolytic therapy but no microcirculatory flow occurs
- Study myocardial viability through information about the integrity of the microcirculatory bed
- Assess presence of coronary collaterals
- Identify coronary artery stenosis in patients with chest pain—its key use
- Enhance the Doppler signal
- Deliver targeted markers or agents

Animal studies have shown that the size of the perfusion defect will correlate with the size of the inf-

arction. Numerous published experimental studies confirm that 1) MCE can identify MI, 2) MCE can determine infarct size from the perfusion defect, 3) residual perfusion during occlusion predicts infarct size, 4) contrast enhancement identifies successful reperfusion, and 5) post-reperfusion defects equal no-reflow.

Work from Itoh in Japan shows that in some patients with successful opening of an epicardial artery through the left anterior descending (LAD) a perfusion defect may continue, the no-reflow phenomena. This exists in about 35% of patients and predicts the lack of recovery of that myocardium. MCE clearly has great potential to identify this phenomenon. MCE in the clinical setting of MI has not been well studied, and the data available are conflicting about its ability to recognize infarction. Importantly, the optimal tech-



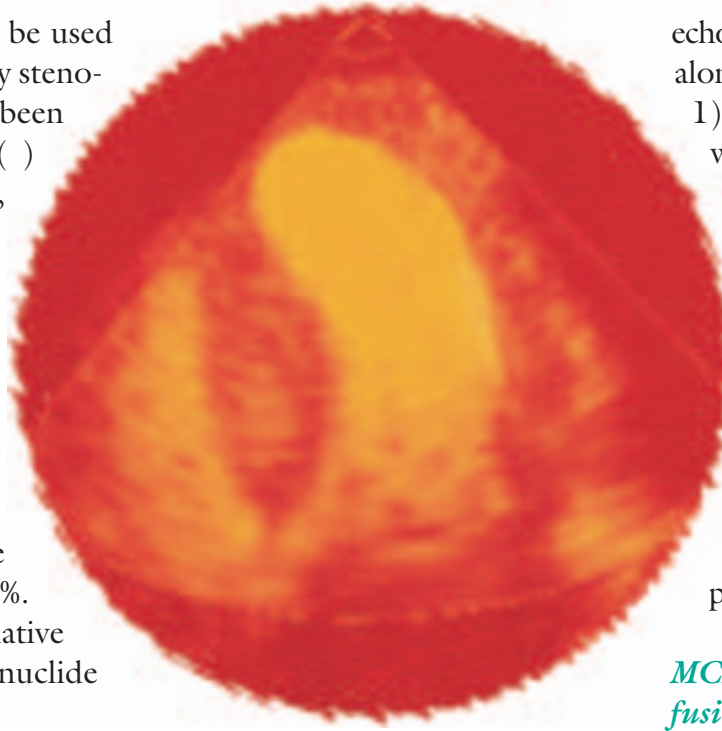
niques to study MI with MCE must be defined and validated.

The detection of coronary artery stenosis is the greatest potential for MCE. Work done by DeMaria's lab established that contrast intensity seen in the myocardium reflects myocardial blood flow. An experimental model of graded coronary stenoses in the LAD using flow measurements and microspheres to assess blood flow showed that the LAD was well perfused at baseline. Opacification was increased with adenosine vasodilation. But, in the presence of a stenosis, abnormal perfusion was seen clearly with MCE. Correlating myocardial contrast intensities (ratio of ischemic to normal area) with actual blood flow using MCE as its own calibration yielded a good correlation ( $r=0.79$ ).

Further, a relative relation between the stenosis severity and contrast intensity was found when comparing the ratio of ischemic to normal myocardial contrast intensity at graded stenoses.

A 92% concordance between color-encoded contrast echos and radionuclide sestamibi studies was found when Kaul applied this technique in 30 patients. The data are preliminary and very sophisticated computer analysis was performed, but give strong encour-

agement that MCE can be used to detect coronary artery stenosis. Similar results have been reported by Grayburn ( ) and Porter ( ). However, the reproducibility of these results has been limited. A European multicenter study using triggered imaging found that diagnostic quality images were obtained in only about 60% of patients and the sensitivity was below 40%. MCE is not yet an alternative to stress echo or radionuclide imaging.



*Challenges to clinical application of MCE*

To apply MCE clinically to detect stenoses, many technical and logistical questions must be answered. These include 1) optimal dosing and agent, 2) bolus injection or infusion, 3) gray scale or Doppler, 4) triggered or real-time imaging, 5) visual analysis or quantitation, and 6) criteria for abnormality.

Work from DeMaria’s lab primarily by Masugata compared harmonic gray scale imaging to power Doppler at various pulsing intervals from 1:2 to 1:10 to assess graded stenoses in 9 open chest dogs with 4 grades of resting stenosis. The difference between baseline and the stenoses with gray scale was most readily observed at long pulsing intervals. In contrast, with power Doppler the differ-

ences were best seen at short pulsing intervals, and at long pulsing intervals the differences in intensity virtually disappear. This fundamental difference illustrates the complexity of using MCE to study clinical phenomena.

The criteria to define abnormality, which will drive when it is appropriate to use gray scale or power Doppler, is being debated. Some say visualization, as with radionuclide, others say measurement is needed. A variety of proposed quantitative criteria are being evaluated, and include 1) absolute reduction in intensity, 2) relative reduction compared to normal, 3) appearance or disappearance rate of contrast, 4) cyclic variation of intensity, 5) reperfusion rate, and 6) tissue signature.

The many artifacts in contrast

echo make reliance on visualization alone problematic. These include 1) attenuation, 2) anisotropy, when the myocardial fibers are aligned parallel to the ultrasound diminishing high intensity signals, 3) bubble destruction, a problem in the near field where energy is highest, 4) rib artifacts that can destroy all ultrasound signal, 5) blooming artifacts with Doppler, 6) motion artifacts with Doppler.

*MCE studies of myocardial perfusion*

Reperfusion rate, the rate bubbles refill the imaging field after bubble destruction, has received the most attention as a measure of abnormal perfusion. But, to use MCE to study abnormal blood flow and myocardial perfusion, normal must be defined

Many variables exist even in normal MCE, such as regional variations in intensity throughout the cardiac cycle. It has been shown that in any one frame an apical defect is not diagnostic. **Low intensity during diastole and high intensity in systole**, and differences in the uptake of peak intensity after introduction of contrast has been shown in normal subjects in DeMaria’s lab. Thus, intermittent imaging will play a key role. For example, at baseline the myocardium is filled with

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microbubbles, which are then exposed to high mechanical energy at 4-10 times the strength used for imaging immediately destroying all the bubbles. At the end of 6 cardiac cycles there was nearly complete opacification.


Many have attempted to devise quantitation criteria. Plotting intensity versus time yielded curves that could distinguish normal from abnormal flow. The curves also provided information about the severity of the grade of stenosis, such as a nearly linear relation

between the rate of rise and increasing stenosis severity. They also developed an exponential equation [ $y = A (1 - \exp^{-bt}) + c$ ;  $y$  being signal intensity,  $b$  the change in intensity over time ( $t$ )].

Dobutamine has been compared to adenosine in work by DeMaria in open chest dogs. Each agent had advantages and disadvantages.

## CLOSING

Clinical application of these impressive data requires that excel-

lent images can be routinely obtained with intravenous injection in 90-95% of patients. The newest instruments and bubbles have made this a near reality. Intensity must be related to perfusion, which has been done experimentally and is not possible in humans. Accurate criteria for abnormal perfusion must be defined, and most likely will be the refilling rate. When this is validated, major trials to compare MCE stress imaging with regular stress echo or radionuclide imaging can be done to determine the additive or superior information expected to be provided by MCE. 

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