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iREVIEWS

STATE-OF-THE-ART PAPERS

Myocardial Perfusion Imaging With Contrast Ultrasound

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This report reviews the development and clinical application of myocardial perfusion imaging with myocardial contrast echocardiography (MCE). This includes the development of microbubble formulations that permit the detection of left ventricular contrast from venous injection and the imaging techniques that have been invented to detect the transit of these microbubbles through the microcirculation. The methods used to quantify myocardial perfusion during a continuous infusion of microbubbles are described. A review of the clinical studies that have examined the clinical utility of myocardial perfusion imaging with MCE during rest and stress echocardiography is then presented. The limitations of MCE are also discussed. (J Am Coll Cardiol Img 2010;3: 176–87) © 2010 by the American College of Cardiology Foundation

A series of inventions and scientific breakthroughs are responsible for the development of myocardial perfusion imaging with myocardial contrast echocardiography (MCE). First, there was the invention of stable microbubble shells using either electromechanical sonication of albumin or lipid emulsions (1,2). Second there was the stabilization of these microbubbles following venous injection by the incorporation of a high molecular weight insoluble gas within the shell, which permitted consistent left ventricular opacification following venous injection (3). Then, it was discovered that the typical ultrasound imaging techniques at a high mechanical index (MI) were destroying these microbubbles as they transited through the myocardial microcirculation. By either triggering ultrasound to one frame every cardiac cycle or by utilizing a very low mechanical index and harmonic imaging, myocardial contrast enhancement from a venous injection of microbubbles was consistently visualized (4). With harmonic triggered imaging, myocardial perfusion abnormalities were visualized in humans using very small intravenous bolus injections of perflourocarbon containing microbubbles (5). Finally, a team of investigators headed by Kevin Wei and Sanjiv Kaul at the University of Virginia made the landmark discovery that these ultrasound triggering techniques could be utilized to quantify myocardial blood flow, and even examine the components responsible for myocardial blood flow (6). This has led to clinical studies demonstrating how MCE can provide important bedside information on myocardial blood flow during stress echocardiography laboratory (7–10), in the acute and chronic assessment of myocardial viability (11–14), and in the emergency department (15). This paper will review the technical aspects of myocardial perfusion imaging with MCE, and how it has been utilized to detect coronary artery disease and guide management.

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Perfusion Imaging Techniques With Myocardial Contrast Echocardiography

Microbubbles in an ultrasonic field are strong scatterers, sending compression and rarefaction waves back to the scanner. At peak negative pressures above 0.1 MPa, the microbubbles respond in a nonlinear manner. In general, what nonlinear behavior means is that the magnitude of compression and rarefaction waves are not the same with each oscillation. At these low incident pressures, the microbubbles exhibit both linear and nonlinear returning waves, whereas the myocardium and other structures primarily exhibit linear responses (16). The nonlinear responses occur in both the fundamental and harmonic frequencies and can be received and filtered by the echocardiographic system. Ultrasound imaging software that selectively receives the nonlinear responses produces a much better signal-to-noise ratio and more sensitive detection of microbubbles than what would be received from conventional imaging software (17).

Microbubbles are destroyed by real-time ultrasound when it is transmitted at higher intensities (MIs >0.3). Destruction can be reduced by decreasing the frame rate to 1 out of every 1 to several cardiac cycles, usually with triggering the frame to the electrocardiogram. This has been referred to as intermittent imaging, and has been used with both harmonic and power Doppler systems (18–21). When the intermittent ultrasound impulse is at a high intensity (>0.9 MI), there is a strong and brief nonlinear echo from the bubble. Interrupting the high-intensity ultrasound for a short period of time allows for replacement of microbubbles, which serve to produce contrast enhancement for the subsequent triggered frame. When microbubbles are administered as a continuous infusion and the ultrasound pulsing interval is incrementally varied, the reappearance of bubbles in the myocardium permits the calculation of mean microbubble velocity and plateau (or peak) myocardial signal intensity (5). Multiplying these 2 variables together, one can quantify myocardial blood flow changes. With these intermittent imaging techniques, it has become possible to noninvasively examine myocardial perfusion in animals and humans using a wide variety of intravenous higher molecular weight microbubbles (22,23). Significant achievements have been made in low MI real-time visualization of myocardial function. Pulse inversion Doppler is a multipulse technique that separates linear and nonlinear scattering using the radiofrequency domain. When used at a very low MI, linear scatterers like myocytes and tissue will have their signals canceled, whereas nonlinear scatterers (like microbubbles) will produce summated signals (24). Pulse inversion Doppler overcomes motion artifacts by sending multiple pulses of alternating polarity into the myocardium. This allows one to visualize wall thickening and contrast enhancement simultaneously at very low MIs (<0.2) while maintaining an excellent signal-to-noise ratio. Because it can receive only even order harmonics, however, there is significant attenuation, especially in basal myocardial segments in apical windows.

Power modulation is another technique that improves the signal-to-noise ratio at very low mechanical indices. This technique, developed by Philips (Andover, Massachusetts), is also a multipulse cancellation technique; however, with power modulation, the power of each pulse is varied. Contrast pulse sequencing (Siemens Acuson Sequoia; Mountain View, California) extends these multipulse techniques by interpulse phase and amplitude modulation (25). Both power modulation and contrast pulse sequencing can be used at a very low MI to assess myocardial contrast in real time with excellent spatial resolution at higher bandwidths (Fig. 1). In these examples, note that background signals from the myocardium are virtually absent.

Qualitative and quantitative methods of myocardial perfusion analysis. Regardless of the route of microbubble injection, an accurate definition of microbubble concentration in the myocardium requires that the relationship between concentration and signal intensity be linear. This precondition is fulfilled at low intramyocardial microbubble concentrations. At a certain microbubble concentration, however, echocardiographic systems normally reach a saturation point, where videointensity is no longer proportional to the microbubble concentration (26). This becomes a factor with bolus injections of microbubbles, in which transient high concentrations can be reached even in regions with reduced myocardial blood flow, leading to a brief period during which contrast enhancement falsely appears normal in these regions. It is not until microbubble concentration falls during the washout period that differences in microbubble concentration are visually evident. It is during this time period that there is a linear relationship between concentration and signal intensity. With bolus intravenous injections

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
LBBB = left bundle branch block
MCE = myocardial contrast echocardiography
MI = mechanical index
PET = positron emission tomography
SPECT = single-photon emission computed tomography
RT = real-time perfusion

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