Editorial Comment

Myocardial Contrast Echocardiography: Too Much, Too Soon?*

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The ability to opacify the central circulation with dense ultrasonic reflectances after the injection of a variety of fluids, so-called contrast echocardiography, was described in 1968 (1). Since that time, the history of contrast echocardiography has been characterized by cycles of enormous expectations and subsequent disappointment. The enthusiasm generated by the initial description of contrast opacification was rapidly blunted by the realization that the contrast effect was removed during transit through the lungs, thereby preventing visualization of the left-sided chambers. Years later, the development of first-generation ultrasound contrast agents that could cross the lungs, such as sonicated serum albumin, promised to complement the left ventricular endocardium on echocardiogram in all patients. However, left ventricular opacification was incomplete or absent in a significant percentage of patients undergoing such contrast studies. Even the demonstration that intracoronary administration of contrast agents could opacify the myocardium in patients and provide important clinical information concerning myocardial viability (2) and the no-reflow phenomenon (3) was offset by the difficult logistics of performing the procedure.

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A group of second-generation ultrasound contrast agents has recently been developed with sufficiently long persistence time as microbubbles to achieve myocardial opacification after intravenous injection (4). These agents have primarily utilized perfluorocarbon gases, which have the properties of high density and low diffusivity and saturation concentration. In conjunction with refined recording techniques such as second harmonic and electrocardiogram (ECG) gated imaging, i.v. administration of these agents has visualized myocardial opacification and delineated perfusion defects in the experimental laboratory (5). In fact, an early study demonstrated a close concordance of myocardial contrast echocardiography with sestamibi single photon emission computed tomography (SPECT) examination in recognizing impaired myocardial reserve in patients with coronary stenoses (6). With the availability to cardiologists accomplished by FDA approval of one of these agents (Optison; Molecular Biosystems, Inc., San Diego, California) in January 1998, we run the risk of entering another cycle of unrealistic, and thus unfulfilled, expectations that contrast echocardiography can be immediately applied to detect coronary artery disease in the routine clinical setting.

In this issue of the Journal, Marwick et al. (6) report the first multicenter clinical trial of myocardial contrast echocardiography (MCE). They studied the ability of one of the second-generation perfluorocarbon agents (NC100100; Nycomed AS, Oslo, Norway) to identify perfusion defects in postmyocardial infarction patients. The results of this study demonstrate limitations in the ability of MCE to provide data of comparable accuracy to radionuclide scintigraphy for this application. The feasibility of obtaining high-quality images reached a maximum of 72% using the highest dose of the agent with ECG-triggered, second-harmonic imaging. These MCE recordings yielded a sensitivity and specificity of 26% and 77%, respectively, in comparison with sestamibi SPECT imaging in segments with adequate gain and quality recordings. On the basis of these findings, the authors conclude that further developments will be required to fulfill the expectations of MCE as a clinical tool.

As acknowledged by the authors, their article has numerous limitations. The study was performed by echocardiographers with little experience or expertise in MCE. It is difficult to argue that researchers inexperienced with a new technology can best define the true utility of the technique. Surgeons and interventional cardiologists would not likely be willing to assess the efficacy of their procedures based upon the outcomes of physicians performing them for the first time. The results are applicable to unprocessed images produced by only one ultrasonic contrast agent. The results may have been influenced by inherent difficulties in precisely orienting SPECT and echocardiographic tomograms to ensure comparison of identical segments. Moreover, quantitative criteria were applied to SPECT images whereas those used for echo were entirely qualitative. Finally, the low incidence of wall motion abnormalities in patients exhibiting SPECT defects calls into question the significance of the radionuclide findings.

The most significant limitation of the study by Marwick et al. (6) is the absence of a clearly defined optimal methodology by which to perform the procedure. At the current time, many questions remain unanswered regarding the best technique for MCE. It is not certain if individual microbubble preparations differ in the ability to achieve myocardial opacification, nor what is the optimal dose for these agents. Although triggered, harmonic imaging thus far appears to yield the greatest myocardial contrast intensity, it is not clear that imaging at fundamental frequencies cannot accomplish MCE. Neither
have the preferred phase (systole vs. diastole) or frequency (one, two, four, etc.) of gating of cardiac cycles been defined. At this time, nearly all experience with MCE reported has utilized gray-scale tissue imaging, but the application of power Doppler recordings may provide significantly better visualization. No agreement exists regarding the instrument settings (gain, dynamic range, etc.) that yield the highest quality images. Of particular significance, the power setting that achieves the best balance between the contrast amplitude recorded and microbubble destruction produced remains speculative. The optimal method by which to process (e.g., subtraction) and display (e.g., color encoding) the echocardiographic data after acquisition continues to be studied. Finally, controversy continues regarding the best method to quantitatively analyze contrast echo data, whereas the range of normal findings and specific criteria by which to identify abnormalities remains undefined.

Obviously, much work needs to be done before contrast echocardiography is ready for routine clinical application to assess myocardial perfusion. It therefore seems a bit premature to compare MCE with radionuclide studies in the absence of having established the optimal technique for image acquisition and processing, the range of normal findings and specific diagnostic criteria. However, unjustified though it may be, the techniques applied in the Marwick et al. (6) article are likely an accurate reflection of what soon will be occurring in clinical laboratories throughout the world.

The results of the study in this issue of the Journal are in disagreement with two earlier reports. Publications by Kaul et al. (7) and Porter et al. (8) found a good correlation of i.v. MCE and dipyridamole radionuclide imaging in patients with known or suspected coronary artery disease. As pointed out by Marwick et al. (6), these two reports emanated from individual (rather than multiple) laboratories in which experienced echocardiographers had a strong commitment to contrast echocardiography. In addition, these other studies utilized vasodilator stimulation, postprocessing of images and quantitation of videointensity. The ease with which typical echocardiography laboratories can incorporate these techniques and reproduce the results reported remains uncertain. However, the studies using dipyridamole stress MCE provides clear evidence of the ultimate potential of MCE to assess perfusion abnormalities in patients with coronary artery disease.

As has occurred before with cardiac ultrasound, the promise of deriving important new clinical data from myocardial contrast echocardiography has led to unrealistic expectations. Many clinicians have anticipated that achieving myocardial opacification by i.v. injection in animals would immediately lead to the ability to detect perfusion defects in patients. Such expectations have been encouraged by the publication of studies in humans reporting a good correlation of MCE with sestamibi SPECT. However, as evidenced by the findings of Marwick et al. (6), initial experience with intravenous MCE in humans has yielded images of lesser quality than those in animals. This experience has emphasized the necessity of defining the optimal methodology to be followed in performing, processing and interpreting MCE, issues that remain largely unsettled. A second-generation perfluorocarbon-based ultrasonic contrast agent (Optison) has recently been approved that provides excellent left ventricular cavity opacification of value in routine use today, and has the attributes to visualize abnormalities of myocardial perfusion in clinical laboratories in the future. It would be a tragedy if the inappropriate expectations for MCE led to disappointment with, and rejection of, the technique before its true clinical potential could be realized.

References