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EDITORIAL COMMENT

Myocardial Contrast Echocardiography Perfusion Imaging

Still Waiting After All These Years*

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I got tired of waiting,
Wondering if you were ever coming around.
–Taylor Swift (1)

When the history of the echo world is written, there will be a long chapter on myocardial contrast echocardiography (MCE). Conceived in the 1960s (2), refined in the 1980s (3,4,), and developed commercially in the 1990s (5), ultrasonic microbubbles have long held great promise for their ability to identify obstructive coronary artery disease. The role of ultrasound contrast agents in left ventricular opacification is well established in intensive care (6) and stress echocardiography patients (7) and is codified in guidelines (8), but it is the possibility of defining myocardial perfusion that sets echocardiographers' eyes atwinkling.

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There was a time in the mid to late 1990s when it was an article of faith that MCE would soon be daily clinical reality, threatening the existence of nuclear cardiology, with annual markets for MCE projected to be one to two billion dollars by 2000. This was based on solid physiologic research (9) and promising single-center trials (10,11), some claiming near biblical levels of accuracy (97% sensitivity and 99% specificity on territory level) (12).

Unfortunately, the salutary results of these small trials have never been replicated in the multicenter setting. An early trial in 203 post-infarct patients demonstrated at best a 31% sensitivity for identifying single-photon emission computed tomography (SPECT) perfusion defects in the 72% of segments that were even interpretable (13).

There have been two subsequent large clinical development efforts for MCE in the United States. The first, by POINT BioMedical, compared their CardioSphere microbubble to SPECT, using coronary angiography as a gold standard. The trial was very carefully done, with a company representative on-site for the imaging of every patient, and both echo and SPECT examinations were interpreted in a blinded fashion by multiple readers in core laboratories. The results of the Phase III trial have unfortunately never been published (just the Phase II trial) (14), but a contemporary presentation demonstrated MCE sensitivity ranging from 63% to 75% versus 63% to 76% for SPECT and specificity of 47% to 59% for MCE versus 53% to 76% for SPECT, failing to meet some of the noninferiority endpoints (J. Goldman and M. Main, personal communication, May, 2013). Also, the SPECT results themselves were apparently poor enough to give pause to U.S. Food and Drug Administration (FDA) reviewers. With FDA approval not forthcoming, POINT Biomedical ultimately ceased operations.

The second development effort involved 2 large Phase III trials of Acusphere's Imagify agent. The RAMP (Real-time Assessment of Myocardial Perfusion)-1 and -2 trials (15) studied a total of 662 patients, comparing MCE to SPECT, using coronary angiography as the gold standard in approximately two-thirds of the patients and clinical follow-up used in the remainder. Multiple blinded reviewers were used for both SPECT and MCE. While the overall accuracy of the MCE readers (66% to 71%) was noninferior to the SPECT results (67% to 70%), there was inconsistency among these highly trained readers, with sensitivity ranging from 50% to 77% and specificity ranging from 55% to 88%. This inconsistency led to an FDA advisory panel recommending against approval of Imagify in 2008, although development efforts apparently are ongoing.

Into this troubled landscape came the largest single multicenter study of MCE from Senior et al. (16), in this issue of the *Journal*, investigating 516 patients, each of whom underwent coronary angiography, SPECT examination, and MCE using SonoVue, a lipid-based microbubble containing sulfur hexafluoride and currently marketed in Europe by Bracco for left ventricular opacification. Both SPECT and MCE were blindly interpreted by three separate experts, while angiograms were assessed quantitatively. Overall, 31% of patients had $\geq$70% stenosis, and, in general, MCE yielded superior sensitivity (75% vs. 49%, $p < 0.0001$) to SPECT but inferior specificity (52% vs. 81%, respectively, $p < 0.0001$). Similar results were obtained in subgroup analysis (single vs. multivessel disease, prior myocardial infarction, proximal disease, 50% stenosis, and other factors). These results were based on a "majority rules" approach to the three readers, who, in general, showed only a fair degree of agreement ($\kappa = 0.37$ for MCE, 0.34 for SPECT).

How to interpret these results? The authors chose to emphasize the positive, concluding that MCE was

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significantly more sensitive than SPECT. The lower specificity was in part ascribed to what the authors implied were "false positive angiograms," whereby the perfusion defect resulted from nonvisualized microvascular disease. While there may be some merit to this argument, it would have been better supported had the investigators measured fractional flow reserve during catheterization. Longer follow-up may also show the prognostic value of these findings. The authors also emphasized the challenges of blinded test interpretation, arguing that results should improve when clinicians integrate patient information into their assessments.

Nevertheless, it is hard to view these results without pessimism. Here we are, 25+ years into commercial efforts to develop MCE, and a well-done study, conducted by the elite of European contrast investigators, yielded marginal accuracy results (63% for ≥50% stenoses, 59% for ≥70%), with little interobserver agreement among 3 highly trained readers using well-established acquisition and interpretation rules. The results for SPECT were similarly cautionary, showing poor sensitivity despite 40 years of clinical development and experience. Indeed, the evidence in all the multicenter contrast perfusion trials has shown SPECT accuracy generally less than 70%, with considerable interobserver variability. What was somewhat unusual in the current study was that SPECT sensitivity was so much lower than specificity, an observation that is not well explained.

The implications of these findings for the regulatory process may be challenging. The study clearly missed one of its primary endpoints (noninferiority of specificity for detection of ≥70% stenosis), a factor that regulatory agencies in Europe and the United States are unlikely to overlook if this trial is used to support approval. Indeed, the hurdle (and subsequent cost) of regulatory approval has risen significantly in the past 2 decades, with few new imaging agents approved (17,18). Recent guidance from the FDA (19) indicates that the regulatory bar has been raised well beyond the simple diagnostic hurdle used decades ago for thallium and technetium sestamibi: "We [FDA] recommend that a medical imaging agent…be able to improve patient management decisions…or improve patient outcomes…." This is a far higher standard than that which was in place 5 decades ago when thallium-201 was undergoing FDA scrutiny. Indeed, when New England Nuclear obtained approval in 1977, it was for simple diagnosis and localization of myocardial infarction (not ischemia), based largely on patients with fixed perfusion defects.(20) One cannot help but wonder how these long-standing nuclear agents would fare in today's regulatory environment.

How might accuracy be improved in a subsequent MCE trial? It starts with the microbubble itself, which must be predictably destroyed by high mechanical index (MI) ultrasound but provide stable, high signal-to-noise ratio across a wide range of lower intensity imaging, properties that depend critically on the bubble shell (21). Attenuation can play havoc with assessment of the base of the heart, but quantitative analysis and integration of wall motion into the interpretation might help with this. Finally, adjusting the infusion based on weight and degree of opacification could provide more predictable imaging properties.

At the end of the day, however, it is worth recalling the prophetic words of a 15-year-old editorial (22) accompanying one of the first multicenter MCE trials (13): "the history of contrast echocardiography has been characterized by cycles of enormous expectations and subsequent disappointment." These swings of emotion may have been reduced in amplitude since then, as expectations are dampened with every unsuccessful effort, but it is hard not to see the MCE story as the echocardiographic equivalent of Groundhog Day.

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REFERENCES

1. Swift T. Love Story. Sony/ATV Tree and Taylor Swift Music; 2008.
2. Gramiak R, Shah PM, Kramer DH. Ultrasound cardiography: contrast studies in anatomy and function. Radiology 1969;92:939–48.
3. Keller MW, Feinstein SB, Watson DD. Successful left ventricular opacification following peripheral venous injection of sonicated contrast agent: an experimental evaluation. Am Heart J 1987;114:570–5.
4. Feinstein SB, Cheirif J, Ten Cate FJ, et al. Safety and efficacy of a new transpulmonary ultrasound contrast agent: initial multicenter clinical results. J Am Coll Cardiol 1990;16:316–24.
5. Lindner JR, Dent JM, Moos SP, Jayaweera AR, Kaul S. Enhancement of left ventricular cavity opacification by harmonic imaging after venous injection of Albunex. Am J Cardiol 1997;79:1657–62.
6. Reilly JP, Tunick PA, Timmermans RJ, Stein B, Rosenzweig BP, Kronzon I. Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients. J Am Coll Cardiol 2000;35:485–90.
7. Plana JC, Mikati IA, Dokainish H, et al. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. J Am Coll Cardiol Img 2008;1:145–52.
8. Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. J Am Soc Echocardiogr 2008;21:1179–201; quiz 1281.
9. Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998;97:473–83.
10. Shimoni S, Zoghbi WA, Xie F, et al. Real-time assessment of myocardial perfusion and wall motion during bicycle and treadmill exercise echocardiography: comparison with single photon emission computed tomography. J Am Coll Cardiol 2001;37:741–7.
11. Elhendy A, O'Leary EL, Xie F, McGrain AC, Anderson JR, Porter TR. Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease. J Am Coll Cardiol 2004;44:2185–91.
12. Morcerf F, Moraes A, Carrinho M, Dohmann HJ. Study of coronary flow reserve with intravenous use of microbubbles (contrast echocardiography) and adenosine: protocol for clinical application in patients suspected of having coronary heart disease. Arquivos Brasileiros de Cardiologia 2002;78:281–98.

13. Marwick TH, Brunken R, Meland N, et al. Accuracy and feasibility of contrast echocardiography for detection of perfusion defects in routine practice: comparison with wall motion and technetium-99m sestamibi single-photon emission computed tomography. The Nycomed NC100100 Investigators. J Am Coll Cardiol 1998;32:1260–9.
14. Wei K, Crouse L, Weiss J, et al. Comparison of usefulness of dipyridamole stress myocardial contrast echocardiography to technetium-99m sestamibi single-photon emission computed tomography for detection of coronary artery disease (PB127 Multicenter Phase 2 Trial results). Am J Cardiol 2003;91:1293–8.
15. Senior R, Monaghan M, Main ML, et al. Detection of coronary artery disease with perfusion stress echocardiography using a novel ultrasound imaging agent: two Phase 3 international trials in comparison with radionuclide perfusion imaging. Eur J Echocardiogr 2009;10:26–35.
16. Senior R, Moreo A, Gaibazzi N, et al. Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial echocardiography with gated single-photon emission computed tomography for the detection of significant coronary artery disease: a large European multicenter study. J Am Coll Cardiol 2013;62:1353–61.
17. Sinusas AJ, Thomas JD, Mills G. The future of molecular imaging. J Am Coll Cardiol Img 2011;4:799–806.
18. Nunn AD. The cost of developing imaging agents for routine clinical use. Invest Radiol 2006;41:206–12.
19. U.S. Food and Drug Administration. Guidance for Industry: Developing Medical Imaging Drug and Biological Products. Part 2: Clinical Indications. 2004. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf. Accessed July 10, 2009.
20. Wagner HN. A Personal History of Nuclear Medicine. London, United Kingdom: Springer; 2006:189.
21. Leong-Poi H, Song J, Rim SJ, Christiansen J, Kaul S, Lindner JR. Influence of microbubble shell properties on ultrasound signal: implications for low-power perfusion imaging. J Am Soc Echocardiogr 2002;15:1269–76.
22. DeMaria AN, Cotter B, Ohmori K. Myocardial contrast echocardiography: too much, too soon? J Am Coll Cardiol 1998;32:1270–1.

Key Words: contrast echocardiography ■ ischemia ■ SonoVue.