INVITED COMMENTARY

How Accurate Is Quantitative Gated SPECT?

Few clinicians would dispute the importance of knowing both the perfusion status and the left ventricular function of patients with various coronary artery disease syndromes. In the setting of stable and unstable coronary artery disease, knowledge of left ventricular function (usually as ejection fraction) has important management implications, because different outcomes have been shown after mechanical revascularization versus medical therapy (*1,2*). Moreover, the widely acknowledged clinical relevance of these parameters is supported by studies showing the statistically incremental prognostic value afforded by knowledge of left ventricular function even when perfusion status is known, particularly after myocardial infarction (*3*).

The powerful clinical management implications of combined knowledge of myocardial perfusion and left ventricular function are a factor underlying the rapid growth and diffusion of gated SPECT technology in nuclear cardiology laboratories. This growth has also been facilitated by the now widespread availability of multidetector camera systems allowing uniformly good count statistics in SPECT studies and by software such as the easy-to-use quantitative gated SPECT (QGS) program (Cedars-Sinai Medical Center, Los Angeles, CA) (*4–6*) and the Emory Cardiac Toolbox (Emory University, Atlanta, GA). The coupling of the imaging hardware and software to more powerful microprocessors has made the everyday use of these software programs routine in most laboratories. Besides providing clinicians with clinically relevant information on both perfusion and function, the incorporation of gated SPECT information into the imaging analysis increases specificity for ruling out coronary disease by improving recognition of attenuation artifacts (*7*).

To our knowledge, a formal analysis of the cost-effectiveness of incorporating gated SPECT perfusion imaging routinely into imaging protocols has not been reported. However, the cost of performing, analyzing, and interpreting gated SPECT in conjunction with standard perfusion imaging should be relatively modest, in comparison with an entirely separate analysis of left ventricular function by radionuclide ventriculography or echocardiography. If we accept the importance of left ventricular functional information in deriving a management strategy for patients, the cost-effectiveness of gated SPECT is a reasonable assumption.

How accurate are gated SPECT measurements of ejection fraction and left ventricular volume? To some degree, the answer may be influenced by many variables, including the gold standard against which gated SPECT is measured and the accuracy, repeatability, and reproducibility of that gold standard. How does one determine accuracy with the greatest statistical precision? As reviewed by Germano and Berman (*8*), by the middle of 1998 more than 20 studies had been published on the correlation between quantitative measurements obtained through gated SPECT perfusion imaging (using various algorithms) and through other measures of left ventricular ejection fraction (LVEF). The studies used different gold standards, some quite quantitative and reproducible (such as first-pass RNA or radionuclide ventriculography) and others less so (such as 2-dimensional echocardiography and thermodilution techniques). Some of these reports were published in full in peer review journals, and the remainder were published as abstracts. Most concerned the use of ^{99m}Tc-based agents, but at least 4 involved ^{201}Tl-based protocols. The analysis of most of the studies focused on the Spearman correlation coefficient, which averaged 0.87 (*8*). Virtually all the studies concluded that estimates of LVEF obtained through gated SPECT were accurate compared with the gold standards. However, not all the reports provided information on variability around the reported correlation line, such as the SEE, which indicates the likelihood that the ejection fraction measured by the new technique will be within a certain range of the ejection fraction measured by the gold standard. In some studies in which this variability was reported, the gated SPECT ejection fraction could be assumed to be between 5% and 10% of the gold standard, a fairly large range. In others, however, the SEE was relatively small, indicating more reliable data. Few of the analyses reported data on agreement between techniques using Bland-Altman plotting (*8*), which more precisely determines agreement between 2 techniques measuring the same parameter and examines nonrandom variability across the range of values measured.

The choice of gold standard in these studies should strongly influence interpretation of the data. Comparing a quantitative, predominantly operator-independent methodology such as QGS (*8,9*) with a technique such as 2-dimensional echocardiography (*10,11*), which has significant operator interaction as well as significant variability, creates problems in determining the value of the new technique. More recently, studies comparing gated SPECT with MRI have begun to emerge (*12,13*).

Several issues relevant to everyday clinical imaging have not been fully addressed by many of these studies correlating gated SPECT ejection fraction with other techniques. These issues include the influence of a stress

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For correspondence or reprints contact: James E. Udelson, MD, Division of Cardiology, New England Medical Center, Box 70, 750 Washington St., Boston, MA 02111.

perfusion defect on the (usually poststress) gated SPECT calculation of ejection fraction, as well as the influence of varying degrees of extracardiac background activity on the accuracy of the method. In most of the reported studies, data from large numbers of patients with both normal and abnormal stress perfusion are combined to examine the correlation, but few studies have focused on patients with abnormal stress perfusion. Johnson et al. (*14*) reported that the poststress ejection fraction may be significantly lower (by more than 5%) than the gated SPECT ejection fraction derived from a separate resting perfusion study in a considerable minority of patients. These patients generally had substantial stress perfusion abnormalities, raising the possibility that the diminished poststress ejection fraction relative to the resting ejection fraction may represent postischemic stunning. As pointed out by Bonow (*15*), however, the quantitative border detection algorithms used in programs such as QGS may not be as accurate in detecting endocardial borders near significant stress perfusion defects. This possibility exists even though the algorithm is seeking count distribution profiles that are not necessarily visible to the naked eye (*16*). Williams and Taillon (*17*) used image inversion to better detect the true borders in the territory of a perfusion defect, but this methodology is not widely available.

The accuracy, repeatability, and reproducibility of the widely used QGS program are critically examined in an important study by Vallejo et al. (*18*) in this issue of *The Journal of Nuclear Medicine*. They examined the effect of injected dose, timing of imaging, extent and magnitude of background activity, and presence or absence of a perfusion defect on the accuracy of QGS measurements of LVEF and volumes relative to quantitative MRI measurements in a dog model. They found, as others have (*8*), that the QGS method is extremely reproducible when the algorithm is applied twice to the same image set, as would be expected for a fully automated algorithm. However, count statistics strongly influenced repeatability when the algorithm was applied to 2 sequentially acquired images. The correlation coefficient between the sequentially measured LVEFs during a 30-min interval was significantly better after a high-dose sestamibi rest study than after a low-dose adenosine stress study.

Background activity also had a strong influence. Repeatability of measurements during a 30-min interval was poor in studies in which the background activity was considered excessive but very good in studies with minimal extracardiac background counts. Generally, left ventricular volumes and particularly LVEF were overestimated by the QGS algorithm compared with MRI. This overestimation was particularly profound among the animals with a perfusion defect imposed by occlusion of the left anterior descending artery. The authors concluded that although the QGS software provides a highly reproducible estimate of LVEF, the background activity has a strong influence (which in part would relate to the time of imaging after injection), as do the injected dose and the presence of a perfusion defect.

These provocative results raise questions. How can we reconcile the results with the many reports in humans on the accuracy of gated SPECT algorithms in determining ejection fraction and volumes? Do the results undermine the general usefulness of applying QGS results in everyday practice?

The apparent discordance has several potential explanations. The first is the choice of gold standard. In the study of Vallejo et al. (*18*), careful quantitative measurements from cine MRI were used. As the authors pointed out, this technique has distinct potential advantages over almost all other techniques for accurate determination of LVEF and volumes. The technique is truly 3-dimensional, structures are completely separated, full interrogation of the entire left ventricular chamber is possible, attenuation is not an issue, and no geometric assumptions are needed because the high spatial resolution of the study allows a reasonably accurate endocardial border definition. Not all of the few previous studies comparing QGS in humans with MRI measurements have used similarly rigorous methodology for evaluation of the MRI studies (*12,13*). The use of this methodology as the gold standard would tend to magnify any inaccuracies in the commercially available QGS system, particularly in a study with relatively few data points. Larger studies that involve gold standards with their own inherent inaccuracies (even first-pass RNA and radionuclide ventriculography) may tend to homogenize such differences, particularly when examined over large numbers of patients using correlation analysis.

Another factor in the apparent diminution of QGS accuracy in this setting is the size of the hearts. Other investigators have reported that in small hearts, the relatively limited spatial resolution of SPECT makes endocardial border definition at end-systole problematic, leading to overestimation of LVEF (*19*). Different filtering algorithms may be an approach to this problem (*20*). In addition, count-based recognition methods rather than border detection methods may obviate these discordances in small hearts (*21*). The size of the ventricular cavity in the dog model of Vallejo et al. (*18*) favors measurements by the technique with the higher spatial resolution.

Do the results of this study undermine the general usefulness of QGS estimates of ejection fraction in routine imaging studies? Perhaps among the most important findings of the study of Vallejo et al. (*18*) is the critical importance of minimizing extracardiac background activity. In studies of resting perfusion, vasodilator pharmacologic stress, and submaximal exercise stress, hepatic uptake may be excessive, as, in some cases, may large-bowel activity adjacent to the myocardium. In addition to affecting the accuracy of the automated QGS program, these foci of extracardiac activity can also affect the summed perfusion imaging data and can confound all quantitative analysis programs. As Germano et al. (*22*) reported, excessive hepatic uptake rela-

tive to cardiac uptake may cause visually apparent artifactual perfusion defects. Hence, the study of Vallejo et al. further emphasizes the importance of optimizing the image acquisition parameters to minimize extracardiac activity. This process often will prolong the waiting time between injection and imaging and requires knowledgeable technologists who can recognize excessive extracardiac activity early, stop the acquisition, and restart it when the ratio of cardiac activity to background activity is better.

The effect of a perfusion defect on the accuracy of QGS measurements of ejection fraction and volume has never, to our knowledge, been examined as closely as in the study of Vallejo et al. (*18*). The data at hand still do not allow us to determine whether the discordance between rest and poststress LVEF that some studies reported truly represents prolonged postischemic dysfunction (stunning) or is a problem with border recognition by the automated algorithm. The study of Vallejo et al. was not designed to examine this issue. The study does, however, raise some caveats about whether geometry-based measurements with assumptions about left ventricular shape are appropriate in studies of the accuracy of ejection fraction measurements in the presence of a perfusion defect. Determining whether the poststress LVEF (which, in the setting of inducible ischemia, is calculated in the presence of a perfusion defect) accurately reflects the resting ejection fraction and provides clinically relevant information requires prospective examination of its relationship to clinically relevant outcomes. In that regard, Sharir et al. (*23*) recently reported that poststress LVEF derived from QGS has incremental value in predicting outcomes beyond those provided by perfusion data, suggesting that even in the presence of perfusion defects, poststress ejection fraction is a clinically useful parameter. Whether it is more useful than the resting ejection fraction or than the difference between the resting and poststress ejection fraction remains to be determined.

The next step in determining how widely applicable the implications of the data of Vallejo et al. (*18*) are to clinical practice would be to repeat the comparison using similarly robust cine MRI measurements in humans, who have generally larger hearts, with and without perfusion defects. We need to examine whether count-based gated SPECT ejection fraction methodologies are significantly better than border detection methodologies in determining LVEF in a perfusion defect setting. Also needed is an examination of the influence of extracardiac activity and a comparison with gold-standard, state-of-the-art cine MRI measurement in humans. Such studies would go a long way toward resolving some of the issues raised by the study of Vallejo et al.

Nonetheless, the importance of incorporating information on left ventricular function into management decisions for patients with myocardial perfusion abnormalities is widely accepted, and clinicians have embraced the information provided by gated SPECT and the commercially available software algorithms. Indeed, a position statement by the American Society of Nuclear Cardiology recommends that gated SPECT be routinely incorporated in all perfusion imaging acquisitions (*24*). The study by Vallejo et al. (*18*) highlights the importance of quality control during perfusion and gated SPECT image acquisition, particularly the adequacy of count statistics and the minimization of extracardiac activity. Future studies should critically examine comparisons of gated SPECT methodologies that interrogate and quantitate function from perfusion images. Using advanced MRI technology as a gold standard, we need to determine the degree to which extracardiac activity and perfusion defects influence each algorithm. While we await such studies, however, attention to quality control and image optimization remains essential for both perfusion and functional analyses and should allow the continued widespread use and clinical applicability of information from gated SPECT perfusion imaging. The user-friendliness and general accuracy of software programs such as QGS have fueled the rapid growth of adjunct gated SPECT in many laboratories and have been significant developments in the field of nuclear cardiology. This ease of use and general accuracy as reported in many studies should not, however, preclude critical evaluation of limitations of this or any other program. Users should routinely appreciate the potential limitations, as illustrated in the study of Vallejo et al., and methods to overcome those limitations. Of course, this approach is similar to that taken with commercially available quantitative analysis programs for standard perfusion imaging, which are also affected by count statistics and extracardiac activity. As in visual interpretation, optimal use of any quantitative program requires an experienced operator and reader and meticulous attention to quality control. With that requirement met, use of QGS to acquire clinically relevant information that cost-effectively optimizes patient care is likely to become widespread.

James E. Udelson
Maan A. Fares
New England Medical Center Hospitals
Tufts University School of Medicine
Boston, Massachusetts

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