EDITORIAL

On the Accuracy and Reproducibility of Quantitative Gated Myocardial Perfusion SPECT

The use of electrocardiographic gating in conjunction with myocardial perfusion SPECT imaging has increased so much over the past 5 y that gated myocardial perfusion SPECT has become accepted as routine.

Gated myocardial perfusion SPECT is especially well suited to addressing the concerns in the era of health care reform: In essence, it allows nuclear cardiologists to simultaneously assess cardiac perfusion and function at only minor extra cost or inconvenience compared with standard perfusion assessment. This capability can be used to improve perfusion SPECT imaging sensitivity for the detection of nonischemic coronary artery disease (CAD) and specificity for the detection of ischemic CAD (by easier recognition of artifacts [*1,2*]), as well as to provide incremental prognostic information used to risk stratify patients with known CAD (*3*).

The diffusion of gated SPECT has been greatly facilitated by the development, validation and dissemination of several algorithms for the measurement of quantitative global or regional cardiac function from gated SPECT images (*4–15*). Quantitative gated SPECT (QGS), which was developed by Germano et al. (*4*), is a widely validated (*4,16–29*) and commonly applied (used on more than 4000 systems) approach to the automatic, three-dimensional quantification of left ventricular ejection fraction (LVEF), left ventricular (LV) cavity volumes and segmental myocardial wall motion and thickening. In this issue of *The Journal of Nuclear Medicine*, Manrique et al. (*30*) present an example of validation of QGS against a planar blood-pool (equilibrium radionuclide angiography [ERNA]) standard, using both ^{201}Tl and ^{99m}Tc-sestamibi gated SPECT in patients with large perfusion defects and ventricular dysfunction. These patients represent a group increasingly targeted by medical therapeutic approaches (*31–33*) and, consequently, it is clearly desirable to monitor this group for the effect of therapy on cardiac function accurately and reliably. Focusing the study on this patient cohort is a rigorous test of the QGS method because it investigates the accuracy of an algorithm based on endocardial detection in patients whose perfusion defects prevent large portions of the myocardium from being "seen."

Manrique et al. (*30*) conclude that quantitative measurements of LVEF by gated SPECT are less accurate and less precise than equivalent measurements by ERNA and that the latter technique should be preferred in serial prognostic evaluations. We strongly disagree with their conclusion, and we can demonstrate that a vast body of evidence, including the data in their own article, does not support their conclusion.

ACCURACY

The basic contention that QGS lacks accuracy because it underestimates LVEF in the presence of large perfusion defects is, itself, inaccurate. If it were correct, it would be logical to expect the underestimation to depend on the extent and severity of the defect, although Manrique et al. (*30*) found that "the LVEF underestimation with gated SPECT was not correlated either to the defect size evaluated by polar map or to the severity of hypoperfusion on the basis of perfusion defect score." Moreover, the authors report that "there was no significant variation of LVEF underestimation whether dyskinesia was observed on ERNA," and that "no increasing underestimation with the gated SPECT method was found as the mean ejection fraction increased." The overall 5% underestimation reported by the authors for QGS-measured LVEF compared with ERNA LVEF is, in fact, consistent with 8-frame gating. As described by Germano et al. (*4*), 8-frame gated SPECT LVEFs measured by QGS are, on average, 4% lower than 16-frame gated SPECT LVEFs measured by the same algorithm in the same patients, and this underestimation is quite uniform over a wide range of LVEF (10%–80%). Manrique et al. present this finding in the Discussion section of their article but fail to point out that the underestimation would likely become statistically insignificant were four LVEF points systematically added to the 8-frame gated SPECT measurements. Of course, 16-frame gated SPECT could have also been performed and would have resulted in a better test of accuracy and a fairer comparison with the ERNA standard. (Manrique et al. [*34*] appear to have reached this very conclusion in a recent article.)

Manrique et al. (*30*) speculate that "one would expect (the underestimation) to increase as LVEF increases," even though that assumption is supported neither by their data nor by specific Bland-Altman analysis performed by Germano et al. (*4*). The only report that supports this effect is not based on the QGS algorithm (*15*). In fact, the accuracy of gated SPECT LVEF measurements by QGS, as well as by other quantitative algorithms, has been reported by several investigators to be excellent, even in the setting of

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prior myocardial infarction or large perfusion defects (*18,25,35–38*). We would like to explain why QGS is not significantly affected by the apparent "absence" of perfusion in large portions of the myocardium and offer a means for the reader to verify our interpretation. Although it may not be apparent on cursory visual analysis, there are generally some counts even in the most depleted areas of the myocardium. This may be due to (a) the fact that an infarct is not transmural or there is subendocardial ischemia (both cases exacerbate the effect of the partial volume effect, bringing what few counts exist down to background level) or (b) the fact that, with filtered backprojection (still the most popular way to generate tomographic datasets from projections), all pixel activities are correlated to some extent. In either case, myocardial radioactivity frequently exists and can be detected if no thresholding is used. By virtue of its preanalysis segmentation of the myocardium, QGS automatically determines the "limits of search" for endocardial and epicardial surfaces and need not use thresholding in the subsequent edge-detection phase (Fig. 1). "Saturating" the gray scale to allocate all gray levels to the lowest activity portions of the image allows determination that there is indeed some myocardial perfusion in the defect area (up to 5% of the maximum count pixel level) and that its distribution is closely tracked by the automatically generated contours. This procedure, which is best accomplished using a color scale, is recommended whenever contour accuracy in the defect areas is in question. Because of the continuity constraints imposed by QGS in its analysis, it is expected that some large aneurisms would be "cut off," matching their suboptimal visualization using gated SPECT, but these occurrences are infrequent and the error introduced is generally small.

REPRODUCIBILITY

The position taken by Manrique et al. (*30*) that the reproducibility of LVEF measurements from gated SPECT is inadequate is difficult to accept, especially in light of their own reported 94% (47/50) automatic success rate using the QGS algorithm. This value is in line with previous reports, which describe success rates of 95% (*18*) to 100% (*4,39*). Manrique et al. report "an operator disagreement with the software determination of valve plane" in three patients, leading to the need for manual correction. Although particularly high extracardiac uptake has been reported to occasionally cause "pulling" of the automatically generated contours in the basal region of the LV (*4*), recent data suggest that this phenomenon may be obviated by a larger reconstruction zoom postacquisition (*40*).

Perhaps more importantly, Manrique et al. (*30*) include the manual reorientation of transaxial images in their computation of gated SPECT reproducibility. This is misleading because a large percentage of all gamma cameras on the market provide automatic reorientation of SPECT images, based on algorithms developed either by our group (*41,42*) or by others (*43,44*). The camera used by Manrique et al., for example, should have access to the algorithm developed by Cauvin et al. (*43*). If gated SPECT using automatic reorientation and function analysis had been compared with ERNA, including background subtraction and function analysis, better reproducibility would have been shown. This is difficult to prove conclusively, because no details are given in the article as to the blood-pool algorithm's operation, degree of automation or validation of accuracy. Still, it is reasonable to expect a totally automatic, three-dimensional gated SPECT algorithm that does not require background subtraction to outperform a two-dimensional algorithm. The reproducibility of ERNA measurements of LV volumes is generally thought to be so poor (*45*) that provision of such measurements is uncommon in routine clinical reporting of gated blood-pool scintigraphy (*46*). Regarding ERNA LVEF measurements, other investigators have pointed out that "...background accounts for 35%–60% of total counts in equilibrium studies. Therefore, inconsistencies in background determination can result in relatively large

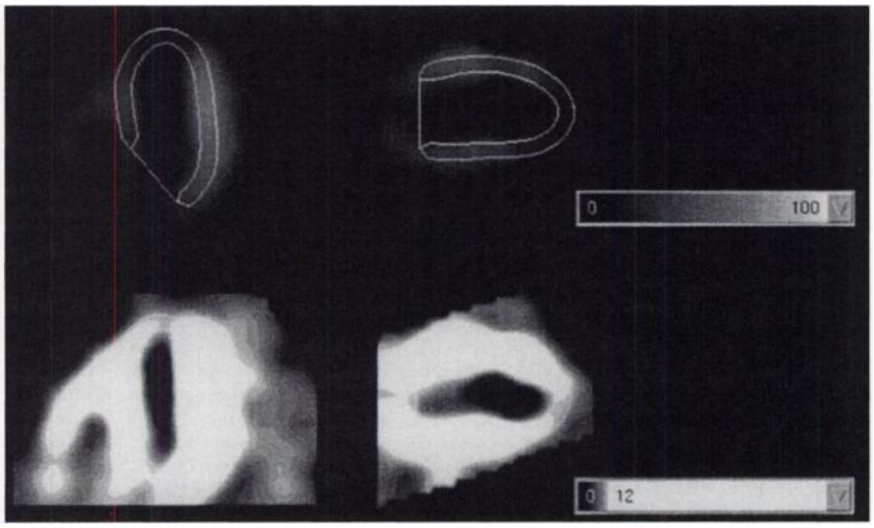

FIGURE 1. Long-axis images of patient with large anterior descending territory defect, with QGS-derived contours in apparent absence of perfusion (top). "Saturating" display scan is practical way to verify accuracy of contour location (bottom).

variations in ejection fraction..." (*47*). Conversely, any completely automatic algorithm like QGS is, by definition, perfectly reproducible. Most published reports on QGS investigate its repeatability, which is a much more stringent measure of agreement. Reproducibility examines the agreement of measured values obtained by applying an algorithm twice to the same dataset, whereas repeatability compares values obtained by applying an algorithm to separately acquired datasets, with all the physiologic and acquisition-related variables involved. Repeatability of QGS-derived measurements has been found to be extremely high with respect to LVEF (*48–50*) and LV volumes (*46,50*).

Manrique et al. (*30*) do make some important points that ought to be of comfort to the practitioner using QGS, namely, the 94% automatic quantification success rate, the independence of the LVEF measurements from (a) the type of agent used (^{201}Tl or ^{99m}Tc-sestamibi), (b) the perfusion defect size or severity and (c) whether "the mitral valve plane is involved." This flexibility and robustness, together with its accuracy and reproducibility, make gated SPECT quantification ideal for serial imaging of patients undergoing therapy or for monitoring of remodeling, as underscored by some initial reports published in abstract form (*51–53*). More applications in this field are sure to follow.

CONCLUSION

Although ERNA is an important and historically critical part of nuclear cardiology, it will likely be replaced by gated blood-pool SPECT (*54*) and gated perfusion SPECT imaging. We should not be afraid of these developments, because they give us better tools to use in the increasingly competitive field of clinical medicine. There are, of course, some areas of gated SPECT that need our attention; for example, we need to develop standardized quality-control tools to gauge the presence and influence of gating abnormalities and to develop automatic methods for analyzing regional ventricular function. The availability of accurate and reproducible quantification, however, is one of the brightest and most advantageous features of the gated myocardial perfusion SPECT technique and one that is likely to continue to fuel its broad acceptance.

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