It's not all in the numbers

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Quantitative analysis is an integral part of nuclear cardiology. It is a major strength and a key advantage that separates this technique from other noninvasive imaging methods. Nuclear cardiology is “inherently quantitative” in that image displays depict the number of counts detected by a gamma camera, reflecting the amount of radiotracer in the entity being imaged.

Perhaps the earliest use of quantitative measurements was by Parker et al who, in contrast to a previously reported geometric method,¹ measured background corrected ^{99m}Tc-labeled human serum albumin ventricular blood pool counts from electrocardiographically gated end-diastolic and end-systolic digital planar left anterior oblique images to derive a counts-based left ventricular ejection fraction (LVEF).² Shortly after the introduction of thallium-201 (²⁰¹Tl) for myocardial perfusion imaging (MPI),^{3,4} efforts to apply quantitation began.⁵ As the clinical potential of MPI became recognized,⁶ methods to quantitate visual regional tracer uptake were developed. While a multiple slice profile method was considered,^{7,8} circumferential count profile techniques became preferred.^{9–11} Building on these, Garcia et al developed a comprehensive computerized space/time quantitation method.¹² After applying proximity weighted interpolative background subtraction, for each of three standard planar views, 60 6° spaced interval radii originating from the visually determined center of the ventricle were created, with maximal ventricular wall counts along each radius plotted as a function of angular

coordinates aligned in reference to the apex, normalized to the maximum value. Portions of profiles from patients with suspected disease that were >2 standard deviations (SD) below “normal” patient (<1% likelihood of coronary disease¹³) means were considered abnormal. It was recognized from the outset that profile curves were representations of relative rather than absolute tracer uptake, thus limited in the ability to detect balanced flow reduction.

The advent of single photon emission computer tomography (SPECT) prompted efforts to quantitate three-dimensional distribution of radiotracer, with generation of two-dimensional polar coordinate maps (i.e., “bullseye” displays), thereby enhancing conceptualization of defect distribution and percentages (%) of abnormal myocardium.^{14,15} Maximal count normalized circumferential profiles were generated from short-axis (SA) slices from the most apical to most basal cuts (analogous to the planar technique), but also from the apical profiles (60°–120°) of the vertical long-axis (VLA) slices to be placed at the center of the plot to represent the apex, with the SA profiles mapped as increasingly larger circles toward the base. Similar to planar techniques, data from low CAD likelihood cases were used such that patient counts >2.5 SD below the mean were considered abnormal. Sophistication increased after the advent of technetium-99m (^{99m}Tc) tracers in that geometric methods were modified such that sampling of SA slices used cylindrical coordinates and sampling of the apical region used spherical coordinates, ensuring perpendicular myocardial radial sampling at all points to more accurately measure tracer distribution.¹⁶ With availability of increased computer power, Germano et al developed an alternative algorithm that replaced circumferential profiles with true three-dimensional sampling, and with the generated sampling rays assessed counts through the entire myocardial thickness from endocardial to epicardial surface (“whole myocardium sampling”), rather than using only maximal counts.^{17,18} A total perfusion defect (TPD) parameter were derived, designed to combine

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measures of defect extent, and severity based on counts in each polar map pixel relative to limits from low-likelihood patients, expressed as a % of the myocardium, with the TPD difference between stress and rest images quantitating ischemia.¹⁹

The aforementioned is the basis for a variety of contemporary quantitative techniques routinely applied to enhance SPECT MPI image interpretation.²⁰ Compared with visual assessment alone, quantitation improves interpretive reproducibility.^{21,22} Robust diagnostic accuracy is consistently shown,^{15,23,24} with some studies reporting higher accuracy than visual analysis.^{19,25} Quantitation should improve risk stratification, although there are few publications to date in this regard.^{26,27} Nonetheless, TPD was used to measure progression or regression of myocardial ischemia in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,²⁸ and is an important element of the multicenter prospective randomized ISCHEMIA study (The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) that uses a TPD ischemia score $\geq 10\%$ as one inclusion criteria to assess invasive vs optimal medical therapy.²⁹

While MPI remains the most widely used cardiac radiotracer imaging modality, another important strength of nuclear cardiology is its ability to image physiologic processes other than perfusion. Quantitative uptake of ²⁰¹Tl and ^{99m}Tc-based “perfusion” tracers for assessment of the ability of cardiomyocytes to take up and retain tracer has been used for diagnosis and decision making related to myocardial viability.^{30,31} Examination of cardiomyocyte metabolism using 18-fluorodeoxyglucose (¹⁸FDG) relies heavily on quantitative techniques. The Positron Emission Tomography and Recovery following Revascularization (PARR) Trials studying patients with ischemic LV dysfunction used sophisticated geometric and count measurement techniques to assess N-13 ammonia (¹³NH₃) perfusion and ¹⁸FDG metabolic uptake, deriving a mismatch score (extent and severity of hibernating myocardium) and a “scar” score as percentages of the myocardium.^{32–34} These values were essential in the PARR-1 trial’s derivation of variables predictive of change in LV function,³⁵ and were used in PARR-2 to examine utility of PET viability imaging for guidance of patient management.^{36,37}

A nuclear cardiology technique studied for many years, but only recently gaining clinical interest in the US, is assessment of cardiac sympathetic adrenergic innervation using analogs of the sympathetic mediator norepinephrine, mostly the SPECT tracer iodine 123 *meta*-iodobenzylguanidine (¹²³I-*m*IBG), but also PET tracers such as C-11 hydroxyephedrine (¹¹C-HED).^{38,39} Soon after the initial report of human cardiac imaging

with ¹²³I-*m*IBG,⁴⁰ the first systematic study of patients with cardiac disease proposed use of a quantitative heart to mediastinal ratio (HMR) on an anterior planar image, and showed correlation of HMR with LVEF in patients with cardiomyopathy.⁴¹ Shortly thereafter, the first study showing prognostic utility of ¹²³I-*m*IBG imaging in advanced heart failure (HF) analyzed ¹²³I-*m*IBG images in terms of the quantitative HMR, finding this value to be more “potent” than other parameters, including LVEF, in predicting death.⁴² Subsequent reports all relied on the planar HMR in predicting outcome,⁴³ culminating in the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study that risk stratified HF patients in relation to an HMR of 1.6.⁴⁴

Nevertheless, although the planar HMR is the essence of much current ¹²³I-*m*IBG imaging, considered by some as akin to a biomarker, the utility of tomographic imaging has been unclear. Theoretically, identification of regional defects, especially in areas of preserved perfusion, should identify patients at risk of electrical instability and thus lethal arrhythmias.^{45–47} The need for tomographic imaging is suggested by a recent analysis reporting that planar HMR, although a strong predictor of all-cause mortality, cardiac mortality, and eventual need for heart transplant, likely does not provide enough contrast and 3D detail for highly accurate prediction of arrhythmic events.⁴⁸ Small cohort studies using semiquantitative visual scoring techniques suggest clinical utility for SPECT ¹²³I-*m*IBG in assessing arrhythmic risk,^{49–57} but utility in a large trial has not been established.⁴⁴ For PET adrenergic imaging, the recent “Prediction of ARrhythmic Events with Positron Emission Tomography” (PARAPET) trial of tomographic imaging with ¹³NH₃, ¹⁸FDG, and ¹¹C-HED in 200 patients with ischemic cardiomyopathy used rigorous quantitative techniques for assessing perfusion, cardiomyocyte metabolism, and adrenergic innervation, finding that an increase in the extent/severity of ¹¹C-HED defects was independently associated with higher arrhythmic risk.⁵⁸ However, because ¹¹C-HED is impractical for most practitioners, development of a robust method for quantitation of SPECT ¹²³I-*m*IBG is warranted.

In this issue of the Journal, Clements et al report development of a quantitative technique for assessing SPECT ¹²³I-*m*IBG images⁵⁹ that they tested on images of a 938 patient subset of HF patients⁴⁴ in reference to 40 patient age-matched controls who were enrolled in the ADMIRE-HF trial.⁶⁰ SPECT processing was skillfully performed with iterative reconstruction that included the deconvolution of septal penetration algorithm developed by several of the authors to account for high-energy collimator-penetrating ¹²³I photons.⁶¹ Voxel count determination used geometric and myocardial sampling techniques previously reported by

Van Train et al and Garcia et al for MPI.^{16,23,62} The authors, however, recognize unique challenges of adrenergic tomographic imaging which is in many ways conceptually different from perfusion imaging. Among these is that while for MPI there are almost always regions with normal perfusion that can serve as a reference to which count profiles are normalized, for ¹²³I-*m*IBG images globally reduced tracer uptake occurs often, more so for patients with HF. Thus the authors designed a “mixed reference” method in which classifying a region as “abnormal” (referred to as “dysinnervation”) varied in relation to global tracer uptake measured by the HMR, with this approach helping to overcome an underestimation of abnormality in patients with severe global dysinnervation.

Another challenge is that unlike for MPI in which validity and accuracy of a methodology is customarily assessed in reference to “gold standard” coronary anatomy findings (as flawed as that can be), there is no such standard upon which to assess adrenergic imaging techniques. The authors therefore used comparison of quantitative results in patients with ischemic vs non-ischemic heart failure (IHF vs NIHF) as the testing reference, and propose their finding of significantly more severe quantitative dysinnervation in IHF patients to be an initial validation of their methodology. While the approach is reasonable,⁶³ perfusion findings can significantly overlap in ischemic and non-ischemic cardiomyopathies (CM).^{64,65} In addition, extrapolating perfusion image phenomena to adrenergic imaging is an unproven assumption.

With ¹²³I-*m*IBG imaging, lung and liver tracer uptake overlying myocardial walls can make SPECT images difficult to interpret completely, and one would expect impairment of quantitative analysis. The authors recognize this limitation that resulted in frequent need to manually identify the LV region of interest, but report that only 8 of 949 images (<1%) were not analyzable. However, it has been this writer’s experience that in only about 80% of SPECT ¹²³I-*m*IBG images can all segments be confidently scored,⁶⁶ in accord with a study using a solid-state camera that reported only 85% of SPECT ¹²³I-*m*IBG images to be of good or better quality.⁶⁷ Although a technique such as that described by the authors will produce data even for poor quality images, one cannot know if the results are legitimate without more rigorous validation.

While technical and logistic challenges can be overcome, one must also consider that adrenergic imaging assesses a physiologic phenomenon different from perfusion, and therefore be cautious about applying the same interpretive paradigm. With perfusion imaging more extensive and severe defect(s) predict poorer outcome.⁶⁸ However, as an important goal of tomographic

adrenergic imaging is lethal arrhythmic risk assessment, how does one know that the size and severity of defect(s) are the parameter of interest? In a subset of ADMIRE-HF patients without an ICD, the likelihood of sudden death was higher in patients with an intermediately decreased (1.30-1.59) than in those with a severely depressed (<1.30) HMR.⁶⁹ Recent reports suggest that intermediate degrees of SPECT ¹²³I-*m*IBG abnormalities might indicate higher arrhythmic risk than more extensive, more severe defects.^{66,70} Genesis of arrhythmias is complex, in large part increased by myocardial tissue electrical heterogeneity.⁷¹ For assessment of arrhythmic risk, nuclear techniques will likely need to go beyond the numbers. While having no dysinnervation is certainly better than having any, perhaps the distribution, pattern, and location of dysinnervation are more important than extent and severity. Dysinnervation distribution may have to include not only what is measured and appears on 2D polar plot displays, but also the gradient between endocardium and epicardium.⁷² Maximal count measurements as used by Clements et al would not completely portray important physiology. The location of dysinnervation also appears important. In studies of patients with Brugada syndrome, Wichter et al found that ¹²³I-*m*IBG defects occurred most often in the inferior and inferoseptal walls.⁵⁶ Zhou et al recently reported that decreased ¹²³I-*m*IBG counts in the border zone between myocardial scar and normal tissue is better than other parameters in predicting electrophysiologic inducibility.⁷³ Thus, new ways of describing adrenergic tomographic image findings, beyond quantitation alone, appear needed.

Quantitation of image findings has been and will continue to be crucially important for nuclear cardiology. Numbers should faithfully portray the physiologic phenomena being examined. Quantitative methods need further development, and will need to be supplemented by defect location and pattern when examining complex pathophysiology such as arrhythmias. Ultimately, quantitative and qualitative findings must be shown useful for guiding patient management as validity can only be assessed in terms of improved patient well being.

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