Quantitation in gated perfusion SPECT imaging: The Cedars-Sinai approach

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Cedars-Sinai’s approach to the automation of gated perfusion single photon emission computed tomography (SPECT) imaging is based on the identification of key procedural steps (processing, quantitation, reporting), each of which is then implemented, in completely automated fashion, by use of mathematic algorithms and logical rules combined into expert systems. Our current suite of software applications has been designed to be platform– and operating system–independent, and every algorithm is based on the same 3-dimensional sampling scheme for the myocardium. The widespread acceptance of quantitative software by the nuclear cardiology community (QGS alone is used at over 20,000 locations) has provided the opportunity for extensive validation of quantitative measurements of myocardial perfusion and function, in our opinion, helping to make nuclear cardiology the most accurate and reproducible modality available for the assessment of the human heart. (J Nucl Cardiol 2007;14:433-54.)

The Cedars-Sinai Medical Center (Los Angeles, Calif) approach to myocardial perfusion single photon emission computed tomography (SPECT) imaging is exemplified in Figure 1; the entire process that takes us from the initial image acquisition to the generation of a final report is broken down into individual steps, each of which can be accomplished automatically through specialized software. Each block in Figure 1 can be seen as an “expert system”—that is, a set of software programs created to perform specific tasks, where tasks are defined by logical and mathematical rules and rules express human decisional processes. Consequently, expert systems are a form of artificial intelligence.

The 3 expert systems in Cedars’ myocardial perfusion imaging “software trail” handle (1) processing (generation of tomographic images from raw projection images), (2) quantitation (extraction of quantitative cardiac parameters from images), and (3) reporting. This report will concentrate mostly on myocardial SPECT quantitation, although positron emission tomography (PET) quantitation, correlative image fusion, and reporting will also be discussed.

Figure 2 shows how Cedars’ expert system for quantitation can be decomposed into a number of subsystems, each of which contains specialized algorithms for quantitation of left ventricular (LV) myocardial perfusion, function, and other parameters. Specifically, an input of rest and stress projection, short-axis, and gated short-axis images results in the completely automatic generation and output of quantitative values for parameters of (1) LV myocardial perfusion (extent and severity of perfusion defects; cagetric scores and summed scores for stress, rest, and reversibility; total perfusion deficit [TPD]), (2) global LV function (LV ejection fraction [LVEF], end-systolic volume [ESV], end-diastolic volume [EDV], diastolic function), (3) regional LV function (myocardial wall motion and wall thickening, regional myocardial diysynchrony), and (4) other parameters (lung/heart ratio [LHR], transient ischemic dilation [TID], LV shape and eccentricity, LV myocardial mass). Of note, it is not necessary to gate both the rest and the stress portions of the study, although doing so allows better identification of severe and extensive coronary artery disease (CAD) through the phenomenon of myocardial stunning.1,2

Whereas the individual algorithms perform different analyses, their behavior is integrated in that they all use the same sampling scheme. Sampling is not based on circumferential profiles; rather, every left ventricle is treated as a 3-dimensional structure, and a standard number of longitudinally and latitudinally equi-spaced myocardial perfusion data samples is extracted, regardless of LV size.3 With this approach, homologous sample points in different patients’ left ventricles are intrinsically registered and can be optimally compared. In addition, sampling rays take into account the entire myocardial thickness (“whole myocardium sampling”), not just the maximal count locations, and therefore can

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be reasonably expected to reduce noise in the sampled data.3

**QUANTITATIVE PERFUSION SPECT**

Quantitative perfusion SPECT (QPS) produces several quantitative measures of myocardial perfusion. As Figure 3 (top row) shows, “raw” perfusion polar map samples (pixels) corresponding to abnormal perfusion (as determined by comparison to homologous pixels in a “normal” map) are blacked out and ratioed to the number of pixels in the individual vascular territories or the entire myocardium so that myocardial perfusion defect extent can be expressed as a percent value. In the example given, the stress defect extent is 25% of the left anterior descending artery and 9% of the right coronary artery, or 16% of the LV myocardium. Similarly, determining the number of standard deviations by which each abnormal pixel is below the normal threshold for the myocardial location it represents and adding those numbers together yield a global myocardial perfusion severity value (“defect severity”). We have also recently combined pixel-based defect extent and severity into a new continuous parameter, TPD, which provides an overall measure of hypoperfusion, either by vascular territory or for the entire myocardium (Figure 3, bottom row). The analyses shown in Figure 3 for a stress SPECT study are typically applied to both stress and rest studies, with the quantitative difference between stress and rest perfusion defect(s) representing a measure of ischemia or defect “reversibility.”

Of note, normal thresholds (“normal limits”) are de-
Figure 3. Top row, “Raw” polar map, parametrically representing SPECT myocardial perfusion measured at stress in a patient; “extent” polar map, in which pixels with abnormal perfusion are blacked out; and “severity” polar map, displaying the number of SDs by which perfusion in the abnormal pixels is below normal. The small numbers in the extent and severity maps represent the percent extent and mean severity for the individual vascular territories. Bottom row, Both perfusion defect extent (Ext) and TPD are normalized and expressed in a 0% to 100% range and can be measured for the entire LV myocardium or the individual vascular territories; however, only the TPD provides an overall measure of hypoperfusion that combines extent and severity. LAD, Left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TOT, total.

rived via a simplified approach that does not require the visual scoring of abnormal scans or the optimization of regional thresholds used in traditional approaches. With this new technique, site- or protocol-specific normal limits can be created by use of only low-likelihood patients, without the need to train the system with expert input. Thanks to the high degree of operator independence and the refined method of image normalization used to avoid “non-Gaussian” count variation near maximal counts, the simplified quantitative approach has been found to achieve performance better than or equivalent to standard quantification or even expert visual assessment (Figure 4).

In addition to pixel-based (continuous) parameters, QPS now automatically calculates segmental (categoric) scores based on normal limits alone, rather than by maximizing agreement with expert visual scores. As with pixel-based assessment, this recent development aims at improving operator independence. Segmental scores can be summed to yield global indices combining extent and severity of perfusion defects, such as the summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS); the latter is defined as SSS minus SRS and measures the degree of reversibility (Figure 5). Risk groups may be identified by use of SSS categories. As with the pixel-based TPD parameter previously described, it is desirable to express overall perfusion defects as percent myocardium involved (percent stress, percent reversible, percent fixed), and we now routinely use this approach for clinical reporting and all prognostic publications. The conversion of summed scores to percent myocardium is accomplished by dividing the summed scores by the worst segmental score possible in the specific model used (68 for 17 segments and 80 for 20 segments) and multiplying by 100 (5-point scoring from 0 [normal] to 4 [absent uptake]). The benefits of this approach are that it provides a measure with intuitive implications (percent myocardium hypoperfused) not possible with the unit-less summed scores, that it can easily be applied to scoring systems using varying numbers of segments (eg, 17, 20, 14, or 12), and that it is...
applicable to quantitative methods that directly measure these abnormalities as percent myocardium. Risk groups based on the percent abnormal stress perfusion, which correlate with SSS risk groups, are less than 5% (normal or minimally abnormal), 5% to 9% (mildly abnormal), 10% to 14% (moderately abnormal), and 15% or greater (severely abnormal). When converted to percent myocardium abnormal, the prognostic implications of the 17- and 20-segment scoring have been shown to be equivalent.
Combined Supine-Prone Perfusion Quantitation

It has been shown by visual analysis that additional prone scans, acquired immediately after stress supine scans, can be helpful in the identification of attenuation artifacts. However, one of the factors limiting widespread use of combined supine-prone imaging has been the lack of an effective quantitative method to use with this protocol. A new QPS technique has been developed that provides an automatically combined prone-supine TPD measurement based on the 3-dimensional registration of prone and supine stress SPECT scans, with quantification of supine defects limited to the polar map regions with overlapping prone defects (Figure 6). In a recent study comparing the combined prone-supine quantification technique with quantification of supine myocardial perfusion SPECT alone, the combined technique has been demonstrated to significantly improve the area under the receiver operating characteristic (ROC) curve, as well as the specificity of myocardial perfusion SPECT, with respect to the identification of obstructive CAD. The prone-supine approach has also been shown to be diagnostically superior to supine imaging in a female population. It is conceivable that further validation of this approach may increase acceptance of combined prone-supine imaging as an alternative to SPECT performed with attenuation correction.

Quantification of Perfusion Changes Without Normal Limits

In addition to quantifying ischemia as the difference between stress and rest perfusion defect sizes obtained by separate comparisons to stress and rest normal limits, it is possible to perform a direct, simplified quantification of stress-induced myocardial perfusion deficit by simultaneous automatic spatial registration and count normalization of rest and stress images, without the use of normal limits. One of the advantages of this approach is that contours are determined only for the higher-quality stress images, enhancing the reliability of myocardial segmentation (Figure 7). The search for the optimal normalization factor is incorporated into the registration procedure via a novel 2-pass technique.
which eliminates the influence of abnormalities, and the approach itself can also be applied to the detection of perfusion differences in serial studies.

When compared in the prediction of coronary artery stenosis in 204 patients whose SPECT images were acquired via a same-day dual-isotope technetium 99m/nalium 201 protocol and in whom coronary angiography had been performed, the area under the ROC (0.88 ± 0.03) was found to be significantly better for the new approach than for existing quantitative approaches using normal databases (0.80-0.82 ± 0.03) and was not statistically different from (though it was higher than) the ROC with expert visual scoring (0.84 ± 0.03).\(^{15}\) Our clinician readers have noted that this new method for assessment of change is proving highly valuable in clinical scan interpretation. If there is no change between stress and rest, the likelihood of ischemia becomes extremely low, and subtle stress-rest defects can usually be attributed to tissue attenuation. In addition, this method is proving highly valuable to clinicians in objectifying the process of determining whether there has been a change in perfusion in serial studies in the same patient.

**QUANTITATIVE GATED SPECT**

**LVEF**

Quantitative gated SPECT (QGS) automatically measures LVEF from gated perfusion SPECT images via a volume-based approach: the location of the LV endocardium is estimated in the 3-dimensional space, and the LV cavity volume is measured as the territory bound by the endocardium and its valve plane for every interval in the cardiac cycle. The time-volume curve identifies the end-diastolic and end-systolic LV cavity volumes, from which the ejection fraction is calculated as follows: \(\text{LVEF} = (\text{EDV} - \text{ESV})/\text{EDV} \times 100\).\(^{16}\) Endocardial and epicardial surfaces can usually be accurately determined even in the apparent absence of perfusion because (1) Gaussian fitting of count profiles operates on the non-thresholded image volume and is therefore able to “pick up” very low levels of perfusion that are difficult to visualize and (2) the algorithm seeks to preserve the continuity of the 3-dimensional myocardial surface gradients by extrapolating the gradients of points immediately adjacent to the nonperfused area.\(^{17}\) The constraint of preservation of myocardial mass throughout the cardiac cycle is imposed and further refines the determination of the endocardial and epicardial surfaces.

A list of published validation studies of gated perfusion SPECT LVEF measurements by QGS are presented in Table 1, along with details about the studies.

**EDV and ESV**

Validation of quantitative LVEF measurements does not necessarily imply validation of the EDV and ESV measurements from which the LVEF is derived; for example, errors in the determination of EDV and ESV would be expected to occur in the same general direction and therefore would at least partially cancel out when the volumes are ratioed for LVEF calculation purposes.\(^{16}\) In addition, absolute volume measurements can be adversely affected by incorrect listing of the pixel size in the image header, particularly in older cameras or “hybrid” systems, where one manufacturer’s camera is interfaced with another manufacturer’s computer. These considerations notwithstanding, a substantial body of published evidence suggests that QGS-derived quantitative measurements of absolute LV cavity volumes from gated perfusion SPECT images agree well with established standards, as summarized in Table 2.

**Normal Limits of QGS Global Function Measurements**

It is extremely important to understand that normal limits for parameters of global cardiac function are different for different quantification algorithms.\(^{18}-^{24}\) Table 3 presents some published data for LVEF, EDV, and ESV relative to QGS and 8-frame gating, which have been found to provide independent and incremental prognostic information (after adjustment for prescan and perfusion data) in both a pooled population\(^{25}\) and gender-specific populations.\(^{26}\) As expected, ESV and EDV values are smaller in women, and interestingly, normalization for body size yielded indexed end-systolic volume index and end-diastolic volume index values that were still smaller in women than in men.\(^{26}\) LVEFs are generally higher in women, partly because of size-related reasons (partial-volume effect\(^{27}\)) but mainly because of physiologic ones.\(^{28}\)

**Limitations of Quantitative Measurement of Global Function**

It has been shown that the relatively low resolution of nuclear cardiology images can lead to the apparent underestimation of the LV cavity size in patients with small ventricles, the end result being an underestimation of cavity volumes (particularly the ESV), with consequent overestimation of the LVEF.\(^{29}-^{31}\) This phenomenon can be alleviated by magnifying the left ventricle either in acquisition (by employing a larger acquisition zoom) and/or in reconstruction (by employing zoomed
Table 1. Validation of quantitative measurements of LVEF from Cedars-Sinai’s QGS software

<table>
<thead>
<tr>
<th>Gold standard</th>
<th>No. of reports</th>
<th>No. of patients</th>
<th>Spearman r</th>
<th>Radiopharmaceutical</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUGA</td>
<td>16</td>
<td>600</td>
<td>0.7-0.95</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201, iodine 123 BMIPP</td>
<td>Moriel et al,81 Bateman et al,82 Everaert et al,83 Carpentier et al,84 Daou et al,85 Yoshioka et al,86 Manrique et al,87 Chua et al,88 Higuchi et al,89 Kikkawa et al,90 Kumita et al,91 Lam et al,92 Nakajima et al,93 Higuchi et al,94 Nanasato et al,95</td>
</tr>
<tr>
<td>MRI</td>
<td>13</td>
<td>336</td>
<td>0.72-0.94</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201</td>
<td>He et al,96 Atsma et al,93 Vaduganathan et al,94 Tadamura et al,95 Vansant et al,96 Tadamura et al,97 Bax et al,98 Bavelaar-Croon et al,99 Faber et al,100 Roelants et al,101 Thorley et al,102 Lipke et al 124</td>
</tr>
<tr>
<td>2-Dimensional echocardiography</td>
<td>9</td>
<td>541</td>
<td>0.72-0.90</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201</td>
<td>Zanger et al,103 Di Leo et al,104 Bateman et al,105 Mathew et al,106 Cwaig et al,107 Bacher-Stier et al,108 Nichols et al,109 Gayed et al,110 Voorvouri et al,111</td>
</tr>
<tr>
<td>First pass</td>
<td>6</td>
<td>717</td>
<td>0.74-0.92</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201, I-123 BMIPP</td>
<td>Germano et al,112 Inubushi et al,112 He et al,113 Vallejo et al,114 Lam et al 115</td>
</tr>
<tr>
<td>Contrast ventriculography</td>
<td>5</td>
<td>381</td>
<td>0.78-0.97</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin</td>
<td>Di Leo et al,104 Paul et al,115 Abe et al,116 Atsma et al 117</td>
</tr>
<tr>
<td>3-Dimensional MUGA</td>
<td>2</td>
<td>35</td>
<td>0.93-0.97</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin</td>
<td>Paul et al,115 Higuchi et al 118</td>
</tr>
<tr>
<td>Thermodilution</td>
<td>1</td>
<td>45</td>
<td>0.94</td>
<td>Tc-99m sestamibi</td>
<td>Germano et al,119 Iskandrian et al,120</td>
</tr>
<tr>
<td>3-Dimensional echocardiography</td>
<td>1</td>
<td>18</td>
<td>0.80</td>
<td>Ti-201</td>
<td>Akinboboye et al 121</td>
</tr>
<tr>
<td>EBCT</td>
<td>1</td>
<td>10</td>
<td>0.94</td>
<td>Tc-99m sestamibi</td>
<td>Toba et al 122</td>
</tr>
</tbody>
</table>

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MUGA, Multiple-gated acquisition scanning; BMIPP, beta-methyl-iodophenyl-pentadecanoic acid; MRI, magnetic resonance imaging; EBCT, electron beam computed tomography.
Table 2. Validation of quantitative measurements of ESV and EDV from Cedars-Sinai’s QGS software

<table>
<thead>
<tr>
<th>Gold standard</th>
<th>No. of reports</th>
<th>No. of patients</th>
<th>EDV</th>
<th>ESV</th>
<th>Radiopharmaceutical</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>13</td>
<td>336</td>
<td>0.7-0.94 (mean, 0.89)</td>
<td>0.87-0.97 (mean, 0.93)</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201</td>
<td>He et al.,102 Atsma et al.,103 Vaduganathan et al.,104 Tadamura et al.,105 Vansant et al.,106 Tadamura et al.,108 Bax et al.,109 Bavelaar-Croon et al.,110 Faber et al.,110 Roelants et al.,111 Thorley et al.,112 Lipke et al.</td>
</tr>
<tr>
<td>2-Dimensional echocardiography</td>
<td>7</td>
<td>431</td>
<td>0.7-0.92 (mean, 0.86)</td>
<td>0.71-0.96 (mean, 0.88)</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201</td>
<td>Langer et al.,113 Bateman et al.,106 Cwág et al.,107 Mathew et al.,106 Nichols et al.,109 Zuber et al.,110 Vourvouri et al.</td>
</tr>
<tr>
<td>MUGA</td>
<td>6</td>
<td>206</td>
<td>0.7-0.88 (mean, 0.81)</td>
<td>0.7-0.95 (mean, 0.81)</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin, Ti-201, 1-123 BMIPP</td>
<td>Daou et al.,114 Yoshioka et al.,115 Chua et al.,115 Nakajima et al.,116 Nanasato et al.</td>
</tr>
<tr>
<td>Contrast ventriculography</td>
<td>3</td>
<td>255</td>
<td>0.67-0.93 (mean, 0.84)</td>
<td>0.79-0.97 (mean, 0.88)</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin</td>
<td>Paul et al.,117 Abe et al.,118 Nakajima et al.</td>
</tr>
<tr>
<td>3-Dimensional echocardiography</td>
<td>2</td>
<td>26</td>
<td>0.94-0.99 (mean, 0.96)</td>
<td>0.97-0.99 (mean, 0.98)</td>
<td>Tc-99m sestamibi, Ti-201</td>
<td>Akinboboye et al.,119 Cittanti et al.</td>
</tr>
<tr>
<td>3-Dimensional MUGA</td>
<td>2</td>
<td>26</td>
<td>0.95-0.98 (mean, 0.96)</td>
<td>0.93-0.97 (mean, 0.95)</td>
<td>Tc-99m sestamibi, Tc-99m tetrofosmin</td>
<td>Paul et al.,115 Higuchi et al.</td>
</tr>
<tr>
<td>Thermodilution</td>
<td>2</td>
<td>45</td>
<td>0.86-0.89 (mean, 0.87)</td>
<td>0.94</td>
<td>Tc-99m sestamibi</td>
<td>Germano et al.,119 Iskandrian et al.</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>1,325</td>
<td>0.88</td>
<td>0.90</td>
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</table>

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MII, Magnetic resonance imaging; MUGA, multiple-gated acquisition scanning; BMIPP, beta-methyl-iodophenyl-pentadecanoic acid.

centered or zoomed off-axis reconstruction),29 although we prefer to consider LVEF as being “in the normal range” whenever it is quantitatively measured as being greater than 75%.

QGS LVEFs are also likely to be underestimated in patients with LV hypertrophy,32,33 because QGS is calibrated for the range of thicknesses most typically encountered in clinical practice.16 Conversely, when gated SPECT imaging is performed with 8-frame gating, there is mild underestimation of the LVEF compared with 16-frame gating, as a result of the smoothing of the time-volume curve. However, the degree of underestimation has been
Table 3. Normal limits for quantitative measurements of global LV function from 8-frame gated perfusion SPECT images via QGS algorithm

<table>
<thead>
<tr>
<th>Gender</th>
<th>LVEF (%)</th>
<th>EDV (mL)</th>
<th>ESV (mL)</th>
<th>EDV (mL/m²)</th>
<th>ESV (mL/m²)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M + F</td>
<td>45</td>
<td>120</td>
<td>70</td>
<td>60</td>
<td>27</td>
<td>Sharir et al²⁶</td>
</tr>
<tr>
<td>F</td>
<td>51</td>
<td>102</td>
<td>46</td>
<td>75</td>
<td>39</td>
<td>Sharir et al²⁶</td>
</tr>
<tr>
<td>M</td>
<td>43</td>
<td>149</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 8. QGS-derived, automatic quantification of diastolic function parameters from 16-frame time-volume curve (black) and its derivative (magenta). TTP, time to peak filling in early diastole; ED, end diastole; ES, end systole; BPM, beats per minute (heart rate); MFR/5, mean filling rate over first third of diastole. (Modified and reproduced with permission from reference ⁴¹.)

shown to be small (3-4 LVEF percentage points) and remarkably uniform over a wide range of ejection fractions.¹⁶,³⁴-³⁶

Diastolic Function Measurement

If a gated SPECT study is acquired by use of a sufficient number of gating intervals,³⁵-³⁹ QGS can quantify various parameters of LV diastolic function from the derivative of its time-volume curve (Figure 8). The peak filling rate (PFR) corresponds to the point of maximum positive slope of the time-volume curve and, as such, is identified by the peak of its derivative; the time to peak filling is the time interval between end systole and the PFR, and the mean filling rate is measured during the first third of the diastolic phase (the portion of the cardiac cycle during which the time-volume curve’s derivative has a positive value). Validations of these and other quantitative measurements of diastolic function have been published,³⁵,⁴⁰ and normal limits for QGS-derived PFR and time to peak filling have been derived and confirmed in agreement with values from traditional techniques.⁴¹

Regional Myocardial Wall Motion and Wall Thickening

QGS measures regional motion as the excursion of the 3-dimensional endocardial surface from end diastole to end systole, via a modification of the centerline method.⁴² Segmental thickening is calculated by use of both geometric (distance between epicardium and endocardium) and count considerations (apparent count increase from end diastole to end systole, resulting from the partial-volume effect).⁴³ Regional wall motion abnormalities present after stress have been described²,⁴⁴-⁴⁶ and may be easier to detect compared with abnormalities in global poststress function.²,⁴⁴-⁴⁷,⁴⁹ Poststress diastolic dysfunction has also been found to be associated with systolic dysfunction in patients with angina.⁵⁰

As with SPECT perfusion quantification, regional quantitative thresholds defining gated SPECT LV wall motion and thickening abnormality can be derived based on the mean and SD of these parameters in a normal patient population.³,⁵¹ Categoric scoring of segmental myocardial wall motion and thickening can also be accomplished automatically, by defining ranges for the absolute measurements obtained by the QGS algorithm.⁵¹

Phase Analysis

QGS creates two 1-dimensional arrays for each LV myocardium sampling point, the first containing the distance (amount of wall motion) between the midmyocardial surface and a reference position for each gating interval and the second containing the myocardial thickness (distance between the endocardial and epicardial surfaces normally to the midmyocardial surface), also for each gating interval. Each
array represents a time-varying, periodic function that can be reduced to its first Fourier harmonic, which is in turn defined by its phase and amplitude. Motion and thickening phase and amplitude for all of the sampling points representative of the left ventricle can be displayed in polar maps, as can the time to maximum displacement, time to maximum thickening, and time to peak systolic velocity.

In addition, motion and thickening curves showing the onset and peak of contraction can be derived and compared across different portions of the left ventricle (segments, walls, coronary territories), with corresponding phase histograms showing phase dispersion in each of those portions on a voxel-by-voxel basis (Figure 9).

**“Motion-Frozen” Images**

One of the most novel ways in which gated SPECT imaging has been used to improve cardiac assessment has been by “warping” tomographic images corresponding to the various gating intervals to a common template, before summing them to generate the "summed (ungated) perfusion SPECT" dataset from which perfusion is visually or quantitatively assessed. This is accomplished by motion tracking of the LV endocardial and epicardial borders for all intervals and subsequent nonlinear image warping of all (or selected) cardiac phases to the spatial position of the end-diastolic phase (Figures 10 and 11). Such “motion-frozen” perfusion images have a visual appearance similar to the end-diastolic images, but they contain counts from all cardiac cycles without suffering from the blurring caused by cardiac motion. Motion-frozen processing of gated SPECT images appears to improve the effective resolution of images and has shown improved performance with respect to the prediction of CAD in patients with high ejection fractions, as well as in patients whose perfusion scans were read as normal by visual analysis.

**Right Ventricular Function**

Because the right ventricular (RV) myocardium is thinner and, on a per-gram basis, has lower blood flow than the left ventricle, its perceived intensity of uptake...
is about 50% of that in the left ventricle; for that reason, the RV myocardium is generally difficult to visualize, unless the patient has RV hypertrophy. Nevertheless, it is possible to apply to the RV algorithms similar to those used for LV function quantitation, determine RV myocardial contours even in non-hypertrophic right ventricles (Figure 12), and derive estimates of both RV ejection fraction and RV volumes. It is anticipated that RV quantitation will be incorporated into future releases of QGS.

OTHER QUANTITATIVE MEASUREMENTS

LHR

For decades, it has been recognized that assessment of the lung uptake of Tl-201 is of prognostic value, given the strong linear relationship between the degree of lung uptake and the pulmonary capillary wedge pressure at the time of injection. The Cedars-Sinai approach to lung uptake is to determine the ratio between lung uptake and myocardial uptake; this potentially adds the ability to determine whether there is a balanced reduction of stress perfusion throughout the myocardium, in which case the LHR could be elevated without a corresponding increase in the lung uptake. The LHR can be automatically quantified in QGS-AutoQUANT by determining an LV “mask” from the anterior or left anterior oblique 45° portion of the projection image data set and then taking the maximal or mean pixel count in a reasonably small region of interest placed over the highest-count portion of the left ventricle. A crescent-shaped mask can be derived from the LV mask and automatically placed in the pulmonary area, and the pixel count can be calculated in a smaller region of interest within it. Then, the LHR is simply calculated as the ratio of counts in the lung and heart regions (Figure 13).

Using QGS-AutoQUANT on Tc-99m sestamibi SPECT images acquired early (15 minutes) after exercise stress in a prospective group of 72 patients, we found that an LHR threshold greater than 0.44 yielded a sensitivity and specificity of 63% and 81%, respectively, in identifying severe and extensive CAD and a sensitivity of 86% in identifying stenosis of 90% or more in the proximal left anterior descending artery.
TID

TID of the left ventricle is considered present when the LV cavity appears to be significantly larger in the poststress images than in the rest images, and a TID index can be easily calculated as the ratio of the QGS-derived poststress LV cavity volume to the rest LV cavity volume, as shown in Figure 14. Like the LHR, the TID index has been shown to be a marker of severe and extensive CAD and can be effective in avoiding the problem of underestimation of disease extent, which is inherent in the assessment of relative perfusion defects.36 (Of note, the TID index and the LHR are not correlated;
Table 4. Normal limits for quantitative measurements of TID index from perfusion SPECT images via QGS algorithm

<table>
<thead>
<tr>
<th>Rest radiopharmaceutical</th>
<th>Stress radiopharmaceutical</th>
<th>Stress type</th>
<th>TID index</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tl-201</td>
<td>Tc-99m sestamibi</td>
<td>Exercise</td>
<td>1.22</td>
<td>Mazzanti et al\textsuperscript{127}</td>
</tr>
<tr>
<td>Tc-99m tetrofosmin</td>
<td>Tc-99m tetrofosmin</td>
<td>Exercise</td>
<td>1.25 (ESV)</td>
<td>Bestetti et al\textsuperscript{128}</td>
</tr>
<tr>
<td>Tl-201</td>
<td>Tc-99m sestamibi</td>
<td>Adenosine</td>
<td>1.36</td>
<td>Abidov et al\textsuperscript{129}</td>
</tr>
<tr>
<td>Tl-201</td>
<td>Tl-201</td>
<td>Dipyridamole</td>
<td>1.19</td>
<td>Hung et al\textsuperscript{130}</td>
</tr>
</tbody>
</table>

All studies were based on ungated LV cavity volumes, except for that of Bestetti et al\textsuperscript{128} which used rest and stress ESVs. On the basis of the reported information with the various protocols, we estimate the upper limit of normal TID index to be approximately 1.12 for a 2-day Tc-99m sestamibi or tetrofosmin protocol, 1.17 for a low-dose rest/high-dose stress same-day Tc-99m protocol, and 1.05 for a high-dose stress/low-dose rest same-day Tc-99m protocol.

thus quantitation of both parameters offers incremental knowledge over quantitation of either one alone\textsuperscript{57}.

QGS-derived thresholds of abnormality for the TID index have been published for various acquisition protocols, as shown in Table 4, and the parameter has been shown to be of prognostic value over the assessment of perfusion defects alone. Specifically, 1,560 patients who had normal stress perfusion SPECT (436 vasodilator and 1,124 exercise stress) and no rest LV enlargement were followed up for 2.30 \(\pm\) 0.67 years for hard events (cardiac death or myocardial infarction) and soft events (revascularization); those with a QGS-derived TID index greater than or equal to 1.21 had a higher total event rate (hard events plus soft events) than the other patients, regardless of stress type\textsuperscript{56}.

LV shape

Pathologic remodeling of the left ventricle is generally associated with a change from the normal prolate to
a more spherical geometry. The degree of global myocardial sphericity can be simply estimated from the minor and major axes of the ellipsoid that best fits the maximal count (or midmyocardial) surface of the left ventricle, and it is reported by QGS as “eccentricity.” A more accurate, regionally sensitive measurement of LV shape can be obtained by taking the 3-dimensional surface bound by the endocardium and the valve plane, searching for the maximal distance between (1) two endocardial points in a select short-axis plane and (2) the most apical endocardial point and the center of the valve plane, and finally ratioing the two (Figure 15). QGS reports this parameter as LV shape index, and preliminary work has demonstrated that a threshold of 0.54 for end-systolic LV shape index results in a sensitivity of 68% and specificity of 95% in the prediction of congestive heart failure hospitalization. When applied to a normal control population, this threshold had a normalcy rate of 99%.59

**Figure 15.** Illustration of 2 cases with similar low LVEF but differing LV shape index. **A.** The patient with no signs of congestive heart failure (CHF) has a more severe perfusion defect than the other patient but has a normal LV shape index and an elongated LV cavity. **B.** The other patient, who has severe congestive heart failure, has an abnormal LV shape index and a more spherical left ventricle. ANT, Anterior; SEPT, septal; INF, inferior; LVSI, systolic LV shape index. (Reproduced with permission from reference 59.)

**Myocardial Mass**

Quantitative measurement of LV myocardial mass is conceptually possible by counting the voxels bound by the 3-dimensional endocardial surface, epicardial surface, and valve plane and then multiplying that value by an individual voxel’s volume as well as by the myocardial density. In practice, the relatively low resolution of nuclear cardiology images generally prevents us from measuring “small” structures such as myocardial thickness with a high degree of accuracy, and LV myocardial mass determination is best accomplished by use of the high-resolution modalities of cardiac magnetic resonance imaging or cardiac computed tomography. Nevertheless, LV mass measurements by QGS-AutoQUANT have been reported to correlate reasonably well with a 3-dimensional echocardiographic standard and can represent a useful adjunctive quantitative tool.
**AUTOMATIC REPORT GENERATION**

The report generation block in Figure 1 can be further dissected as shown in Figure 16. Input data to the expert system include (1) information on the patient’s demographics (name, age, identification number, etc) and medical history (various risk factors, previous occurrence of myocardial infarction or invasive revascularization procedures, and so on), (2) result of the stress electrocardiographic study, and (3) quantitative and semiquantitative results from the nuclear study. All data are either manually input in a computer on the local area network or through a portable personal digital assistant or automatically imported from the radiology information system, hospital information system, electrocardiography machine, or QGS/QPS/AutoQUANT quantitative software.

One of the “intelligent” functions that automatic report generation (ARG) provides is to ensure the consistency of the input data. For example, QGS and QPS generate an internally consistent interpretation of the quantitative perfusion and function results. (Figure 17 shows the perfusion scan findings panel.) The data are presented to the reviewing physician, who can alter them if he or she deems it appropriate (eg, individual perfusion scores could be modified if the clinician suspects that they may be due to attenuation artifacts). When the quantitative analysis’ results and interpretation have been accepted, they are forwarded to the report generator for integration with the other data; however, if the clinician’s modifications have rendered the data inconsistent (eg, by changing the overall perfusion scan findings from “definitely abnormal” to “equivocal”) (Figure 17), ARG will generate error/warning messages (Figure 18) and provide the opportunity for data reconciliation. This approach is particularly helpful in achieving timeliness of reporting. A recent American Society of Nuclear Cardiology position statement recommends a turnaround time of 1 business day for completed interpretation and 2 business days for final report transmittal, but through the combination of automated processing, ARG’s consistency rules, and electronic faxing, our clinicians are capable of sending out reports within 1 hour of study acquisition.

The key function of a report generator, of course, is that of combining the input data via a number of rules and expressing the output (patient diagnosis and possibly prognosis) in a standardized and optimized fashion and in language that is readily interpretable by the referring physician. In Cedars-Sinai’s ARG implementation, 4 output pages are automatically generated by the expert system. The first is conceived as a cover letter addressed to the referring physician and gives an “executive summary” of the nuclear study. This includes patient identification and relevant history, the reason why he or she was referred to the nuclear laboratory, the type of protocol used, the findings expressed in terms of quantitative and semiquantitative perfusion and function abnormalities, the overall diagnostic interpretation, and a prognostic statement expressing the likelihood of future cardiac events in that patient, based on published data for patients with similar pathologies. The other 3 pages give detailed information on myocardial perfusion, myocardial function, and electrocardiographic findings, respectively, complete with individual segmental scores, polar map displays, tables, and images.

**Figure 16.** Block diagram of Cedars’ ARG for typical gated perfusion SPECT study. *AutoQ, AutoQUANT. ECG, Electrocardiography. (Modified and reproduced with permission from reference 58.)***

**Figure 17.** Quantitative SPECT perfusion results and their interpretation, as created by QPS with ARG. (Reproduced with permission from reference 58.)

**Figure 18.** Error messages generated by ARG’s consistency rules, when the overall perfusion scan assessment in Figure 16 is manually changed from “definitely abnormal” to “equivocal.” (Reproduced with permission from reference 58.)
Figure 19. Quantitative Rb-82/FDG mismatch/scar analysis by QPET. Rb-82 stress-rest perfusion and F-18 FDG viability images are shown on the left. Pixels in the hypoperfused region of the Rb-82 rest images (blackout region in the rest polar map) are compared with the corresponding pixels on the viability polar map (not shown), creating mismatch and scar polar maps. In this case the hypoperfused region with a TPD of 21% is classified as being primarily scarred (scar, 20%; mismatch, 1%). Automatically generated scar segmental scores (third segmental map on right) are also provided in addition to standard stress and rest scores.

QUANTITATIVE PET

Though not specifically developed for PET, QGS has been successfully applied to gated PET function quantitation of fluorine 18 fluorodeoxyglucose (FDG), 64–70 nitrogen 13,71,72 and rubidium 82.73,74 However, to take advantage of the higher resolution of PET images compared with SPECT, as well as the improved visibility of the basal portion of the LV myocardium (thanks to the attenuation correction intrinsic to PET), the QGS algorithm has been modified to provide an optimal determination of LV contours when PET images are presented as input. This modified version of QGS (QGS-PET) and a similarly optimized version of QPS (QPS-PET) are combined into Cedars’ software suite for the quantitative assessment of myocardial PET perfusion and function, QPET (quantitative PET).

QPET can process transaxial and short-axis gated and ungated rest and stress PET images. Rb-82 and N-13 ammonia PET perfusion normal limits are built, and perfusion parameters such as TPD defect extent or segmental stress-rest scores are derived similarly to SPECT studies. One advantage of gated Rb-82 PET analysis is the possibility of computing true stress ejection fractions, as stress acquisitions are obtained immediately after pharmacologic stress.75 Another aspect of quantitative PET imaging is the differentiation between hibernating (viable) and scarred myocardium by F-18 FDG imaging.76 QPET allows quantitative estimation of scarred and viable myocardium by direct comparison of the rest perfusion images to the FDG viability images, computing changes in the viability study as compared with the perfusion study only in regions hypoperfused at rest.77,78 This approach does not require the use of normal limits for the FDG studies, because the direct changes between perfusion and metabolism are quantified after appropriate normalization as in the analysis of stress-rest changes.15 An example of such analysis is shown in Figure 19.

INTEGRATION OF ANATOMIC DATA WITH QUANTITATIVE PERFUSION ANALYSIS

Recent advances in computed tomography angiography (CTA) allow the acquisition of gated 3-dimen-
Figure 20. Integration of QPS perfusion quantification results with anatomic maps of coronary vessels extracted from a corresponding 64-slice CTA study. The left anterior descending artery with a questionable lesion on CTA is shown to directly correspond to the reversible SPECT defect.
sional cardiac isotropic volumes with submillimeter resolution, capable of identifying atherosclerotic lesions in coronary vessels. Because these coronary lesions may be responsible for perfusion defects seen on SPECT or PET, it is likely beneficial to directly superimpose the anatomic data extracted from CTA with quantitative perfusion or viability data obtained by SPECT or PET, to resolve equivocal findings. Evidence is mounting that this approach may be clinically useful.\textsuperscript{9,80} Cedars-Sinai’s software (CT Fusion) is capable of combining extracted vascular trees with QPS quantitative 3-dimensional surface perfusion maps; coronary trees can be represented as the vessel centerline coordinates or the segmented 3-dimensional volumes, and these vessel representations can be superimposed to SPECT or PET perfusion data. Registration of the vascular trees can be performed automatically via registration of centerlines to SPECT/PET LV surfaces or by interactive alignment of the original CTA images with transverse SPECT or PET data. Figure 20 illustrates such integration of stand-alone SPECT images with CTA.\textsuperscript{123}

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