Gated SPECT in assessment of regional and global left ventricular function: Major tool of modern nuclear imaging

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INTRODUCTION

Over the last few decades, the assessment of myocardial perfusion from stress and rest myocardial perfusion single photon emission computed tomography (SPECT) (MPS) has become central to the management of patients with known or suspected coronary artery disease (CAD).[1] More recently, electrocardiography (ECG)–gated SPECT, with the ability to measure left ventricular (LV) ejection fraction (EF) and ventricular volumes, as well as to evaluate presence of regional wall motion abnormalities (RWMAs), has become a routine part of clinical protocols, expanding the clinical utility of MPS. Recent American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines for the clinical use of cardiac radionuclide imaging consider ECG-gated SPECT as the "current state of the art" and indicate the following: "The ability to observe myocardial contraction in segments with apparent fixed perfusion defects permits the nuclear test reader to discern attenuation artifacts from true perfusion abnormalities. The ability of gated SPECT to provide measurement of LVEF, segmental wall motion, and absolute LV volumes also adds to the prognostic information that can be derived from a SPECT study."[2]

Gated SPECT is now performed in over 90% of all MPS studies in the United States.[3] This review is intended to describe the major milestones in which ventricular function assessment has emerged and added to perfusion assessment by use of gated SPECT. The important developments relating to perfusion parameters from MPS are not covered in this review.

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HISTORICAL OVERVIEW OF TECHNICAL AND CLINICAL DEVELOPMENT OF ASSESSMENT OF VENTRICULAR FUNCTION BY GATED SPECT

Technical Milestones

The era of modern clinical nuclear cardiology began in the late 1960s with the introduction of the Anger scintillation camera, which was able to provide dynamic images of the cardiac distribution of radioactivity. Early in the 1970s, the ability to accurately assess ventricular function noninvasively, initially with end-systolic and end-diastolic equilibrium radionuclide ventriculography and the use of an ECG-gating device[4] and shortly thereafter with early medical imaging computers, led to the description and validation of the multiple gated acquisition (MUGA) scan, allowing nuclear cardiology to become a useful, routine clinical tool. At nearly the same time, nuclear cardiology found its first unique niche with initial clinical reports of the ability of nuclear cardiology to assess regional myocardial perfusion at rest and during stress with potassium-43 and rubidium-81. Although Rb-81 was commercially available for a short time and was used clinically for these measurements, the widespread clinical use of myocardial perfusion scintigraphy really began in 1976 when thallium 201 became commercially available. The "thallium scan" rapidly became the most widely used noninvasive imaging method for detecting CAD in patients with an intermediate likelihood of CAD and soon thereafter became widely used for purposes of risk stratification in patients with known or suspected CAD. During the late 1970s, exercise radionuclide ventriculography via both equilibrium and first-pass approaches became another commonly performed stress imaging modality. Thus, by this time, nuclear cardiology had emerged as being able to assess rest and stress myocardial perfusion and rest and stress regional and global ventricular function, albeit with 2 separate studies. In several laboratories, such as ours at Cedars-Sinai Medical Center (Los Angeles, Calif), these 2 tests were noted to often provide clinically useful complementary information.[5,6]

In the late 1970s SPECT via a rotating Anger camera detector became widely available, increasing the

Table 1. Review of published quantitative algorithms for gated perfusion SPECT

	Institution: Commercial name	
	Cedars-Sinai: QGS and AutoQUANT	**Emory university: EGS and cardiac toolbox**
Operation	Automatic	Automatic
Dimensionality	3-D	3-D
Method	Gaussian fit[10,11]	Partial volume[15,16]
Validation of LVEF	First pass,[10,41-44] MUGA,[44-58] 3-D MUGA,[59,60] MRI,[61-73] 2-D echo,[52,74,76-82] 3-D echo,[83] contrast ventriculography,[59,84,85] EBCT,[86] thermodilution[87]	First pass,[16] MUGA,[56] MRI,[16,65,69] 2-D echo[80]
Diastolic parameters	MUGA[54,55,57,60]	
Volumes	MUGA,[49,50,52,56-58] 3-D MUGA,[59,60] MRI,[61-73] 2-D echo,[52,74,76-82] 3-D echo,[83] contrast ventriculography,[59,84,85] EBCT,[86] thermodilution,[87] excised hearts[184]	First pass,[16] MUGA,[56] MRI,[16,65,69] 2-D echo[80]
Wall motion	Visual[11]	MUGA[186]
Wall thickening	Visual[11]	2-D echo[103]

Data are from reference 9.
3-D, Three-dimensional; *2-D,* two-dimensional; *echo,* echocardiography; *EBCT,* electron beam computed tomography.

ability of myocardial perfusion scintigraphy to localize and quantify regional myocardial perfusion defects.[7] However, assessment of ventricular function by nuclear cardiology still required the performance of a separate blood pool imaging study. Gated MPS (gated SPECT) was not clinically feasible until 1990, when technetium 99m sestamibi was approved for use in the United States. Its higher myocardial count rates (compared with Tl-201) improved image count statistics so that adequate images could be obtained with SPECT from the different parts of the cardiac cycle by use of ECG gating.[8]

The next important milestones in the technical development of the field were the widespread use of multidetector cameras and the dramatic increase in the speed of computer systems, which made gated SPECT clinically feasible.[9] By the mid 1990s, several centers had begun to routinely perform gated SPECT studies, allowing assessment of myocardial perfusion and ventricular function from a single study.

Besides the progress in development of the radiopharmaceuticals and the camera computer systems that could acquire high-quality gated images, a highly important achievement along this path was development of commercially available software packages, allowing quick and automated quantification of parameters of both myocardial perfusion and function. Software developed at Cedars-Sinai Medical Center was the first totally automated "suite" of computer programs, called QGS (quantitative gated SPECT),[10,11] capable of providing simultaneous assessment of LV perfusion; global function (either systolic and diastolic); regional wall thickening and motion; and separate analysis of diastolic, systolic, and ungated data sets; as well as quantification of multiple ancillary parameters (LV mass, geometry, lung-heart ratio, transient ischemic dilation [TID] ratio). Currently, there are several gated MPS computer software packages, including programs from the University of Michigan (Ann Arbor, Mich),[12-14] Emory University (Atlanta, Ga),[15,16] Stanford University (Stanford, Calif),[17,18] and Yale University (New Haven, Conn),[19] as well as some others. These software packages have been validated in head-to-head comparisons with clinically proven imaging methods such as echocardiography and magnetic resonance imaging (MRI) of MUGA (Table 1). In addition to ventricular function measurements, these software packages are able to quantify regional myocardial perfusion parameters, as well as the ventricular function measurements. For both function and perfusion computer assessments, there has also been extensive research demonstrating excellent repeatability of the results.

Finally, the important technical milestone adding to the clinical importance of gated SPECT is the ability to (1) store the large amounts of digital data, including raw data sets and reconstructed images, with the capability to easily retrieve this information as needed, and (2) gen-

Table 1. Continued

Institution: Commercial name			
University of Michigan: 3D-MSPECT and 4D-MSPECT	**Stanford University: MultiDim**	**Yale University: GSCQ**	**Various others**
Automatic	Semiautomatic	Automatic	Semiautomatic
3-D	3-D	3-D	2-D
Gradient[12,14]	Moment[17,18]	Maximal pixel, partial volume[19]	Partial volume,[32,33,183] threshold,[35-38] elastic surface,[30] image inversion[40]
MUGA,[56] 2-D echo,[81] MRI,[72,73,88,89] contrast ventriculography,[13,14]	First pass,[91] MUGA,[18,49,92] 2-D echo[92,93]	First pass,[44] MUGA[19,44,94]	First pass,[40] MUGA,[36,38,39,56,95] MRI,[96,97] 2-D echo,[80] contrast ventriculography[40,98,99]
MUGA,[56] MRI,[12,72,73,88] excised hearts[184]	First pass,[91] MUGA,[49] contrast ventriculography[92]	Excised hearts[184]	MUGA,[38-56] 2-D echo,[80,185] contrast ventriculography[99]
MRI[8]			2-D echo[187]

erate automatic reports with the possibility of storing of all of the relevant clinical information in the large data registries. Directly related to this ability is also short- and long-term follow-up data accumulation in the local nuclear imaging databases in some of the large academic centers,[20] as well as generation of large multicenter gated MPS registries.

Clinical Developments Related to Gated SPECT

Clinical evolution of the method of gated MPS followed shortly after the development of technical aspects of the field. Interest in gated SPECT and its development was based on its ability both to assist with technical artifacts encountered during image interpretation and to provide additional clinically useful measurements of LVEF, volumes, and wall motion simultaneously along with myocardial perfusion results on a routine basis. The initial clinical use was to increase specificity in image interpretation. Myocardial perfusion defects that do not change between rest and stress are generally considered to represent areas of prior myocardial scarring. Because of nonuniform attenuation of radioactivity by tissue, reconstructed SPECT images in patients without disease frequently show apparent nonreversible perfusion defects, most commonly in the inferior wall in men and in the anterior wall in women. It can be difficult from the perfusion scans alone to differentiate attenuation artifacts from true fixed perfusion defects. Gated SPECT improved this assessment by allowing the motion and thickening of the involved myocardial segments to be evaluated. Early in the experience with gated SPECT, Taillefer et al[21] reported that gated sestamibi SPECT studies in women were more specific than nongated Tl-201 SPECT studies, presumably because the visual readers took into account the motion of segments with apparent fixed perfusion defects in the anterior wall. The concept used is that if wall motion or thickening of a segment with an apparent fixed perfusion defect is normal, the defect is probably artifactual. Use of gated SPECT for this purpose is limited to the assessment of fixed perfusion defects, because reversible defects due to stress-induced ischemia typically exhibit normal motion on the poststress images (in the absence of stunning, as discussed later). Even if the gated SPECT finding does not actually change the reader's overall interpretation, it increases observer confidence about the presence or absence of abnormality. This phenomenon was first reported by Smanio et al[22] and has subsequently been confirmed by other investigators.[23] Regarding increased reader confidence provided by gating in the MPS interpretation, the recent American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines for the clinical use of cardiac radionuclide imaging state that "although this phenomenon is difficult to verify and quantify, it is reasonable to expect that it would result in a reduction in the number of 'equivocal' studies reported."[2]

Soon thereafter, the ability of gated SPECT to define the presence of poststress worsening of LV function, either segmental/regional or even global (if severe or multiple RWMAs were caused by stress), was described.[24] This phenomenon, representing exercise-induced stunning, became recognized as a marker of the presence of a severe stenosis, usually implying the presence of a critical ($\geq$90%) stenosis of the associated epicardial coronary artery, supplying the "stunned" segment.[25] This finding formed the basis for the concept that stress ventricular function could add to the detection and risk assessment of patients with true abnormalities.

Arguably the most important clinical development and achievement of the entire field of nuclear cardiology is that MPS now plays a central role in mainstream clinical cardiology practice as a means for risk stratification of the patient with known or suspected CAD. On the basis of large databases including clinical information on tens of thousands of patients who underwent nuclear imaging and were subsequently followed up, robust evidence has emerged showing that MPS is effective for this application. These results have supported a change from a diagnosis-based approach to the decision about who should be considered for revascularization to a risk-based paradigm in which nuclear imaging plays a prominent role.[26] With a risk-based approach, the focus is on identifying patients at risk for major cardiac events, especially cardiac death, as well as all-cause mortality, because to date only mortality endpoints have been proved to be affected by coronary revascularization procedures.

The ability of MPS to risk-stratify patients has been shown in a wide variety of clinical reports, involving thousands of patients, undergoing MPS with different stressors (exercise, vasodilator, dobutamine), with different tracers (thallium, sestamibi, tetrofosmin), and in a wide variety of clinical settings and patient subgroups. Recently, the ability of gated SPECT, with assessment of ventricular function parameters, as well as myocardial perfusion, has been shown to further enhance the ability of MPS as a risk-stratification tool.[27]

We will describe in detail some of the technical and clinical developments in the field of gated MPS.

Gated MPS Acquisition Protocols

In a nongated SPECT acquisition, the camera detector(s) rotated around the long axis of the patient, acquiring 1 projection image at each of many evenly spaced angular locations (steps) along the acquisition orbit.[28] With gated SPECT acquisition, several projection images (8 or 16 and, recently, even 32) are acquired at each

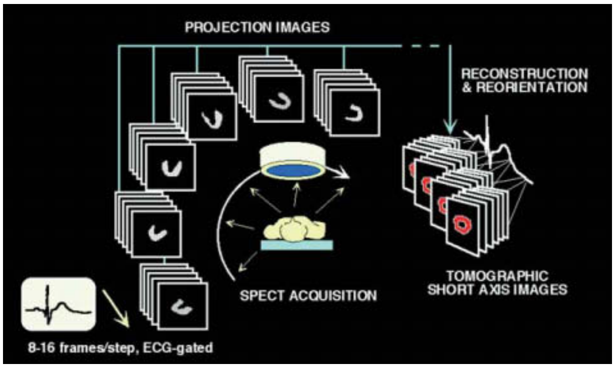

Figure 1. Schema of ECG-gated perfusion SPECT acquisition and processing. (Reprinted with permission from reference 9.)

projection angle, with each image corresponding to a specific portion of the cardiac cycle termed *interval* or *frame* (Figure 1). The gating of a SPECT acquisition is easily implemented by use of the QRS complex of the ECG signal, because its principal peak (R wave) corresponds to end diastole. The gating hardware interfaces with the acquisition computer that controls the gantry, and data corresponding to each frame are automatically sorted by the camera into the appropriate image matrix. All projection images for a given interval can be reconstructed/reoriented into a SPECT or tomographic image volume via filtered backprojection or iterative reconstruction techniques, and volumes relative to the various gated SPECT intervals can be displayed in 4-dimensional format (x, y, z, and time), allowing for the assessment of dynamic cardiac function. In addition, summing all individual intervals' projections at each angle before reconstruction produces an "ungated" or "summed gated" SPECT image volume, from which perfusion can be assessed. Thus gated SPECT acquisition yields both a standard SPECT data set and a larger gated SPECT data set. Of note, if counts are not included in the gated data set because they are associated with heartbeats falling outside of the "acceptance window," it is desirable for the standard (summed) data set to contain them; this can be achieved through use of an "extra frame" (a 9th frame in 8-frame gated SPECT acquisitions or a 17th frame in 16-frame gated SPECT acquisitions), where all rejected counts are accumulated.[29] The strong appeal of gated SPECT imaging is a direct consequence of the ease and modest expense with which perfusion assessment is "upgraded" to the assessment of perfusion plus function and accounts for the phenomenal growth of the technique over the past decade (Figure 2). Initially, only poststress gated acquisitions were commonly used. Over time, with increasing experience and with increasing speed of the computer systems, it became the routine of most laboratories to perform gated SPECT

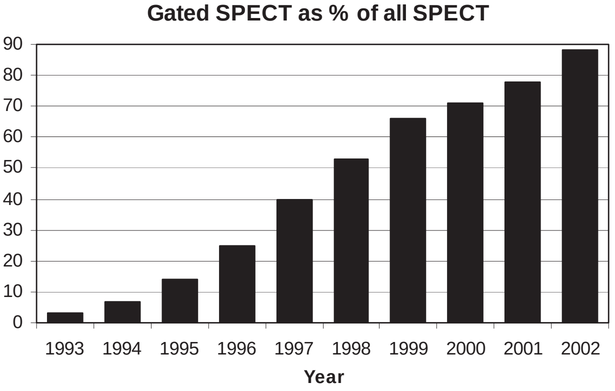

Figure 2. Growth in percentage of all perfusion SPECT studies acquired by use of ECG-gated technique (courtesy of IMV Medical Information Division, Des Plaines, Ill). (Reprinted with permission from reference 9.)

both at rest and after stress, allowing for a study to be interpreted as showing poststress stunning through comparison of wall motion on the prestress and poststress gated studies.

Initial protocols with sestamibi and tetrofosmin were described as beginning 1 hour after stress tracer injection. Early after sestamibi became commercially available, Taillefer et al[29a] demonstrated that imaging could be performed as early as 15 minutes after stress injection. The adoption of this earlier poststress imaging time has most likely had the effect of increasing the frequency of observations of poststress stunning, because it is known that this process, by definition, resolves with time. Although imaging earlier than 15 minutes after stress is generally not recommended because of "upward creep of the heart," it is possible that with the application of effective motion-correction algorithms,[30] imaging could be started as early as 5 minutes after stress, further increasing the frequency of observed myocardial stunning by gated SPECT.[31]

Available Algorithms for Analysis of Gated MPS

Concomitant with the increased adoption of gated perfusion SPECT protocols, the past 10 years have witnessed a substantial increase in the development and use of algorithms for the quantitation of global and regional ventricular function by use of gated SPECT. In fact, it is now estimated that essentially all gamma cameras used for cardiac SPECT are directly connected to a computer or workstation running gated SPECT software for function quantitation, at least in the United States. Several software approaches for analysis of ventricular function from gated SPECT are currently commercially available. Table 1 presents a synopsis of published data on commercially available quantitative gated SPECT algorithms, including their principles of operation and the validation of parameters that they quantitate.[10,11,14-19,32-103] When combined with objective quantitative perfusion analysis approaches, the ability of these algorithms to provide automatic, operator-independent quantitative assessments of ventricular function and myocardial perfusion at rest and after stress provides nuclear cardiology with one of its most distinct advantages over other noninvasive cardiac imaging modalities.

Standard Gated MPS Study

A wide variety of global and regional function variables can be measured from gated SPECT (Figure 3). Quantifiable global parameters of function from gated perfusion SPECT include LVEF, end-diastolic volume (EDV) and end-systolic volume (ESV) of the LV cavity, mass, and TID of the left ventricle based on gated or ungated volumes. Diastolic function assessment was initially not thought to be possible with gated SPECT, but recent research shows that it is feasible if a sufficient number of gating intervals are acquired[54,55,60,104-106] (Figure 4). Quantitation of right ventricular function is generally not performed with gated MPS except in very special cases,[107] but it can be routinely performed with gated blood pool SPECT, which is outside the scope of this review. Regional parameters of function quantitated from gated perfusion SPECT images include LV myocardial wall motion and thickening.

LVEF. Quantitative measurements of LVEF by use of gated perfusion SPECT are usually volume-based rather than count-based methods. In particular, the time-volume curve allows the EDV and ESV of the LV cavity to be identified (Figure 5), from which the EF is calculated as follows: $\% \text{ LVEF} = (\text{EDV} - \text{ESV})/\text{EDV} \times 100$.

Virtually all published validation studies of gated perfusion SPECT LVEF measurements by commercially available algorithms are presented in Table 1, along with details about the studies.*

It is apparent that the agreement between gated SPECT and gold standard measurements of LVEF is generally very good to excellent. Indeed, it has been pointed out that 2-dimensional gold standards may be intrinsically less accurate than gated SPECT algorithms operating in the 3-dimensional space, because of geometric assumptions required by the former.[10]

Although most gated SPECT measurements of LVEF in the literature have been derived from images acquired by use of 8-frame gating, 16-frame gating is becoming increasingly popular. Sixteen-frame gating requires additional data storage and processing time and could result in images with unacceptably low counts.

*References 10, 14, 16, 18, 19, 41-56, 62-67, 72, 74-93.

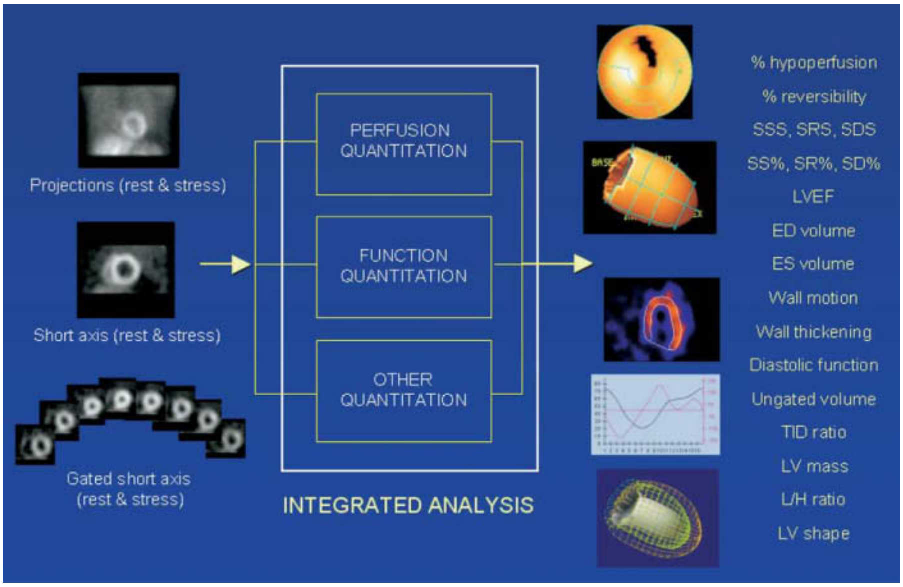

Figure 3. Diagnostic parameters derivable from gated MPS study. *SSS*, Summed stress score; *SRS*, summed rest score; *SDS*, summed difference score; *ED*, end-diastolic; *ES*, end-systolic; *L/H*, lung-heart. (Reprinted with permission from reference 9.)

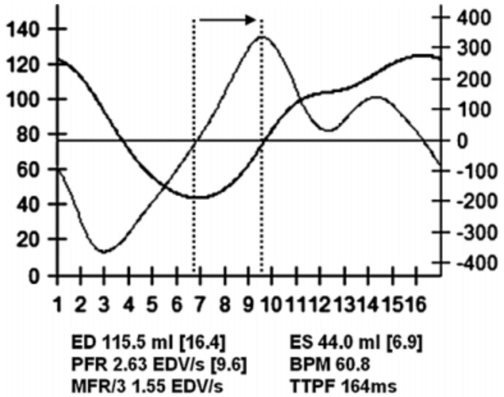

Figure 4. Example of patient's volume and filling curves over time in 16-frame gated MPS. *ED*, End diastole; *ES*, end systole; *PFR*, peak filling rate; *BPM*, beats per minute (heart rate); *MFR/3*, mean filling rate over first third of diastole; *TTPF*, time to peak filling. *Numbers in brackets* represent exact frame numbers from which the parameters are derived. The *arrow* shows TTPF, defined by the time from end systole to the greatest filling rate in early diastole. Peak filling is normalized to EDV. (Reprinted with permission from reference 106.)

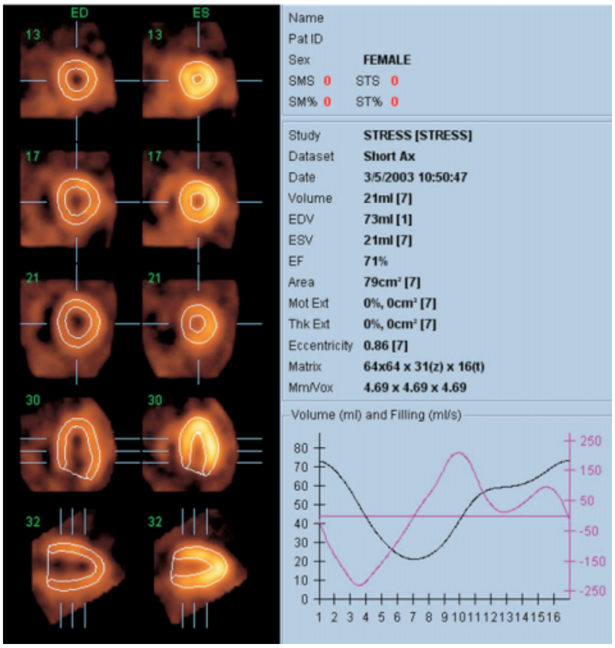

Figure 5. Volumes bound by endocardium and valve plane at end diastole (*left column*) and end systole (*middle column*) are highest and lowest point on time-volume curve (*black curve*) (frames 1 and 7, respectively, in this patient), from which LVEF is calculated. The *pink curve* is the derivative of the time-volume curve, from which parameters of diastolic function can be quantified. (Reprinted with permission from reference 9.)

However, it can also provide more accurate estimates of LVEF, because there is more precise end-systolic imaging. Gated acquisitions with at least 16 frames are considered essential for diastolic function assessment. Quantitative measurements may also depend on the type of radionuclide used. As was originally suggested with respect to nongated dual-isotope SPECT imaging (rest Tl-201/poststress Tc-99m sestamibi), resolution diff-

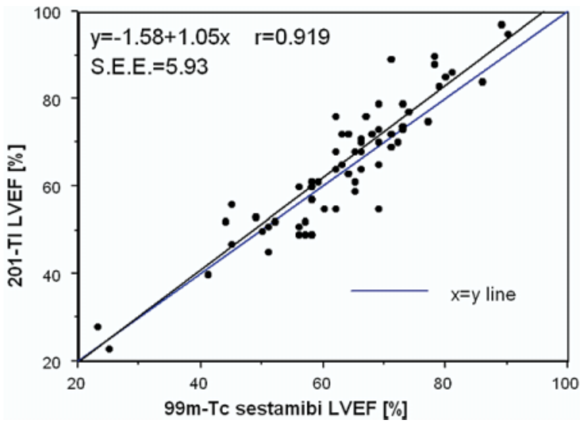

Figure 6. Relationship between LVEFs measured by QGS in nonischemic 64-patient population studied by use of gated Tc-99m sestamibi and Tl-201 SPECT. (Reprinted with permission from reference 110.)

erences should be minimized by using the same low-energy high-resolution collimator for the Tl-201 and Tc-99m acquisitions.[108] This approach is also advocated for gated SPECT imaging. Nevertheless, it is to be expected that Tl-201 images will be more "blurred" compared with Tc-99m sestamibi or Tc-99m tetrofosmin images, as a result of both the increased amount of Compton scatter associated with Tl-201 and the use of a smoother prereconstruction filter. This would translate into a mild overestimation of Tl-201 LVEF and moderate underestimation of Tl-201 EDV and ESV compared with Tc-99m–based LVEF, EDV, and ESV as reported for the QGS algorithm[64,109-111] and shown in Figure 6 with respect to LVEF. Given the many published validations of quantitative gated Tl-201 SPECT measurements against various gold standards,[†] it is unlikely that major quantitative discrepancies exist between Tl-201– and Tc-99m–based gated SPECT, as long as the studies are properly acquired and processed. This was also demonstrated in direct comparisons between separate[109,111] and simultaneous dual-isotope gated SPECT acquisitions.[42,114]

Volumes. It should be appreciated that one can usually more accurately measure ratios of LV cavity volumes, such as the LVEF or the TID ratio,[115] than the volumes themselves; for example, errors in the determination of EDVs and ESVs would be expected to occur in the same general direction and therefore would at least partially cancel out when the volumes are converted to ratios for LVEF calculation purposes.[10] Consequently, validation of quantitative LVEF measurements does not necessarily imply validation of the EDV and ESV measurements from which the LVEF is derived. Errors in the absolute measurement of LV cavity volumes can be attributed, in part, to the same factors that affect the measurement of LVEF. Specifically, (1) compared with 16-frame gating, the use of 8-frame gating will artificially increase ESVs and have little effect on EDVs, and (2) EDVs and ESVs will both be underestimated when quantitative analysis is performed on unzoomed images of small ventricles, especially with lower-resolution radioisotopes. In addition, absolute volume measurements can be adversely affected by incorrect listing of the pixel size in the image file header. The previously mentioned considerations notwithstanding, a large body of published evidence suggests that quantitative measurements of absolute LV cavity volumes from gated perfusion SPECT images agree well with established standards.[‡]

Visual assessment of regional wall motion and thickening. Visual assessment of the LV RWMA has become increasingly popular in modern nuclear cardiac imaging. The degree of wall motion is scored with a 6-point system (0, normal; 1, mild [equivocal] hypokinesis; 2, moderate hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis). Wall motion analysis is performed by visualization of the endocardial edge of the left ventricle, a process that is aided by the alternation between "contours on" and "contours off." Many commercially available programs allow readers to use a 3-dimensional representation of the function data ("views" in the QGS application), which provides 3-dimensional contours in 3 different interactive perspectives.

Visual assessment of wall thickening takes advantage of the direct relationship between the increase in the apparent brightness of a wall during the cardiac cycle (partial-volume effect)[33] and the actual increase in its thickness. The degree of wall thickening is scored with a 4-point system (ranging from 0 [normal] to 3 [absent thickening]).

During the last decade, we substantially improved our knowledge of the diagnostic value of the RWMA. It is related not only to the technical development of nuclear cardiology but also to developments in cardiac MRI, especially the understanding of the mechanisms of "delayed hyperenhancement,"[117] and direct comparison of the MRI and MPS images. In general, regional wall motion and wall thickening abnormalities accompany each other. The most common cause of discordance between wall motion and wall thickening is found in patients who have undergone bypass surgery; in these cases "abnormal" wall motion with preserved thickening of the interventricular septum is an expected normal variant. Similar discordance between wall motion and wall thickening can also occur in patients with left

†References 46, 48, 49, 51, 64, 65, 76, 79, 83, 92, 111-113.

‡References 16, 49, 50, 52, 56, 58, 59, 61-72, 74, 76-78, 80, 82-84, 87, 88, 91, 92, 100-102, 116.

bundle branch block, in which preserved thickening with abnormal motion of the interventricular septum is also a common variant. At the edges of a large infarct, normal thickening with minimal or absent motion may be observed in the peri-infarction zone, with reduced motion being a result of the adjacent infarct. The presence of thickening is considered to be indicative of viable myocardium; conversely, "normal" wall motion of an abnormally perfused segment that does not thicken could be associated with passive inward motion of a nonviable myocardial region (tethering), resulting from hypercontractility of adjacent noninfarcted segments.

Combined Rest/Poststress Regional Function Analysis

Modern computer software allows side-by-side comparison of the rest and poststress gated images to identify the development of new wall motion abnormalities; this comparison becomes even more effective with new workstations' dual-monitor displays. Wall motion abnormalities that occur on poststress images but are not seen on resting images imply the presence of ventricular stunning and are highly specific for the presence of CAD.[64,65] Moreover, even if resting gated SPECT studies are not available, the presence of discrete poststress RWMAs can often be an indicator of the presence of a severe coronary stenosis (≥90% diameter narrowing). This finding might be missed by perfusion defect assessment alone, particularly in patients with a greater degree of ischemia in a region other than that demonstrating the wall motion abnormality.[65]

Quantitative Assessment of Wall Motion and Wall Thickening

Modern image interpretation software provides quantitative methods for the evaluation of the degree of wall motion and wall thickening of each segment of the left ventricle that might augment the visual analysis of ventricular function from gated SPECT data. Algorithms for the automatic quantitative measurement of absolute endocardial motion and relative myocardial thickening between end diastole and end systole have been developed and validated[66,67]; however, their clinical use is far less common compared with visual expert assessment.

Reproducibility of Global and Regional Quantitative Function Measurements

The published results concerning the reproducibility and repeatability of measurements of quantitative function parameters from gated perfusion SPECT for commercially available algorithms demonstrate very good to excellent agreement between independent measurements.[§] Even semiautomatic algorithms that require minor operator intervention (slice selection, manual isolation of the left ventricle, manual identification of the LV cavity center, and so on) generally enjoy equal or greater reproducibility compared with conventional nuclear or non-nuclear techniques used for LV function assessment.[128] Considering the high reproducibility of the method, quantitative gated perfusion/function SPECT becomes an increasingly important tool in the sequential evaluation of patients who have progressing disease or are undergoing medical or surgical therapy.[26,129]

Stunning

Johnson et al[24] first reported in 1997 that of 61 patients with reversible ischemia imaged by use of a 2-day, treadmill stress and rest gated Tc-99m sestamibi SPECT protocol, 22 (36%) had significantly lower poststress LVEF compared with resting LVEF. The threshold of ±5.2% (2 SDs) for statistically significant differences had been determined from a separate group of 15 patients undergoing serial rest gated SPECT on consecutive days. The authors attributed the reduction in LVEF in those 22 patients to postischemic myocardial stunning persisting 30 minutes after stress, noting that all 20 patients in yet another group without reversible ischemia demonstrated excellent agreement between the poststress and rest quantitative LVEF measurements.

The association between reversible ischemia and a decrease in poststress LVEF has been successively reported by a large number of investigators for exercise stress[31,130-136] and even for pharmacologic stress.[137-143] It has been suggested that subendocardial ischemia rather than stunning might be the main causative factor for the apparent LVEF decrease, because quantitative algorithms might fail to adequately trace the endocardium in regions with the greatest ischemia and thus underestimate LVEF[144]; however, studies designed around sequential poststress gated SPECT acquisitions by use of Tc-99m–based (non-redistributing) radiopharmaceuticals have shown that systolic dysfunction tends to resolve over time despite persisting stress perfusion defects, implying that true stunning is at least a partial cause of the observed phenomenon.[31,142,145-147] Interestingly, poststress decreases in LVEF have been reported even in patients with normal perfusion[148] and are associated with significant CAD[25,133,142] and adverse prognosis.

In addition to poststress decreases in global LV function, RWMAs present after stress have been described[25,137,149,150] and may be easier to detect compared with abnormalities

§References 10, 11, 18, 24, 41, 50, 52-54, 56, 58, 70, 78, 91, 110-112, 118-127.

in global poststress function.[25,135,137,151,152] Poststress diastolic dysfunction has also been found to be associated with systolic dysfunction in patients with angina.[153]

Although myocardial stunning is a well-recognized phenomenon in conjunction with both treadmill stress[154,155] and adenosine vasodilator stress,[141,156,157] there is less agreement with regard to its duration. With respect to quantitative gated SPECT imaging, the duration in published reports ranges from less than 30 minutes[147] to 1 hour or more with exercise stress[150,158] or pharmacologic stress.[137,159] The frequency with which poststress decreases in LV function are encountered in a clinical laboratory will likely depend to a large extent on the type of patients imaged, with published data ranging from 5% to 10% of patients[78,79,160,161] to as many as 44% of patients.[148] In general, the finding is considered to be a result of severe ischemia occurring during stress and is usually associated with a critical (>90%) coronary stenosis.

TID Ratio

TID of the left ventricle was first described for the epicardial borders of stress/redistribution planar Tl-201 studies.[162] In the era of gated SPECT the same software that was used for defining the edges of the left ventricle for purposes of assessing ventricular function was applied for the automatic measurement of TID by use of SPECT. The TID ratio is calculated as the ratio of the ungated LV cavity volume after stress and at rest. The TID ratio measured by SPECT may reflect true stress-induced stunning of the left ventricle, extensive subendocardial ischemia, or a combination of the two mechanisms. Nevertheless, this parameter has been demonstrated to be a moderately sensitive and highly specific marker of severe and extensive CAD,[115,163] with higher specificity than the lung-heart ratio. Of note, multiple investigators have reported that the TID ratio and lung-heart ratio are not correlated (ie, it is quite unlikely to find both to be abnormal in any given patient),[164,165] suggesting that these measurements may provide complementary information.

The threshold for TID ratio abnormality depends on the choice of rest and poststress radiopharmaceuticals, method of stress, and possibly patient sex[166,167] but appears to be relatively independent of the particular quantitative algorithm used; published values range from 1.14 for a same-day post-exercise/rest Tc-99m sestamibi protocol[167] to 1.22 to 1.23 for a rest Tl-201/post-exercise Tc-99m sestamibi protocol,[115,167] with pharmacologic stress producing somewhat higher thresholds, as high as 1.36 with adenosine stress and dual-isotope MPS.[163] It is also possible to derive the TID ratio from EDV or ESV of the LV cavity,[168] although the implications and potential advantages of this approach have not been studied in depth.

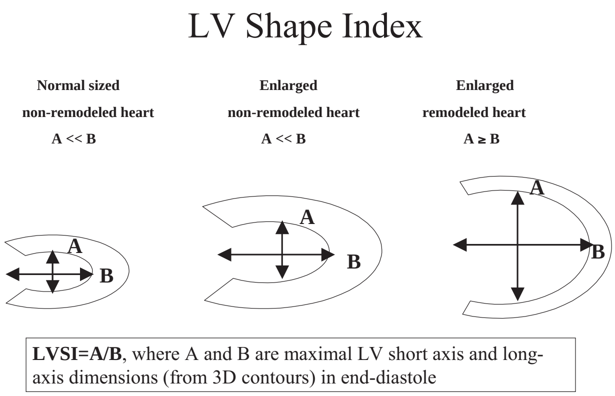

Figure 7. Schema of algorithm for measurement of 3-dimensional (*3D*) LV shape index (*LVSI*). (Reprinted with permission from reference 169.)

LV Shape

The left ventricle can be reasonably approximated by an ellipsoid,[10] and consequently, it is easy to estimate its shape by use of the major and minor axes of the ellipsoid that best fits it. The closer the axes are in size, the closer to a sphere the ellipsoid becomes, a case consistent with LV remodeling associated with congestive heart failure or other pathologies. A potentially more accurate algorithm for shape assessment has also been proposed that is based on the regional search for the maximal distance between endocardial surface points[169] (Figure 7).

Integration of Gated SPECT in Diagnostic Workup of Patients With Suspected CAD

According to current guidelines,[2] the consideration of using a stress imaging study is preceded by assessment of the pretest likelihood of CAD, by use of Bayesian analyses of patient age, sex, risk factors, and symptoms, as initially developed by Diamond and colleagues.[170-172]

As shown in the proposed clinical algorithm of management of patients with suspected CAD (Figure 8), those patients who are clinically classified as low-likelihood (<15%) patients do not require stress testing at all. They would, of course, require modifications of coronary risk factors by means of the primary or secondary prevention depending on their coronary risk factors. It should be noted in this regard that patients with exertional shortness of breath should not be classified as having a low likelihood of CAD. We recently demonstrated that these patients have mortality outcomes that are even higher than those in patients with typical angina.[20] From a standpoint of disease likelihood, unless pulmonary or noncoronary heart disease or another known source of exertional dyspnea is present, these

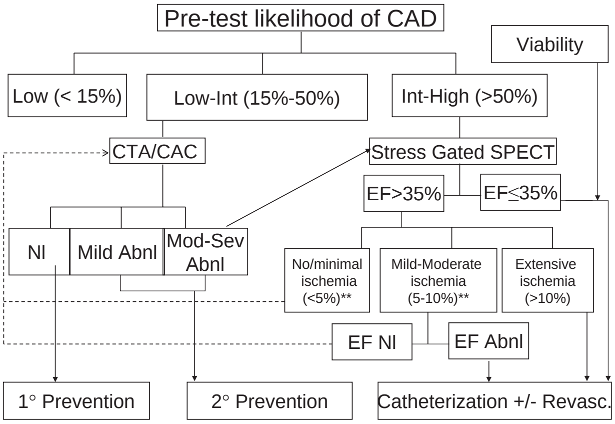

Figure 8. Integration of combined perfusion and function assessment by gated MPS in clinical algorithm of management of patients with suspected CAD. *Int*, Intermediate; *Revasc*, revascularization. *N1*, normal; *Abnl*, abnormal; *CTA*, CT coronary angiography; *CAC*, CT coronary artery calcium. Viability assessment is performed by use of any of the proven methods (Tl-201 rest-redistribution, low-dose dobutamine echocardiography, contrast MRI, or fluorine-18 fluorodeoxyglucose–positron emission tomography).

patients should most likely be considered as having a high likelihood of CAD.

In patients who are identified as having an intermediate to high pretest likelihood of CAD (>50%) after stress testing, referral for cardiac catheterization may become appropriate, depending on the magnitude of inducible ischemia on stress testing. By means of gated MPS, patients in this group would have severe LV dysfunction, however, they may become candidates for revascularization regardless of the perfusion study, particularly if a viability test (eg, rest/redistribution thallium study, nitrate-augmented sestamibi or tetrofosmin study, fluorodeoxyglucose–positron emission tomography, low-dose dobutamine function study, or cardiac magnetic resonance study) shows a significant amount of viable myocardium. A group of patients with a high probability of severe or extensive CAD can also be identified who may require urgent catheterization; this would include patients with significant stress-induced ischemia and especially new RWMAs and ischemic stunning or patients who have positive ancillary signs such as TID.

In the past we have suggested that patients with a low to intermediate pretest likelihood of CAD, who are able to exercise, can be referred for regular treadmill stress testing without imaging. More recently, we have suggested that coronary calcium testing (in asymptomatic patients) or coronary computed tomography angiography (in symptomatic patients) is now a more effective approach for patients with this low to intermediate pretest likelihood of CAD.[173]

Added Value of Gated SPECT in Clinical Risk Stratification

Assessment of ventricular function variables from gated SPECT has added to perfusion assessments in clinical risk stratification. One form in which this has become apparent is seen in the manner in which gated function studies have improved the identification of patients with severe and extensive CAD. This was previously mentioned in part by noting the added value of TID assessment, an automated measurement that is an offshoot of the methods used for assessing ventricular function. Evidence that the function variables from gated SPECT provided additional useful clinical information over perfusion by gated SPECT was described by Lima et al.[174] They demonstrated that perfusion defect assessment alone frequently severely underestimated the extent of CAD in patients with triple-vessel or left main CAD. Importantly, they demonstrated that the added assessment of regional function from gated SPECT significantly improved the identification of these patients as having multivessel CAD.[174] Recently, our group has documented that the normal limits for LVEF and LV volumes are different in men and women, potentially impacting, to a degree, the manner in which the results of gated SPECT are used in management decisions.

Given the relatively short time in which gated SPECT has been in widespread use, it is not surprising that there are limited reports with respect to its added value or role in risk stratification, because studies of this nature require a follow-up period of several years. Sharir et al[174a,175,176] provided the first published reports on prognosis with poststress gated SPECT, studying a group of 2686 patients, followed up for 20.9 ± 4.6 months; in their study LVEF provided incremental information over perfusion defect extent and severity for the prediction of cardiac death (Figure 9). Surprisingly, this study showed that, after consideration of LVEF, SPECT perfusion data were no longer predictive of adverse outcomes.

We believe that these early studies did not find additional prognostic value from the perfusion variables because of a recently identified referral bias in which patients with the greatest extent and severity of ischemia preferentially underwent early (≤60 days) revascularization. These patients, representing those at highest risk, were then censored from assessment of the prognostic value of the test. Conversely, we have recently shown in a study of 3369 patients that LVEF did not influence this referral process; hence the risk associated with LVEF was not impacted by revascularization selection.[177] The effect of censoring the patients who underwent early revascularization, therefore, was that far more patients with high-risk perfusion abnormalities than those with high-risk function abnormalities were removed from the

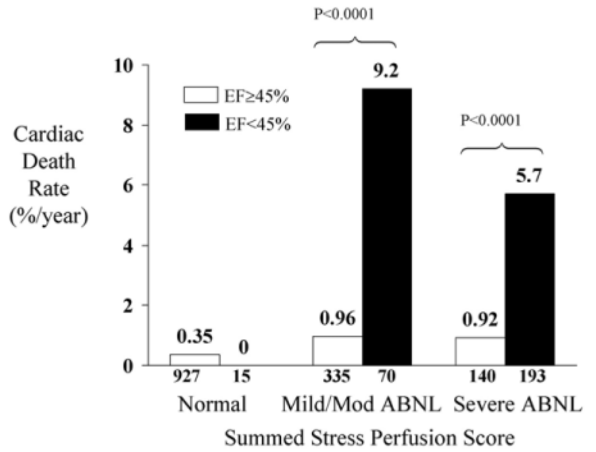

Figure 9. Frequency of cardiac death per year in patients as function of scan result (normal, mildly to moderately [*Mod*] abnormal [*ABNL*], and severely abnormal) and poststress EF of 45% or greater (*white bars*) and EF less than 45% (*black bars*) by quantitative gated SPECT. Significant differences ($P < .0001$) are present between lower and higher poststress EF in both abnormal scan groups. *Numbers under bars* represent numbers of patients. (Reprinted with permission from reference 9.)

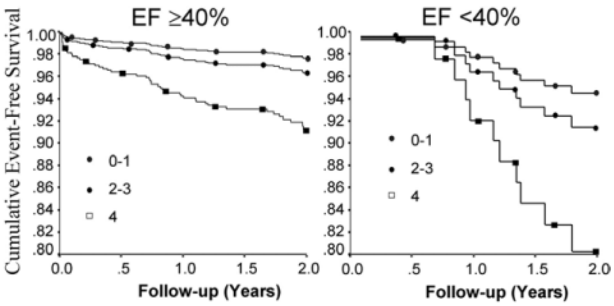

Figure 10. Cumulative event-free survival rates in patients as function of reversibility score (0-1, 2-3, and 4) and poststress EF of 40% or greater (*left*) and EF less than 40% (*right*) by quantitative gated SPECT. Significant risk stratification is achieved by perfusion results in both EF categories. (Reprinted with permission from reference 179.)

study (censored), artifactually reducing the prognostic power of the perfusion abnormalities.

Data from this group also showed a role for LV volumes from the gated information in risk stratification of patients. Indeed, LV ESV provided added information over poststress LVEF for prediction of cardiac death.[178] Furthermore, this group later reported that perfusion variables are stronger predictors of nonfatal myocardial infarction, whereas after risk adjustment, poststress EF was not predictive of nonfatal myocardial infarction.[175]

A recent report by Thomas et al[179] from a community-based nuclear cardiology laboratory followed 1612 consecutive patients undergoing stress SPECT over a follow-up period of 24 ± 7 months (0.2% lost to follow-up). Overall, patients with normal SPECT findings had a hard event rate of 0.4%, as compared with 2.3% for those with abnormal SPECT findings ($P < .0001$). Furthermore, these authors found that poststress EF added incremental value over pre-SPECT and perfusion data. Even after adjustment for these variables, each 1% change in LVEF was associated with a 3% increase in risk of adverse events. In this study perfusion data also added incremental value over EF data. In both patients with EF lower than 40% and those with EF of 40% or greater, the results of stress perfusion risk-stratified patient risk (Figure 10). Travin et al[27] subsequently reported a series of 3207 patients who underwent stress SPECT and were followed up for adverse events. They found that both abnormal wall motion and abnormal EF were associated with increased risk; an abnormal gated SPECT wall motion score was associated with an annual event rate of 6.1% compared with 1.6% for a normal score, and an abnormal LVEF versus a normal LVEF was associated with an event rate of 7.4% versus 1.8%, respectively ($P < .001$ for both comparisons). Similar to previous studies, myocardial infarction was predicted by the number of territories with a perfusion defect but not by EF. On the other hand, as reported by Thomas et al, cardiac death was predicted by the number of territories with a perfusion defect and an abnormal EF. Finally, also as reported before, the results of gated SPECT added incremental value over both normal and abnormal SPECT perfusion.

Incremental Prognostic Value of Gated SPECT: What Can Gated SPECT Add to Perfusion Findings?

A problem of particular interest with regard to outcome research in modern cardiology is the impact of including both patients treated medically and those treated with early revascularization on the results of survival analyses. Importantly, this approach allowed, for the first time, a means by which to identify, on the basis of noninvasive testing, which patients are likely to accrue a survival benefit with one therapeutic approach compared with another.[180] However, this study did not include data regarding LV function or LVEF; hence the interrelationship of inducible ischemia and LV function have not been defined. These data have, however, been reported in preliminary form.[181] In this report the authors examined the hypothesis that although EF predicts the risk of cardiac death, only measures of ischemia will identify which patients will accrue a survival benefit from revascularization compared with medical therapy after stress SPECT. In this study 5366 consecutive patients

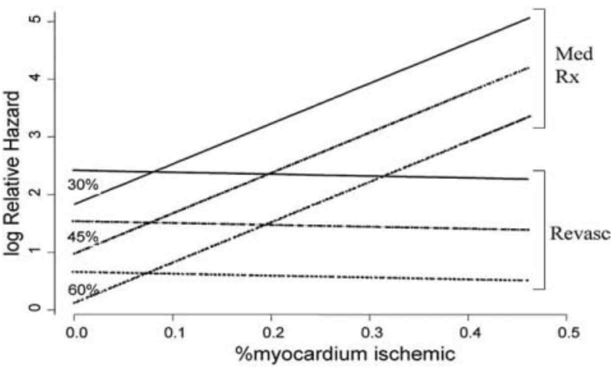

Figure 11. Predicted relationship based on Cox proportional hazards modeling between log hazard ratio versus percent ischemic myocardium in patients treated medically (*Med Rx*) or with early revascularization (*Revasc*) after stress SPECT. Three pairs of lines are shown for poststress LVEFs of 30%, 45%, and 60%. Within each pair, patient risk is unchanged across values of percent ischemic myocardium with early revascularization and increases significantly in patients treated medically. With decreasing EF, risk in both patients who underwent early revascularization and those treated medically increases for any level of percent ischemic myocardium. This increase in risk demonstrates the incremental value of LVEF over other factors. Similarly, the increase in risk with increasing percent ischemic myocardium in the setting of medical therapy demonstrates the incremental value of SPECT measures of inducible ischemia. Finally, the differential risk with medical therapy versus revascularization identified by percent ischemic myocardium demonstrates its ability to identify treatment benefit. Model $P < .00001$. (Reprinted with permission from reference 9.)

without prior revascularization were followed up for 2.8 ± 1.2 years, during which 146 cardiac deaths occurred (2.7%, or 1.0% per year). After adjustment for pre-SPECT data and the use of a propensity score to adjust for nonrandomized treatment assignment, the authors found several interesting findings. First, as has been previously shown,[175] LVEF was the most powerful predictor of cardiac death. In addition, as shown before,[27,179] stress perfusion results added incremental value over EF for prediction of cardiac death. Most importantly, only the percent ischemic myocardium was able to predict which patients would accrue a survival benefit with revascularization over medical therapy. Importantly, with respect to a relative benefit (which patients will have improved survival with revascularization over medical therapy), only inducible ischemia was a predictor. On the other hand, LVEF played a crucial role in identifying the absolute benefit (number of lives saved per 100 treated, number of years of life gained with treatment) for a given patient (Figures 11 and 12). This finding is similar to that of the meta-analysis of randomized clinical trial data discussed previously comparing medical therapy with revascularization.[182] Prediction of absolute benefit after gated SPECT is also a function of clinical risk factors, as previously described,[180] such as patient age, sex, diabetes mellitus, and type of stress performed.

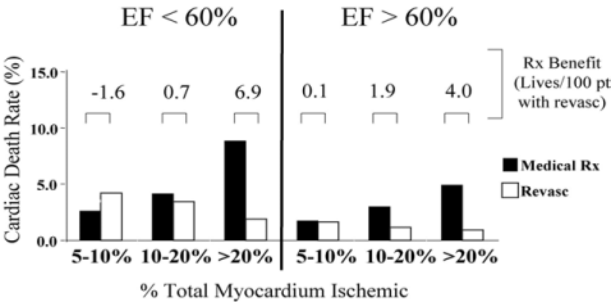

Figure 12. Predicted cardiac death rates based on final Cox proportional hazards model for patients with EF less than 60% versus those with EF greater than 60%. Results were further stratified by percent ischemic myocardium (5%-10%, 10%-20%, and >20%). Within each category of inducible ischemia, predicted cardiac death rates are shown separately for medical therapy (*Rx*) after stress SPECT (*black bars*) versus early revascularization (*Revasc*) (*white bars*). In both low- and high-EF subgroups, the risk associated with revascularization is significantly lower in the setting of marked ischemia. The number of lives saved per 100 patients treated (*pt*) (difference between predicted survival rate with early revascularization versus medical therapy) is shown over the bars. The number of lives saved per 100 patients treated is significant in patients with 20% ischemic myocardium and is greater in those with low EF than in those with high EF. Model $P < .0001$. (Reprinted with permission from reference 9.)

CONCLUSION

We have reviewed the development of assessments of ventricular function by use of gated MPS and the ways in which these measurements have contributed to the emergence of gated SPECT with regard to its important role as a major tool of modern cardiac imaging. We conclude that gated MPS imaging has shown a unique capability to provide precise, reproducible, and operator-independent quantitative data regarding myocardial perfusion, global and regional systolic and diastolic function, stress-induced RWMAs, ancillary markers of severe and extensive disease, LV geometry and mass, and finally, the presence of scars and viability. Adding functional data to perfusion provides highly effective means of increasing both diagnostic accuracy and reader confidence in the interpretation of the results of perfusion scans. Assessment of global and regional LV function has improved the prognostic power of the MPS study, which has been shown to play a central role in guiding patient management decisions, particularly regarding the need for revascularization, even without function variables.

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