The additive prognostic value of gated myocardial perfusion scintigraphy in patients with coronary artery disease

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The Additive Prognostic Value of Gated Myocardial Perfusion Scintigraphy in Patients with Coronary Artery Disease

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The studies described in this thesis were performed at the department of Cardiology and Radiology, division of Nuclear Medicine, of the Leiden University Medical Center, Leiden, the Netherlands.

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Voor mijn ouders
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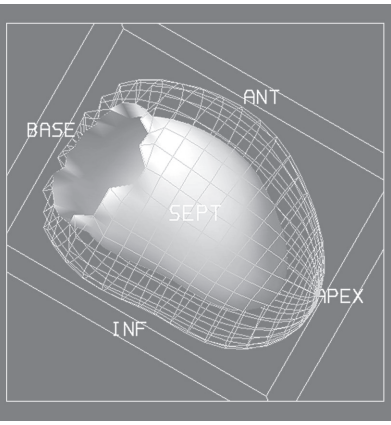


The application of gated SPECT in nuclear cardiology. Introduction and outline

INTRODUCTION

Coronary artery disease is the leading cause of death in western countries and has a major impact on modern society [1,2]. In the latter part of the last century several dramatic changes, because of technological advances or improved therapeutic options, occurred in the care and management of patients with coronary artery disease. As a result of both new or improved diagnostic and therapeutic capabilities, significant chances took place in the population with respect to the occurrence of various patterns of ischemic heart disease. The improvement in survival after acute myocardial infarction resulted in a markedly increased population of patients with more or less extensive cardiac disease. Patients tend to be older and to have a more severe extent of disease. The advances in medical management come with an increase in cost [3]. Costs have become the major factor in the development and implementation of clinical protocols for the management of this patient group [4,5]. In this setting it becomes more important to go beyond establishing a diagnosis of coronary artery disease, and towards the level of risk stratification [3]. This need for risk stratification applies to patients with either acute or chronic coronary artery disease.

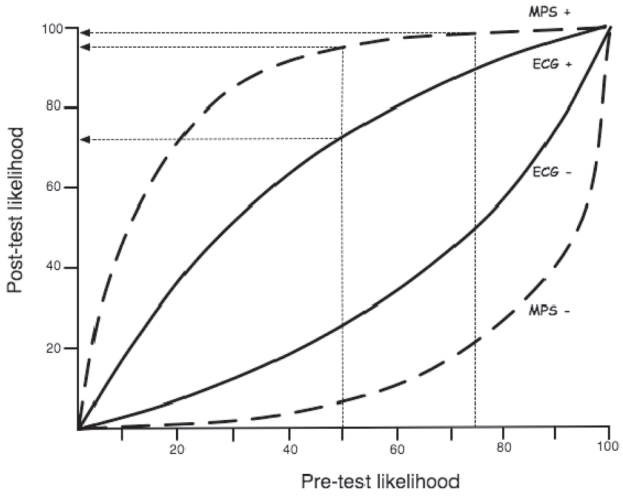
Stress test is a technique to assess information about myocardial perfusion. However, under certain conditions the sensitivity or the specificity of the stress test dropped to low levels. For instance in patients with a history of myocardial infarction, or with an acquired left bundle-branch block, or in those unable to attain the required exercise level, the electrocardiographic criteria often proved too crude [6,7]. Especially in women, the diagnostic power of the stress test appeared to be quite disappointing [8-11]. Although some reports indicate that gender-specific criteria may result in significant improvements [12]

Coronary angiography enables us to assess coronary artery stenosis, wall motion and left ventricular ejection fraction (LVEF). Unfortunately this is a costly and invasive procedure. Myocardial perfusion scintigraphy provides additional information about myocardial perfusion, but with far less anatomical detail. It is essentially noninvasive. Main use of myocardial perfusion scintigraphy is in risk stratification and in the assessment of the presence of reversible ischemia in patients with known or suspected coronary artery disease. As such it is used as a diagnostic pre-filter. It was concluded that patients with either a very high, or a very low prior risk for ischemic heart disease should not undergo myocardial perfusion scintigraphy [13] (figure 1). In a large proportion of patients with an intermediate probability of reversible ischemia, no reversible ischemia is actually present. These patients do not have to undergo invasive procedures. Such patients are preferably treated with medication only. This management strategy proved to be cost-effective in patients at an intermediate risk for cardiac events due to coronary artery disease [14-18].

RADIOPHARMACEUTICALS

In the early 70's thallium-201 (^{201}Tl) was introduced as a potassium analogue [19-21]. It has more favourable radio-physical features than radioactive potassium.

Figure 1. Pre- and post-test likelihood of coronary artery disease calculated using Bayesian principles for exercise ECG and Myocardial Perfusion Scintigraphy (MPS).



MPS += abnormal MPS study; MPS - = normal MPS; ECG += abnormal exercise ECG; ECG - = normal exercise ECG (adapted from reference 13).

Although ^{201}Tl performed reasonably well in patients at an intermediate risk, the number of patients that were wrongly diagnosed (false positive and false negative combined) still exceeded 10% [15, 22-26]. Thallium was not an ideal pharmaceutical for perfusion scintigraphy. It has a low photon energy (80 keV) and a rather long half-life of 72 hrs. Technetium-99m (^{99m}Tc) has a half-life of 6 hours and therefore permits the use of a larger amount of radioactivity. Also the higher photon-energy (140 keV) results in less scatter and less attenuation. Both factors contribute to an improvement in image quality.

A number of ^{99m}Tc-based pharmaceuticals has been developed and introduced for myocardial perfusion imaging, based on the assumption that their use would result in an increased image quality and thereby a significant improvement in diagnostic performance. The former proved to be true in practice, especially with the use of single photon emission computed tomography (SPECT) and more recently the use of gated SPECT. Some studies indicated a reduced number of borderline diagnoses especially with the application of gated SPECT technology [27,28].

^{99m}Tc-hexakis-2-methoxy-2-methylpropyl-isonitrile (^{99m}Tc-MIBI) was one of the first and most successful ^{99m}Tc-based pharmaceuticals. Tetrofosmin became available somewhat later in the nineties. Its clinical introduction and initial evaluation in humans took place 'in the wake' of the introduction of ^{99m}Tc-sestamibi for myocardial perfusion scintigraphy. Tc-99m-1,2 bis [bis (2-ethoxyethyl) phosphinol] ethane, (tetrofosmin, Myoview®, Amersham International U.K.) is cationic and lipophilic. The most likely mechanism for the uptake of ^{99m}Tc tetrofosmin is by potential driven diffusion of the lipophilic cation across the sarcolemmal and mitochondrial membranes [29-32]. ^{99m}Tc-tetrofosmin shows little if any redistribution. The absence of redistribution is the reason for ^{99m}Tc-tetrofosmin administration during both stress and rest. The uptake in the myocardium is rapid. Approximately 1.2% of the injected dose of ^{99m}Tc-tetrofosmin can be found in the myocardium within five minutes. It remains stable for the first hour, then gradually drops to 1.0% at 2 hours and 0.7% at 4 hours. At 24 hours only 0.2% of the injected dose was still present in the myocardium. The clearance from the bloodstream is rapid, with less than 5% remaining in the blood pool at 10 minutes post-injection. Approximately

66% of the injected dose activity is excreted within 48 hours post-injection with approximately 40% excreted in the urine. Faecal clearance varies between 17 and 41% with a tendency towards lower faecal clearance after exercise [33].
The uptake in many organs was dependent upon the exercise level at the time of injection. The uptake in lungs, liver, gallbladder, kidneys, thyroid and gastrointestinal tract all showed a 1.2 to 2.2-fold decrease in uptake after exercise [33]. Early liver uptake dropped rapidly from 4.9-10.6% of the injected dose at 5 minutes to less than 1.6% at two hours [33]. The gallbladder activity reaches its peak at 2 hours. At rest it can contain up to 11% of the injected dose. The relatively high liver activity is the major disadvantage of ^{99m}Tc-based pharmaceuticals. Therefore, image acquisition starts 45 to 60 minutes after administration. The lung uptake is low, resulting in heart-to-lung ratios of 3 to 5 minutes post injection and rapidly improving with time [33].
Side-effects are very rarely seen. After intravenous injection a very small number of individuals notices a "metallic" taste, or reports mild nausea. To date so far, no serious side-effects have been reported [34].
Besides information on myocardial perfusion it is also important to be informed about the left ventricular function. The high count density achieved with ^{99m}Tc-tetrofosmin and the fact that ^{99m}Tc-tetrofosmin retains in the myocardium make it possible to analyse left ventricular function, even until several hours post injection.

LEFT VENTRICULAR FUNCTIONAL IMAGING MODALITIES

The left ventricular ejection fraction can be derived from scintillation by several different diagnostic methods. The ventricular pump function can be measured by imaging the cardiac transit of an intravenously administered bolus of radioactivity, first-pass radionuclide angiography [35,36]. A bolus of tracer is imaged as it passes through the cardiac chambers. End-diastolic (EDC) and end-systolic (ESC) counting rates are measured during left ventricle (LV) bolus transit and corrected for the background, represented as a time activity curve. The peak shows the heart in end-diastolic phase (ED) and the lowest point of the curve shows the heart in end-systolic phase (ES). The left ventricular ejection fraction is calculated by the formula: LVEF=(ED-ES)/ED. The ejection fraction is based on the amount of radioactivity (number of 'counts') and is not based on the geometry of the ventricle.
The second, more commonly used, method is equilibrium radionuclide ventriculography [35]. With the latter method autologous red blood cells are labelled with ^{99m}Tc-pertechnetate resulting in high-contrast imaging of vascular space. ECG triggered (synchronic with the R-top signal) data on gated ESC and EDC acquired over several hundred cardiac cycles are summed, and corrected for background. Depending on the method of data acquisition the RR-interval is divided into 16 to 24 frames. The division of the cardiac cycle into more frames is called 'multiple-gating'. Computer programs assess count-rate changes, yielding measurements of global and regional ejection fraction, volumes, and emptying and filling rates of left and right ventricle [35,37,38]. The analysis of global and regional left ventricular function can be assessed either at rest or during stress. This is all viewed in cine format. The contractile reserve

can be assessed by this method and used as a sensitive test for impaired global and regional ventricular function.
A number of potential errors that can affect the accuracy of LVEF measurements has been explained in literature, such as poor definition of blood pool edges, inadequate gating, insufficient separation of left and right ventricles, significant soft tissue attenuation over the left ventricle and inappropriate background subtraction [35].

Evolution of myocardial function and perfusion imaging.

In 1984 Narahara et al. [39] were the first to report the ability of combining assessment of ventricular function and myocardial perfusion during one single test using bicycle exercise. Gold-195m with a half-life of 30.5 seconds was used for first pass radionuclide angiography (RNA) and thallium-201 was used for the assessment of the myocardial perfusion. Immediately after the administration of 2 mCi of thallium-201, approximately 20 mCi of gold-195m was injected to obtain an exercise first-transit study that required 30 seconds of acquisition time. Within 5 minutes after the acquisition of the first-transit study and the termination of exercise, the acquisition of the myocardial perfusion imaging started. Three hours thereafter, the redistribution images were obtained.
Verani et al [40] used iridium-191m, with a half-life of 4.96 seconds, for measuring the LV function with RNA, a few years later. The myocardial perfusion was measured using ^{201}Tl immediately following first pass RNA. Later, several studies reported the use of ^{99m}Tc-labeled agents to obtain information about the condition and behaviour of ventricular function with RNA and myocardial perfusion simultaneously [41,42]. In 1989 Najm et al [43] reported that they assessed a method of providing information on the left ventricular function as an adjunct to myocardial perfusion imaging using Tc-99m MIBI (2-methoxy-2-methyl-isopropyl-isonitrile). Radionuclide fractional shortening was calculated from the anteroposterior and the septum to lateral wall axes (on the anterior oblique 45° view) in diastole and systole. Data were acquired from 18 frames per cardiac cycle. The global fractional shortening correlated closely with left ventricular radionuclide ejection fraction.
The introduction of single photon emission computed tomography (SPECT) [44-46] and the continuously improving imaging hardware and reconstruction software allowed the creation of three-dimensional images of the left ventricle. The SPECT technique has several advantages over planar imaging for the analysis of perfusion and function, such as improved resolution, differentiation of overlapping myocardial regions, improved sensitivity and specificity of diagnoses, depiction in planes familiar to cardiologists and colour images improving interpretation and presentation. Due to these developments the assessment of left ventricular function and perfusion during one single acquisition has assumed enormous proportions; In 1990 Marcassa et al. [47] analyzed regional wall thickening with Tc-99m MIBI with a method based on the partial volume effect (the systolic-diastolic changes in the detected radioactivity would reflect changes in myocardial wall thickness). The myocardial perfusion images were gated in 16 frames per R-R interval. The left ventricular end-diastolic and end-systolic edges were manually drawn; this was the only operator-dependent procedure.
Faber et al. (1991) reconstructed a tomographic radionuclide ventriculogram with a 16-frame gated SPECT acquisition using ^{99m}Tc-MIBI and a cylindrical co-ordinate system was used to determine left ventricular surface points [48]. Global variables, such as volumes, ejection fraction, and myocardial mass were computed. Otherwise from asking the user to identify

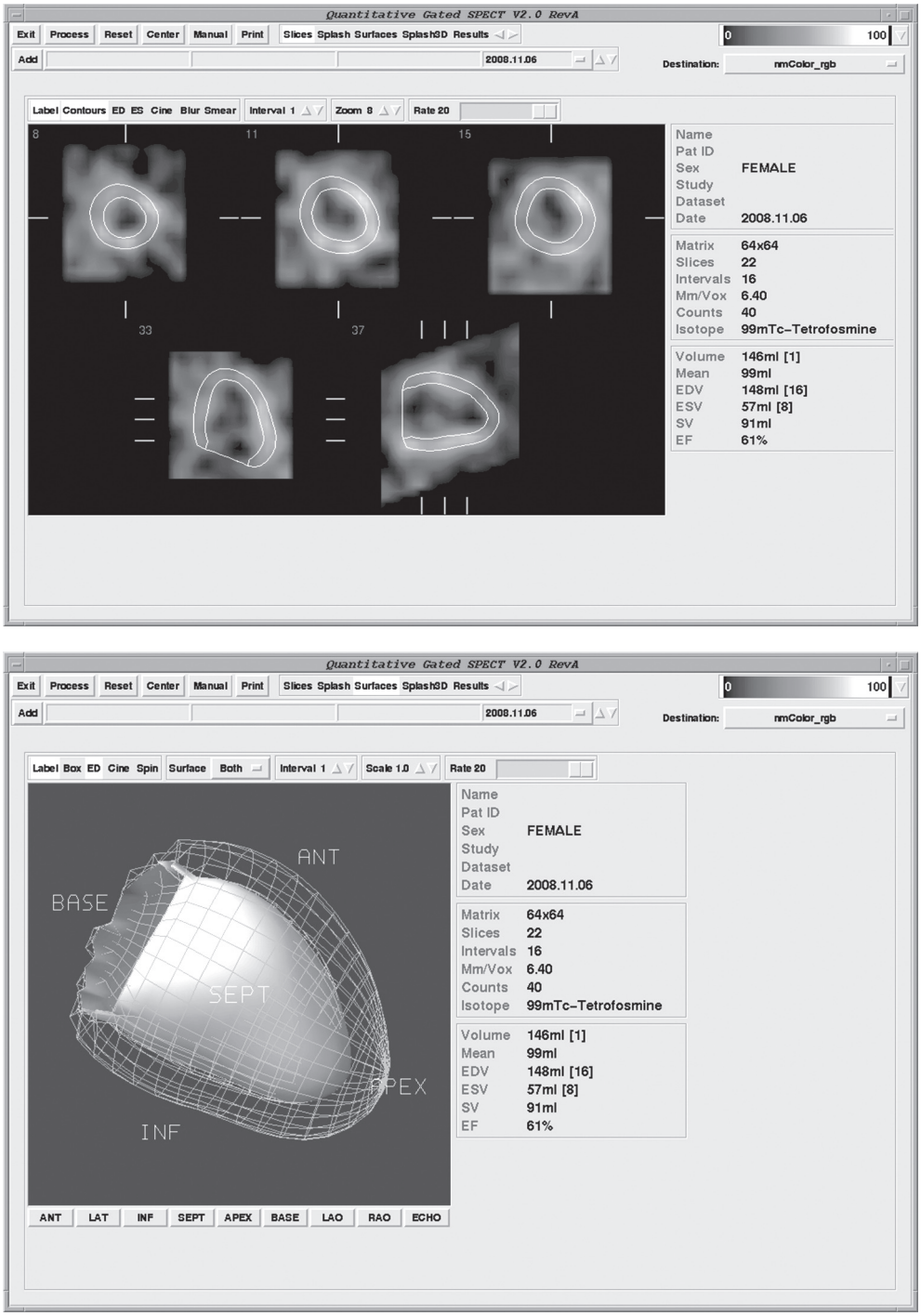
the left ventricular long axis, the method was entirely automatic. The automatically calculated motion and perfusion values from gated SPECT images were validated by comparing them with those determined from hand-traced surfaces of cardiac rotation magnetic resonance (MR) images. In 1993 DePuey et al. [49] reported on the calculation of the LVEF using an 8-frame gated SPECT myocardial perfusion acquisition after injection of ^{99m}Tc-MIBI. The endocardial borders were manually drawn at a count level of 34% of the maximum. The LVEF was derived from end-diastolic and end-systolic endocardial borders. LVEFs calculated from gated MIBI SPECT ranged from 0.21 to 0.73 and correlated linearly with gated blood-pool values with correlation coefficients ranging from 0.79 to 0.88. Intra-observer and inter-observer reproducibility in determination of LVEF from gated MIBI SPECT were suboptimal (r=0.75).
Hambye et al. [50] reported in 1997 on ECG-gated SPECT imaging. Eight time-frame gated SPECT data was collected, using ^{99m}Tc-sestamibi. Ejection fraction was calculated using a semiautomatic edge-detection technique based upon a threshold-searching method and compared with values obtained from first-pass or equilibrium radionuclide angiography. End-diastolic and end-systolic bins were selected manually by the observers on a short-axis image, using a colour cine-loop display. End-diastolic and end-systolic endocardial borders were drawn automatically on the mid-ventricular vertical (VLA) and horizontal long-axis (HLA) images at 80% of the maximum profile activity. An elliptical interpolation was applied at end-diastole and end-systole between the borders determined on these orthogonal slices to calculate the corresponding volumes. In patients with regions of severely impaired perfusion, especially those involving extended regions of the left ventricle, the thresholding algorithm was unable to draw the endocardial border accurately and therefore manual determination was necessary. Despite slight discrepancies between gated SPECT with other radionuclide angiographic methods at extreme LVEF values (under- or overestimation with gated SPECT for absolute values below 40% and over 65% respectively), there was a good correlation observed over a wide range of values. Good reproducibility was noted, with an inter- and intra-observer variability of -0.2 ± 3.5 (range –7.6 to 6.9%, r=0.97) and -0.2 ± 2.2% (range –5.9 to 3.5%, r=0.99) respectively.
In that same year, Calnon et al. [51] developed a new gated SPECT method for computing the global LVEF based entirely on changes in maximum regional myocardial counts during systolic contraction, independent of endocardial edge detection or other geometric measurements. By quantifying the changes in maximum pixel counts (partial volume effect), regional systolic wall thickening could be assessed.

QUANTITATIVE GATED SPECT (QGS).

introduction

A disadvantage of the described techniques to acquire left ventricular function is the non-automatic delineation of the myocardial border and hence operator dependency which may lead to a higher inter-observer variability compared to a totally operator independent method. Germano et al. [52-59] developed a complete automatic algorithm: quantitative gated SPECT (QGS). With this method it is possible to quantify the left ventricular cavity volumes, the left ventricular ejection fraction and to visualize left ventricular wall motion and wall thickening.

Figure 2. Left: Screen display with short and long axis images with overlaid endocardial and epicardial contours.



Short axis images are used as input. under: Four dimensional (three dimensional plus time) display screen utilized for the assessment of global and regional myocardial function. Gated short axis images are used as input.

This algorithm uses gated short-axis data sets after stacking them together to form a three-dimensional image volume (figure 2).

Automatic segmentation of the left ventricular myocardium will take place, based on initial heuristic thresholding, binarization, and clustirification of the three-dimensional image, followed by iterative cluster refinement using pixel erosion and pixel growing (repetitive dilatation). The classical Hough transform is applied to detect contiguous local maxima forming approximate circles [60,61]. Each circle is assigned a score proportional to the average count value along its circumference and the ratio of that value to the average count at the center, so as to favour doughnut-like count distributions. The circle with the highest score is deemed the most likely to represent the left ventricle and is expanded by 2 pixels outwards. For three-dimensional short-axis volumes, all voxels outside the cylinder with that circle for section are discarded. Once the left ventricle has been isolated and its centre of mass is automatically determined, rays are drawn from it according to a spherical sampling model. From this a first estimate is defined of the three-dimensional midmyocardial surface, which is then fitted to an ellipsoid. The best-fit ellipsoid defines new sampling co-ordinate system, along which count profiles normal to the myocardium are measured and fitted to asymmetric Gaussian curves. Endocardial and epicardial surfaces are determined based on the Gaussians' standard deviations. The valve plane is determined by fitting a plane to the most basal myocardial points. Contours are generated even in apparent absence of perfusion because Gaussian fitting operates on the segmented but non-thresholded image, and is thus able to discern very low levels of perfusion. Thereby, contours are generated by maximazing the smoothness of the surface patch defined by the invalid points (extrapolating those of points immediately adjacent to the nonperfused area) [52-59].
Left ventricular volumes are calculated by straight summation of the volumes of the voxels bound by the endocardium and the valve plane. The LVEF is derived from the end-diastolic and end-systolic cavity volume, all without operator interaction [52-59]. The relation between 8 frame and 16-frame measurements of gated SPECT LVEF has been investigated for QGS algorithm [53]. Due to the smoothing of the time-volume curve, the 8-frame gating was shown to somewhat underestimate LVEF (3.7 LVEF percentage points compared to 16-frame LVEF gating). The degree of underestimation is remarkably uniform over a wide range of ejection fractions.
Regional wall motion is the excursion of the three-dimensional endocardial surface from end-diastole to end-systole. Segmental thickening is calculated using both geometric and count considerations (partial volume effect) [52-59].
Gated SPECT takes full advantage of the properties of ^{99m}Tc perfusion agents, namely high count rates and stable myocardial distribution with time. Because the tracer distribution in the myocardium is stable, spatial and temporal changes in the myocardial tracer activity during the cardiac cycle reflects regional myocardial wall motion and wall thickening. An advantage of this technique is the possibility to assess perfusion and function during one single acquisition.

Gated SPECT imaging validation by other methods.

Functional data on the left ventricle acquired by the gated SPECT technique has been compared with other well-known imaging modalities such as magnetic resonance (MR) imaging, contrast angiography, echocardiography, gated blood pool imaging and RNA [53,62-71]. These studies

reported a good to excellent agreement between these imaging modalities and gated SPECT. Bavelaar-Croon et al. [70] found a correlation coefficient of 0.85 for the LVEF measured by gated SPECT as compared to MR imaging. They also found an excellent correlation coefficient for both the left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV): r=0.94 and r=0.95 respectively. Higher mean LVEDV and LVESV were measured by gated SPECT as compared to MR imaging, but the differences were not significant. This finding is due to inclusion of part of the outflow tract with MR imaging. Vaduganathan et al. [66] found in 25 patients with an acute myocardial infarction an exact agreement for wall motion scores in 92% of the segments with a kappa of 0.82 between gated SPECT and MR imaging. Correlations between the two techniques were also good for LVEDV, LVESV and LVEF resp. r=0.81, r=0.92 and r=0.93. Atsma et al. [69] compared LVEF data acquired by gated SPECT and LVEF measured by contrast ventriculography in 74 patients. The authors found a good correlation (r=0.84) between the two imaging modalities. They also found exact agreement of segmental wall motion scores on a 4-point scale in 89% of the segments with a kappa value of 0.76. Bacher-Stier et al. [67] reported a correlation coefficient of 0.86 between the LVEF measured by gated SPECT and echocardiography in rest. Moreover, using echocardiography as reference standard, regional wall motion abnormalities were identified by gated SPECT with high sensitivities (88%-100%) and high specificities (82%-98%).

Quantative Gated SPECT, the version used in this thesis.

Visual interpretation of myocardial wall motion and wall thickening has been shown to provide important diagnostic and prognostic information in various groups of patients with known or suspected coronary artery disease [72]. However, substantial operator dependency, intraobserver and interobserver variability in interpretation compromise the reproducibility of non-automatic and non-quantitative techniques. Germano et al. [54,73] has developed a new approach to a quantitative analysis of the regional wall motion and wall thickening. The algorithm uses also ellipsoid fitting and sampling of the myocardium and generates non-slice-based analysis of relative myocardial perfusion, independent of the size, shape, and orientation of the left ventricle. In addition to a numeric measurement of the extent, severity, and reversibility of perfusion defects, the approach provides automatic, computer-derived segmental scores, analogous to the semiquantitative 20-segment, 5-point (0-4) visual scores model, and the option for building customized normal databases. Perfusion at each myocardial sampling point was calculated as the average uptake along the count activity profile (endocardial-epicardial segment) normal to the myocardium and passing through that point [54,56,58,73]. Endocardial and epicardial surfaces were derived even in areas of apparent absence of perfusion using rule-based criteria ensuring the continuity of surface myocardial count profiles (as described above) [56,58]. Normal limits and abnormality criteria for relative myocardial uptake, for each of the 20 myocardial segments, seen during stress ^{99m}Tc-sestamibi imaging and rest ^{201}Tl imaging were developed [56,58,73]. This thesis is based on Cedars-Sinai's Quantitative SPECT (QGS) software program developed by G. Germano (version 2.0, revision A"figure 2) [52].

CONSIDERATIONS AT THE START OF THE STUDY

Diagnostic value of gated SPECT myocardial perfusion imaging.

The sensitivity of exercise perfusion imaging for detecting angiographicaly significant CAD ranges from 85-91% [13]. The specificity ranges from 70-94%. The addition of SPECT to exercise testing increases the diagnostic accuracy to detect CAD, with no significant differences between men and women [74-76]. Factors that effect the diagnostic performance are referral bias [76], reduced stress tolerance [77,78], anti-angina medication [79-80], imaging problems like tracer activity below diaphragm [81,82], photon attenuation and scatter, patient motion, low count statistics, reconstruction artifacts [23]. It can be such a large bias that it is likely to have a negative impact in discussions on the role of perfusion scintigraphy in patient management.

The addition of left ventricular function parameters assessed by gated SPECT has improved the diagnostic value [27,28]; as an attenuation artifact usually will show a fixed perfusion defect with concomitant preserved wall thickening and/or motion, whereas a region with a fixed perfusion defect due to myocardial infarction will show absence of wall thickening and or motion. Gated SPECT may show absence of wall thickening potentially indicating necrosis or stunning, and conversely, gated SPECT may show concomitant preserved wall thickening in the infarct region suggesting preserved viability.

Potential limitation of perfusion imaging is the measurement of relative myocardial blood flow, rather than absolute blood flow. In patients with multivessel CAD, the degree of ischemia may be underestimated because of globally reduced perfusion of the left ventricle. Overall sensitivity for identifying any SPECT abnormality of the combined perfusion/ function assessment in three vessel disease is 80-95%, and for two or single vessel disease 92% and 86%, respectively [83-85]. The overall specificity is 72% [85].

Transient ischemic LV dilatation (TID) on myocardial perfusion imaging indicates a significant enlargement in LV size on the stress images compared with the rest images. Abnormal TID is related to a greater amount of ischemic burden as wel as multivessel-type or LAD territory perfusion abnormality [86-88].

In the line of risk stratification viability assessment is an important subject. For example, in patients with established extensive coronary artery disease, it is considered worthwhile to salvage even small areas with viable contractile cells [89]. However, revascularisation in patients with extensive coronary artery disease is associated with a considerable risk of periprocedural complications, so it is only justified in patients with remaining viable but dysfunctional myocardium [90,91].

Several imaging modalities are potentially available. Positron emission tomography can be used to detect areas of increased ^{18}F-fluoro-deoxy-glucose (FDG) uptake, as a prove of altered glucose metabolism. Alternatively, the gated SPECT technique can help distinguish contractile from non-contractile myocardial tissue at places with borderline perfusion [92]. Improvements in local perfusion after specific therapy is taken as conformation of viability.

The main use of myocardial perfusion imaging is in the assessment of the presence of reversible ischemia, as such it is used as a diagnostic pre-test for coronary angiography. The prognostic side of myocardial perfusion imaging, as extra information on a diagnostic study, is not commonly used. The prognostic side of myocardial perfusion imaging could be used in a

more structural manner for the management of patients with coronary artery disease. Patients with a very low probability [<1 % per year] for cardiac events can be discharged from follow-up. This management can lead to a gain in efficacy and cost-effectiveness. The evaluation of the incremental prognostic value of the left ventricular ejection fraction, as can be obtained from gated SPECT data, may be important for the risk stratification of patients with extensive coronary artery disease.

Subpopulations

Myocardial perfusion scintigraphy is used for a wide range of distinct clinical purposes (subgroups). Among these subpopulations the relative frequencies of certain findings, and thereby both the prognostic value, and the diagnostic performance of perfusion imaging will vary enormously. For instance, the majority of the data on prognostic value of the parameters assessed by gated SPECT has been obtained in a mixed gender population and may not be applicable to women. Women often have smaller LV volumes. It has been shown that gender related differences in normal limits exist [93-95]. In addition, a multicenter phantom study showed a wide range of results in different standard end-systolic and end-diastolic volume combinations. Moreover, the LV ejection fraction (LVEF) was overestimated and both the end-systolic volume (ESV) and end-diastolic volume (EDV) were underestimated. Especially, this is the case for small volumes. Cutoff values for LV functional parameters should be validated in each center [95].

As the case mix varies from institution to institution, the interpretation of pooled data is difficult at best [96].

The importance of rigorous and extensive reporting at the subgroup level, especially for risk assessment, was emphasized in an invited commentary in the American Journal of Epidemiology [97].

THE LEIDEN TETROFOSMIN DATABASE

At the Leiden University Medical Center ^{201}Tl was routinely used for myocardial imaging until its replacement by ^{99m}Tc-tetrofosmin. After a trial period, tetrofosmin is being used in all patients referred for myocardial perfusion scintigraphy since August 1995. In addition to some basic demographic data, relevant clinical parameters, from the medical history or on the level of exercise reached during the stress test are reported in a well-standardised manner. Reporting was routinely performed by an experienced nuclear medicine specialist and a cardiologist in consensus reading. Since November 1997, the patients underwent imaging according the gated SPECT technique routinely.

All data were systematically and prospectively entered in a computerised database, that on July 1st 2000 held data on more than 2350 procedures in over 2000 patients.

Where available, data was added on any angiography procedure, angioplasty procedure or coronary bypass operation performed prior to or shortly after the scintigraphic procedure.

This extensive database, including follow-up data, formed the basis for the studies presented in this thesis.

AIM AND OUTLINE OF THE THESIS

The aim of the thesis is to further expand our insights in the prognostic and diagnostic value of myocardial perfusion imaging using the gated SPECT technique according to the Cedars-Sinai's Quantitative Gated SPECT (QGS) software [52].
We studied the robustness of the QGS technique, assessing the quantitative segmental score of wall motion, wall thickening and left ventricular volumes. Following this validation, the additional prognostic value of gated SPECT on subgroup level was investigated.

In **Chapter 2** we evaluated the reproducibility and operator dependence for the quantitative regional left ventricular functional parameters assessed by Cedars-Sinai's Quantitative automated gated SPECT (QGS) software.

In **Chapter 3** left ventricular function parameters at rest were compared to LV function parameters 30 minutes post-stress in patients with a myocardial infarction: evaluation with gated SPECT.

In **Chapter 4** the prognostic value of gated SPECT in patients with a left bundle branch block was evaluated.

In **Chapter 5** we evaluated the additive prognostic value of perfusion and functional parameters assessed by gated SPECT in women.

In **Chapter 6** a review is presented of the relevant literature on prognostic value of gated SPECT imaging.

Chapter 7 contains a summary, general discussion and future perspectives.

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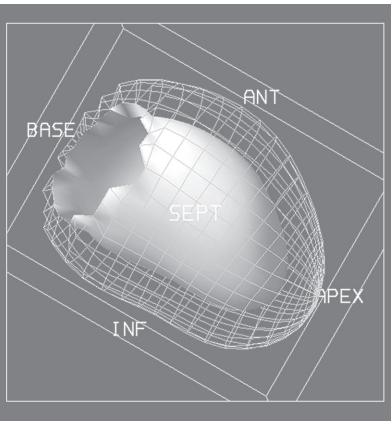
Chapter 2



Evaluation of the Quantitative Gated SPECT [QGS] Software Program in the Presence of Large Perfusion Defects

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ABSTRACT

Objectives: To evaluate the reproducibility and operator dependence for the quantitative regional left ventricular functional parameters (LVFP) assessed by Cedars-Sinai's Quantitative automated gated SPECT (QGS) software.

Methods: The QGS algorithm was reviewed in detail and potential operator dependencies were defined. Series of prototypes were selected, consisting of a) normal perfusion, b) perfusion defects in all perfusion regions, c) perfusion studies of patients with angiographic confirmed normal coronary arteries, proximal (≥70% stenoses) single and multiple vessel disease, and d) spurious activity in close proximity. While defining and re-orienting the volume containing the left ventricle, the operator adjusted 8 variables/ degrees of freedom (DF). The software was used without further operator interventions. Results were expressed as a coefficient of variation (COV). Separate COV were calculated per distinct DF. A segment was considered not robust when the COV did exceed 20% in a single DF, 15% in at least 2 DF, or 10% in at least 3 DF.

Results: Regional left ventricular EF and volumes showed excellent reproducibility.

Normal perfusion and the vessel disease prototypes showed an excellent COV (for all re-orientation steps [33/prototype]) mostly below 5% for LVFP. However, regional wall motion and thickening became less reliable in the presence of large perfusion defects or artifacts.

Conclusions: Quantitative estimates for regional left ventricular functional data show excellent reproducibility using automated gated SPECT. However, there may be substantial operator dependency in the presence of large defects or spurious activity in close proximity.

INTRODUCTION

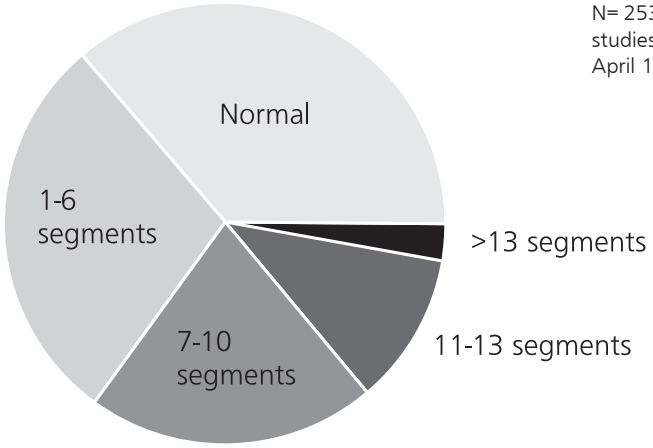
Techniques for automated quantitative approach of myocardial perfusion imaging have been developed and refined over the past decades. Automation and quantitation in nuclear cardiology are important to minimize inter- intra operator variability and increase reproducibility [1]. New quantitative image processing software should undergo systematic independent evaluation and thorough search for clinical conditions under which the underlying algorithms may fail or loose precision. With regard to the validation of the Cedars-Sinai's Quantitative SPECT (QGS) software, several requirements have already been met. The algorithm and its basic validation have already been described [2-15]. However, one particular issue is still not fully solved: reproducibility of the quantitative assessment of regional functional parameters in the presence of severe major defects or artifacts. In cross-validations with other techniques, results have been evaluated on population level. Any failure in specific subgroups will be diluted by the large amount of successful analysis over the investigated population. The software used in the QGS technique is complex and, under certain conditions, falls back on alternative algorithms. This complexity makes cross-validations with other techniques difficult. Therefore, our assessment was based on a system analyses to test the reliability of the quantitative assessment of the left ventricular volumes (end-diastolic and end-systolic), LVEF and regional segmental wall motion and wall thickening. In this approach we tried to identify conditions under which the algorithm becomes operator-dependent. We especially reviewed the algorithm for interfering clinical conditions, such as large perfusion defects, activity below the diaphragm and operator-dependent factors in the image processing. The operator-dependent factors contain only the reorientation that the operator has to perform after raw data acquisition. The rest of the data processing can easily kept constant, is assumed to be stable.

Assessment of the average defect size in a representative population from our institution showed that of the total population one third has a large perfusion defect defined as 7 or more hypoperfused segments using a 20-segment model (figure 1). This indicates that this is a very large patient group.

The aim of this study was to evaluate systematically the reproducibility of all quantitative functional results of the QGS-software program.

Figure 1. Distribution of defect sizes, using a 20-segment model.

N= 2536 consecutive myocardial perfusion studies using 99mTc-tetrofosmin between April 1995 and July 2000.



METHODS

Study population.

Seventeen patients were selected who underwent 99m-Technetium (tetrofosmin) gated SPECT myocardial perfusion scintigraphy at the Leiden University Medical Center between November 1997 and 1 January 2000. Study selection was partially based on the findings of the system analysis: based on clinical conditions and operator-dependent factors (described below). This selection was supplemented to cover a representative range of defect sizes, locations and artifacts on perfusion imaging studies. The selection resulted in examples of studies with isolated perfusion defects in all different regions of the left ventricle, spurious activity below the diaphragm and left ventricle aneurysm. A second series was selected based on findings at coronary angiography. For each unique constellation of defect, artifact, stenosis or combination thereof, a typical example (a so-called prototype) was selected.

Patients with severe perfusion defects or severe angiographic stenosis were selected, as this represents the worst-case scenario for the software. Each prototype was subjected to the analysis, as described below. Global characteristics of the selected prototypes are shown in table 1.

Table 1. Global characteristics of the selected prototype studies used in the assessment of robustness.

Prototype	EDV	ESV	LVEF	Rejects	Defects	Perfusion/ Angiographic findings
A	86	38	56	0	0	normal perfusion
B	210	116	45	0	7	inferior defect
C	104	76	27	0	7	anterior defect
D	158	91	43	0	2	infero-lareral defect
E	92	46	50	0	8	antero-septal defect
F	199	132	33	4	8	apical defect
G	315	269	15	0	10	large defect*
H	247	207	16	0	12	aneurysm
I	178	124	30	19	5	activity below diaphragm
J	94	45	52	0	2	normal coronary arteries
K	222	163	27	2	8	proximal LAD stenosis
L	210	148	30	3	11	prox. LAD, RCA stenosis
M	183	135	26	0	5	prox. LAD, RCX stenosis
N	56	14	76	0	0	prox. RCA stenosis
O	135	67	50	0	3	prox. RCA, RCX stenosis
P	78	21	73	0	0	prox. RCX stenosis
Q	105	51	52	0	0	3 vessel disease

EDV =end diastolic volume [ml]; ESV =end systolic volume [ml]; LVEF = left ventricular ejection fraction [%]; Rejects: number of analyses out of 33, rejected because of obvious misfit on visual inspection. Defects: number of segments with uptake below 40% on automated end systolic bull's eye projection using 20 segments. * Large perfusion defect, with only activity in the basal segments.

Gated SPECT protocol.

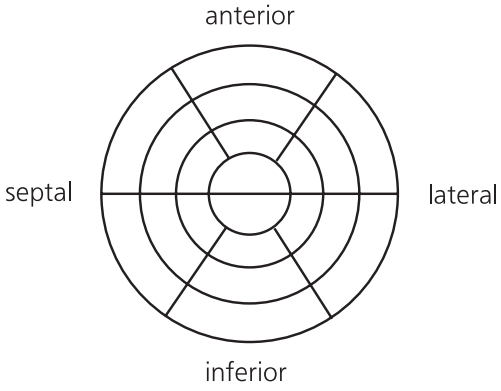
Perfusion studies.

Myocardial perfusion scintigraphy was performed using 500 MBq ^{99m}Tc-tetrofosmin, as previously described [16]. Stress images (bicycle exercise, or adenosine 0.14 mg/kg/min for 6 minutes, or dobutamine up to 40 µg/kg/min) and rest images were obtained. Shortly after injection of tetrofosmin the patient was instructed to drink some milk to stimulate and accelerate hepatobiliary clearance. All gated acquisitions took place with the patients in prone position, 30-45 minutes (stress) or 45-60 minutes (rest) post-injection. Imaging was performed with a triple-head 360° rotating gamma camera equipped with high resolution collimators (GC-9300 GMS, Toshiba, Japan). A total of 90 frames of 30" duration in a 64 x 64 pixel matrix were obtained at 4° intervals using a non-circular orbit. Sixteen bins per cardiac cycle were acquired. All studies were prefiltered with a 9th order Butterworth filter with a cut-off frequency of 0.26 cycles/pixel. Filters were kept constant for all studies. No attenuation correction was applied.

Quantitative gated SPECT analysis.

Gated SPECT analysis was performed using the Toshiba implementation of the QGS-software, version 2.0, revision A". In which quantitative assessment of end-diastolic and end-systolic perfusion, wall motion and wall thickening using the 20-segment bull's eye representation of the QGS model [figure 2], as well as estimates for end-diastolic (EDV) and end-systolic (ESV) ventricular volume and derived stroke volume and LVEF is incorporated. The underlying algorithms have been reviewed in literature [2-13,17]. The software algorithm implementation is the same in the different camera systems. Volumes were expressed in milliliters (ml), wall motion in millimeters (mm), with a reported accuracy of 0.1 mm, whereas wall thickening was expressed as a percentage of the fitted end-diastolic thickness.

Figure 2. The 20 segment bull's eye model of the left ventricle used by the QGS system



Coronary angiography

Coronary angiography was performed according to the standard Judkins technique. An obstruction in 1 of the 3 major epicardial coronary arteries of ≥70% on visual examination was considered significant. For this study, coronary angiograms were only evaluated if they had been performed within 90 days after myocardial perfusion scintigraphy. Only proximal coronary artery stenosis were included. Proximal stenosis were defined as: left anterior descending coronary artery (LAD): proximal of the first diagonal branch; Left circumflex artery (LCX): proximal of the obtuse marginal branch; and right coronary artery (RCA): from the origin till the second acute marginal branch.

Statistical analysis.

Systems analysis. The QGS algorithms and the entire acquisition- and filtered backprojection procedures were systematically studied, to identify error-sources that could potentially result in loss of precision of the QGS algorithms. This effort was specifically aimed at:

1. identifying clinical conditions, such as large perfusion defects; the presence of significant amounts of activity below the diaphragm; or anatomical variations, which could interfere with the reliability of the algorithms;
2. identifying operator-dependent factors in the image processing that could be rigidly and reproducibly standardized;

identifying operator-dependent factors in the image processing that could not be standardized in a fully reproducible manner.

Our approach was essentially a system analysis. The system analysis revealed that the software applied several alternative algorithms, to initially detect and preliminary establish exact location, orientation, size and crude shape of the left ventricular cavity. The choices made by the software are dependent on relative count density, location and intensity of spurious activity in, for example, liver, intestines, spleen, lungs, or stomach, as well as on the extent and level of uptake of the segments of reliably detected myocardium. For many of these effects, it could be deduced that the size, shape, orientation and location of the operator defined bounding box (reconstruction slices in which the left ventricle is situated) could potentially influence the choices made by the program and hence could result in variation in quantitative results for wall motion, wall thickening, EDV, ESV and LVEF. Due to the complexity of the software, it was not possible to reliably predict the choices made by this software under various conditions. Hence the systems analysis resulted only in global and qualitative, rather than specific and quantitative descriptions of conditions that might lead to failure due to excessive operator dependence. Results from this analysis were used to select representative clinical studies for further robustness analysis.

Criteria for defect size (extent) and severity.

Criteria on normal perfusion studies were described earlier [18, 19]. Based on an earlier analysis [7, 20], it was concluded that segmental uptakes below 40% in the QGS 20-segment end-systolic perfusion quantification corresponded best with severe perfusion defects. The extent of the perfusion defect is the summation of all segments with a severe perfusion defect. Seven or more segments with severe compromised perfusion in the 20 segment bull's eye were defined as large. This corresponds with $\geq$ 26% myocardial abnormality according to the method described by Berman et al. [21].

Operator dependence.

When making the reconstruction for QGS analysis the operator has to set a range of reconstruction parameters, forming a sort of bounding box in which the left ventricle is situated. During this procedure the operator has to set 8 degrees of freedom (see below). For each individual prototype, an initial representative reconstruction and QGS analysis was performed followed by repeat reconstructions and QGS analyses, in which a single parameter (a degree of freedom) was systematically varied. These parameters defined the size, location and angular orientation of the bounding box of the data subset of the entire reconstruction volume that was made available to the QGS software. The following parameters were varied:

1. angle of rotation in the transversal plane: +20°, °+10°, -10°, -20°;
2. angle of rotation in the sagital plane: +20°, °+10°, -10°, -20°;
3. horizontal translation of the selected bounding box: +4, +2, -2, and -4 voxels;
4. vertical translation of the selected bounding box: +4, +2, -2, and -4 voxels;
5. translation along the long axis: +4, +2, -2, and -4 voxels;
6. variation in width of the bounding box: +4, +2, -2, and -4 voxels;
7. variation in height of the bounding box: +4, +2, -2, and -4 voxels;
8. variation in length of the bounding box: +4, +2, -2, and -4 voxels;

In some instances, visual inspection showed an obvious failure of the QGS software to fit the model to perfusion data. These cases were excluded from further analysis. All parameters that could be standardized between studies were kept constant.

For each individual segment, or EDV, or ESV, or LVEF, the spread in results due the systematic operator-dependent variation in size, orientation and location of the bounding box was expressed as a standard deviation [SD]. This was done both for wall motion and wall thickening. Each standard deviation was also expressed as a percentage of the respective average (coefficient of variation, [COV]), for a completely normal reference study.

This preliminary analysis resulted in 16 bull's eye representations of segmental operator dependence; one for each of the 8 degrees of freedom controlled by the operator, and one each for wall motion and wall thickening. This analysis was performed for all prototypes.

Integration of results.

For reasons discussed in detail below, the 8 degrees of freedom were not considered to be statistically fully independent. The results from each set of 8 different bull's eye images were used to generate a bull's eye representation, indicating -per segment- whether its quantitative results were considered reproducible for that particular prototype. Two sets of rules were used, for reasons described below:

- one set was based on the COV for each segment;
- the other set used absolute values for the SD for wall motion and wall thickening.

The rules used to assess reproducibility per segment were:

1. If the COV exceeded 20% in at least one degree of freedom, lack of reproducibility was concluded;
2. If the COV exceeded 15% in at least two degrees of freedom, lack of reproducibility was concluded;
3. If the COV exceeded 10% in at least three degrees of freedom, lack of reproducibility was concluded.
4. If the SD exceeded 1.0 mm (wall motion), or 10% (wall thickening), lack of reproducibility was concluded;
5. If the SD exceeded 0.75 mm (wall motion), or 7.5% (wall thickening) in at least 2 degrees of freedom, lack of reproducibility was concluded;
6. If the SD exceeded 0.5 mm (wall motion), or 5% (wall thickening) in at least 3 degrees of freedom, lack of reproducibility was concluded.

Rules 1 to 3 were applied to the bull's eye representation for COV; rules 4 to 6 for the SD bull's eye.

Criteria for reproducibility.

To our knowledge, no criteria have been previously published to define clinically relevant uncertainties or inaccuracies regarding the exact quantification of regional wall motion and wall thickening. Basically 3 different types of criteria were available: 1) COV, based on the observed averages in the same study; 2) COV, based on observed averages in normal studies; and 3) SD, without reference to the average values of either the same study, or normal studies. It is obvious that COV, based on observed averages in the same study has little value. For example in the presence of akinesia, locally segmental COV for wall motion will become extremely high, even though the absolute SD is quite modest. The COV, calculated using observed averages in normal studies is more meaningful for most segments, but not for all. For example, the wall motion in basal septal segments is very small and hence the COV will become high. This obviously has no clinical significance. We therefore have chosen to apply a mixed technique. For the majority of the segments criterion 2 is the preferred choice. Where a segment failed criterion 2, we reported on criterion 3 too. It is obvious, given the considerable anatomical variation in size, shape and orientation of the left ventricle, that reference values will show relatively large variation, when expressed as COV, at the basal and septal sides of the ventricle. For this reason we considered a segment in the basal and septal region not robust when both the COV and SD are not robust.

A recent publication by Sharir et al [17] may provide some guidance, as the normal variation between normal subjects sets an upper limit to the variation encountered in normal subjects. On average the segmental values for standard deviation for wall motion and wall thickening in this group both corresponded to approximately 20% COV. This number was taken as the upper acceptable limit for operator-dependent within-prototype segmental variation when using the COV methods (criteria 1, 2 and 3 in the section above).

With regard to the criteria based on the observed segmental variation (SD), two assumptions led to similar thresholds. The final values were 1.0 mm and 10% for robustness of wall motion and wall thickening. First, it was considered reasonable to attribute at most half of the between subjects segmental variation to operator dependent variation in processing. Secondly, a detailed analysis of the relation between cut-off value and number of rejected segments revealed that for wall motion a limit of between 0.9 and 1.6 mm resulted in a clear separation of obviously robust and obviously non-robust studies. For wall thickening, a similar analysis showed that over a very wide range of cut-off values for severity of perfusion defect (25 - 55%), a cut-off value of 10% for maximum allowable variation (expressed in SD) in wall thickening did not result in any changes in the number of rejected segments.

As mentioned above, a COV exceeding 20% at the basal segments is meaningless if the normal wall motion at such segment is, for example, only a modest 1.5 millimeter, as no clinician would demand a 0.3 mm reproducibility from gated SPECT technology. Furthermore, the smallest angle between the long axis of the left ventricle and the valvular plane shows considerable variation. This adds to the arguments in favor of selectively applying criterion 3 for the basal ring.

RESULTS

Selected studies

Table 1 describes the 17 selected prototypes with regard to extent and severity of perfusion defect and, if applicable, the matching angiographic data. In addition, the EDV, ESV and LVEF are also given in table 1.

For each prototype, summary bull's eye representation for robustness of segmental wall motion and wall thickening is given in figures 3A-Q. In these bull's eye representations, segments that were not robust based on the COV criteria are marked accordingly. Where applicable, those segments not considered robust based on both COV and SD criteria are identified.

Table 2 gives results per prototype for end-diastolic, end-systolic, LVEF, and an indication on the robustness of each measure for each prototype. The mean values for EDV, ESV and LVEF were respectively 157 ml, 103 ml and 41%.

Operator dependence

Figure 4 shows a typical example of how quantitative results per segment per degree freedom result in the summary bull's eye maps for COV and SD. In this figure the 2 summary bull's-eye representations for each individual degree of freedom are shown. In case of a typical study showing normal perfusion (figure 3A), all segments (beside this, also the EDV, ESV and LVEF values) are robust, except for the segments at the basal edge, which is not robust, based on COV. Analysis based on COV most other prototypes are not robust at the basal edge, especially at the septum. For the analysis based on SD only operator dependence in the basal area in a few segments are seen. A clear hierarchy seems to exist regarding robustness of the global parameters, with EDV being most and ESV being least robust. With regard to the segmental wall motion and wall thickening results, in general, only a poor correlation was found between defect size or location and the number and location of segments showing large variation. In case of very large defects the variation at the center of the defect tends to be minimal, unless spurious activity is close to the defect.

DISCUSSION

Our results show excellent reproducibility for left ventricular function parameters using the Cedars-Sinai's Quantitative Gated SPECT software. However, large perfusion defects, or the presence of spurious activity near the left ventricle may increase operator dependence.

The QGS software relies on a series of assumptions that cannot be fully tested under experimental conditions. Therefore systematic comparison with other imaging modalities is important. Several groups have compared the quantitative results from the QGS software with similar results from other modalities. Generally in mixed datasets, the concordance with regard to the LVEF is good for contrast ventriculography and ultrasound techniques [6-9]. Similarly, the concordance with regard to wall thickening is quite good [12]. Some data are also available on wall motion, but these data are usually limited to the use of an ordinal scale, rating wall motion as normal, hypokinetic, akinetic or dyskinetic. When using this ordinal scale, concordance with contrast ventriculography and ultrasound is good [12]. The methods used in literature

Figure 3. The Bull's Eye representations of the Prototypes A-Q.

so far, however focused on global comparisons in heterogeneous groups of patients, thereby diluting systematic discrepancies in case of specific defects or artifacts. Hence such studies are unsuitable for the validation of gated SPECT quantitation in the presence of defects. To our knowledge, so far no calibrated phantoms exist that can simulate major defects or artifacts.
In this study we focused on the operator dependent factors in image processing, which are not easily kept constant. Filtering of data or positioning of the patient, for example, can be well standardized and therefore this was not evaluated in this study. Evaluation of the algorithm revealed that the size, shape, orientation and location of reconstruction slices are operator dependent factors that are hard to keep constant, and therefore potentially influence the choices made by the program in processing the quantitative results for wall motion, wall thickening, EDV, ESV and LVEF.

Prototypes.

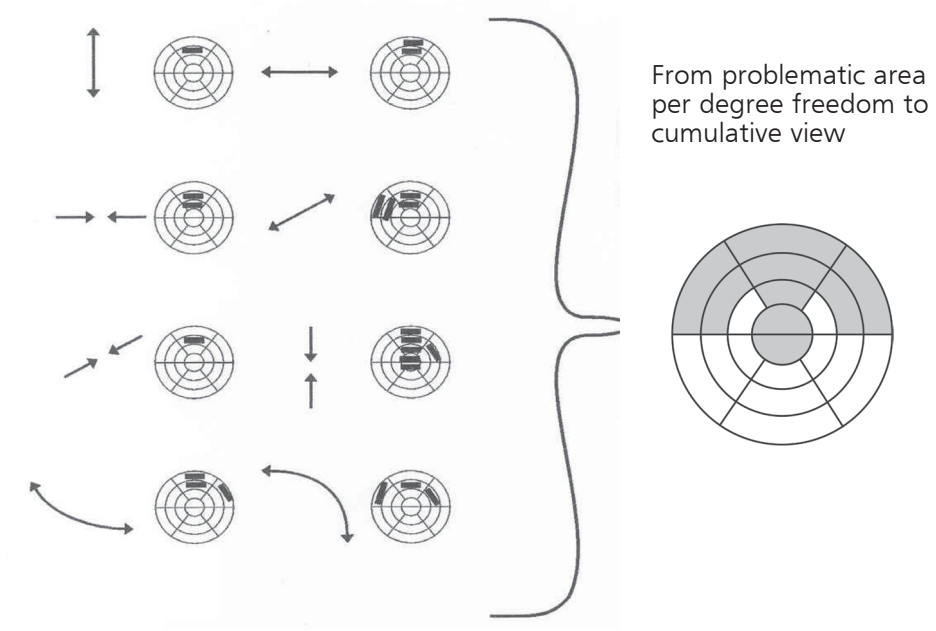
It is difficult to evaluate the effects of certain types of defects on quantitation in a reproducible manner. Some arbitrariness will remain regarding the choice of suitable reference studies. We have explicitly chosen studies that showed complete perfusion defects during scintigraphy or significant stenoses at coronary angiography as a starting point. We assumed that the algorithms are less likely to be affected in case of similarly sized defects, with only moderately decreased perfusion. In this respect the selected studies can be considered as worst case scenarios for the algorithms used. Only in case of extensive areas of lack of robustness did we add studies showing decreased, but not absent perfusion. There is a little known about cut-

Table 2. Robustness of the left ventricular volumes and EF.

Prototype	EDV		ESV		LVEF	
	COV	SD	COV	SD	COV	SD
A	0	0	0	0	0	0
B	0	0	1$	0	0	0
C	0	0	1*	1*	0	0
D	0	0	0	0	0	0
E	0	0	0	0	0	0
F	0	0	0	0	0	0
G	1#	1$	1*	1*	0	0
H	1*	1*	1*	1*	1*	1*
I	1*	1*	1*	1*	0	0
J	0	0	0	0	0	0
K	0	0	1*	1*	0	0
L	0	0	0	0	0	0
M	0	0	0	0	0	0
N	0	0	0	0	0	0
O	0	0	0	0	0	0
P	0	0	0	0	0	0
Q	0	0	0	0	0	0

EDV= end-diastolic volume; ESV= end-systolic volume; LVEF= ejection fraction. COV= coefficient of variation; SD= standard deviation; 0= robust; 1=not robust. * COV > 20%; # COV > 15%; $ COV > 10%.

Figure 4. Summary Bull's eye of the different degree of freedom..



off point for severe perfusion defects. Some studies report on mean count activity. Chua et al [7] presented a mean count activity of 19.9% ± 10.5 % of maximal myocardial count activity. Hashimoto et al [20] reported that myocardium with a per cent peak count of 40% or less has very low probability of myocardial viability. This is in line with our cut-off value for severe perfusion defect.

Integration of results obtained per degree freedom.

The variations in quantitative results, as found per degree freedom, were clearly not independent in a statistical sense. Each variation, as found, is the vector sum of multiple components, including the filtering [smoothing] effects of any oblique re-orientation of the voxel space. As the latter component is present in the results for all degrees of freedom, but would be encountered only once during normal operation, vector addition would overestimate the cumulative effects considerably. Therefore a pragmatic alternative was chosen: only the worst 3 degrees freedom were evaluated (for exact criteria see methods). The analysis resulted in a large amount of summary results that could not be presented in a meaningful manner without this or a similar data-reduction approach. Each individual prototype resulted in 43 summary statistics per degree freedom evaluated, for a total of 344 standard deviations, which is obviously too high for practical use. It was therefore considered impractical to present quantitative results instead of the presented segmentwise dichotomous results. The chosen practical limits loosely represent 20% variation, expressed as COV (referring to a normal study), 1.0 mm for wall motion, or 10% for wall thickening. It must be borne in mind that these limits, when expressed as 95% confidence bands correspond to $\pm$ 40%, $\pm$ 2.0 mm or $\pm$ 20% segmental variation respectively and hence cannot be considered too restrictive. This is in line with literature [22].

Practical implications and guidelines.

This study was designed to identify the limits of the reproducibility of the QGS system. It also gives an indication of the intra-operator variability for different kinds of perfusion defects. Figure 3 summarizes the robustness of the QGS system for the different prototypes. The prototypes represent worse-case scenarios and show that when the number of perfusion defects is limited, the software has excellent reproducibility with regard to EDV, ESV, LVEF, wall motion and to a less extent wall thickening. This is in line with Paeng et al [23] who reported good reproducibility in group of 31 patients. Also, they found less concordance for wall thickening, especially in the septal and inferior region.

When perfusion defect sizes are large, especially when the defects themselves are severe (<40% in the quantitative analysis that is part of the QGS software), wall thickening quantitation becomes unreliable in more than just one occasional segment, and figure 3A-Q should be consulted. Spurious activity in close proximity of the left ventricle can interfere with quantitation. The correlation between location of perfusion defects and lack of reproducibility is not very good. The operator dependent variation in segmental wall motion quantification remains < 10% in virtually all segments even in the presence of most of the major perfusion defects. Exceptions can be found in figure 3A-Q. Spurious activity in close proximity of the left ventricle can interfere with quantitation.

In this study QGS-software, version 2.0, revision A" was used. More recent versions of the software are available in which the algorithm has an automatic re-orientation procedure, leaving little room for operator intervention. Also for the later versions an evaluation like this study is necessary to evaluate its reproducibility in the different specific subgroups.

Limitations of this study.

The number of prototypes is relatively small and should be considered a compromise. In our series of experiments, it became obvious that precise territorial mapping for each defect type is not feasible and that the reported generic guidelines probably reflect the best achievable results. Furthermore, as no suitable gold standard exists with regard to the assessment of segmental wall motion and wall thickening, evaluation of systematic errors is cumbersome.

Recent guidelines recommend to use a 17 segment model for the left ventricle [23]. Recently, Berman et al [21] reported on methods to convert a 20-segment scoring system to a 17-segment model. The 17-segment model demonstrated a trend toward fewer mildly abnormal scans and more normal and severely abnormal scans. In this study we used a 20 segment model. It has been shown that partitioning may play significant role in the reproducibility. Paeng et al [22] showed significant differences between the 20 segment model and repartitioning the myocardium in 5 regions. The absolute differences between repeated measurements of the 20 segment model and the 5 segment model for wall motion and systolic thickening were 0.77 ± 0.62 mm, 7.2 %± 7.2 % and 0.52 ± 0.49 mm, 4.5%±3.7% respectively. Absolute differences between the groups were significant (t test $P<0.001$). In a 17 segment model the absolute differences will be more close to the 20 segment model, and will probably not greatly influence our results.

Conclusions

For the Cedars-Sinai's Quantitative Gated SPECT software quantification the global parameters, such as end-diastolic end-systolic left ventricular volume and LVEF are less influenced by operator

dependent settings than segmental measures for wall motion and wall thickening, and can be considered operator-independent. The quantification of wall motion and thickening are robust for operator dependent variation in processing. In the presence of major perfusion defects or significant spurious activity below the diaphragm, however, especially wall thickening becomes more operator dependent in some cases.

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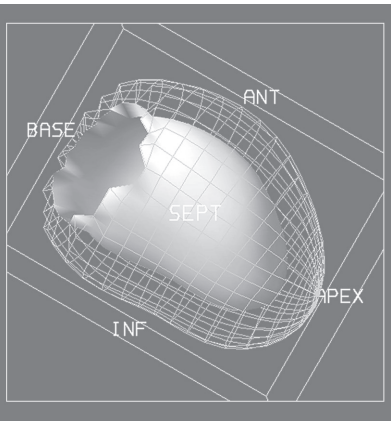
Chapter 3



Comparison of left ventricular function at rest and post stress in patients with a myocardial infarction: evaluation with gated SPECT

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J Nucl Cardiol. 2001;8:10-8.

ABSTRACT

Background. Quantitative electrocardiogram-gated single photon emission computed tomography (SPECT) myocardial imaging (QGS) is a means of providing functional information about the left ventricle and myocardial perfusion. However, the functional information derived 30 minutes post-stress may be different from the left ventricular (LV) function determined at rest. This study determined whether LV function post-stress would be different from LV function at rest in patients with an earlier myocardial infarction.

Methods and Results. LV perfusion and ejection fraction (LVEF), were determined by means of both the rest and post-stress acquisition in 58 patients with an earlier myocardial infarction and in 23 patients with a low likelihood of coronary artery disease by using technetium-99m tetrofosmin and the QGS program. The interobserver and intraobserver variability of LVEF was excellent, within a margin of 2%. No significant differences in LVEF were observed between post-stress and rest in the 23 patients with a low likelihood of disease (ΔLVEF 0.04+/-3.2%, p = not significant). Conversely, the patients with an earlier myocardial infarction showed a significantly lower LVEF post-stress, compared with that at rest (ΔLVEF -1.9+/-4.2%, p=0.002). In 33 patients (57%), the LVEF post-stress was 2% or more lower than the LVEF at rest. Furthermore, reversible ischemia, which was present in 16 patients (28%), did not interact with the ΔLVEF post-stress, compared with the ΔLVEF at rest (p=not significant). Parameters such as the stress modality (adenosine stress or exercise), the number of stenosed vessels, or the perfusion defect severity score did not influence the ΔLVEF post-stress, compared to ΔLVEF at rest.

Conclusions. In patients with an earlier myocardial infarction, LV function post-stress may not represent true resting LV function. Consequently, this result justifies the stratification of patients before starting the gated SPECT study. In patients with an earlier myocardial infarction, the gated acquisition should be performed during the rest study.

INTRODUCTION

Bacause left ventricular ejection fraction (LVEF) is a major determinant of prognosis in patients with coronary artery disease, it is important to assess LVEF in addition to myocardial perfusion [1]. The recently developed quantitative gated single photon emission computed tomography (SPECT) program (QGS) provides reliable information on LVEF, LV wall thickening, LV wall motion, LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) in addition to myocardial perfusion [2-4]. Gated acquisition of the stress myocardial perfusion images 30 minutes post-stress is generally considered myocardial perfusion at maximal stress where LV function is the resting situation. However, post-stress LV dysfunction may develop in patients with stress-induced ischemia, probably because of myocardial stunning [5-8]. This implies that when gated SPECT is obtained 30 to 45 minutes post-stress, LVEF and LV volumes may not represent the true resting LV function. Furthermore, the influence on LV function obtained by using pharmacological stress (adenosine, dipyridamole or dobutamine), as compared with that obtained by using exercise stress, is not fully elucidated [9-14]. The recently developed QGS program is applied routinely in an increasing amount of nuclear imaging departments worldwide [2-4]. So far, no studies involving pretest stratification of patients have been published. The aim of this study was to determine whether LV function post-stress would be different from basal LV function at rest in patients with a previously sustained myocardial infarction and whether there was a different influence on LV function between pharmacological stress and conventional exercise stress. This information may facilitate the stratification of patients before they undergo a gated SPECT study.

METHODS

Patients

We studied 58 consecutive patients with an earlier myocardial infarction. There were 10 women and 48 men (mean age, 61.8 ± 11.6 years; range 50 to 80 years). In all patients, a persistent defect in at least 3 of 18 LV segments was shown with gated SPECT myocardial perfusion imaging. Exclusion criteria were left bundle branch block, irregular heart rhythm, and reconstruction artifacts caused by tracer activity in intestines lying next to the heart. The baseline characteristics of the 58 patients are listed in table 1. A control group of 23 patients, who had a low pretest likelihood of coronary artery disease and normal results on a myocardial perfusion scintigram (Table 1), was selected.

Stress protocols

All patients underwent a 2-day imaging stress/rest protocol, in which the gating was done during both the rest and the stress myocardial perfusion SPECT acquisition. In 24 patients (41%), a symptom-limited exercise stress test was performed in the upright position with a bicycle ergometer. In all patients undergoing physical exercise, beta-blocking agents were discontinued at least 48 hours before the test. The exercise stress protocol included a stepwise increase in workload depending on gender, age, weight and height. This protocol is routinely applied in our institution. When the prespecified maximum workload (depending on gender, age, weight

Table 1. Patients characteristics and stress modalities used.

	Myocardial infarction (N =58)	Control Subjects (N=23)
Q-wave on ECG	51	n.a
Elevated enzymes (CK,CK-MB) with no Q-wave on ECG	7	n.a
Age (y)*	61.8 ± 11.6 (range 50-80)	58.5 ±10.4 (range 47-85)
Men*	48	13
Women	10	10
Stress modality -Ergometry	24	13
-Adenosine	27	9
-Dobutamine	7	1
1-vessel disease	17	n.a.
2-vessel disease	14	n.a.
3-vessel disease	12	n.a.
No angiogram	15	n.a.

* P <0.05 for difference in age and gender between patients and control subjects. Controls subjects were defined as patients with a low pre-test likelihood of coronary artery disease and normal results on a myocardial perfusion scintigram. n.a.=not applicable

and height) is achieved, the physical validity is considered to be at least 100%. Exercise stress endpoints were severe angina, physical exhaustion, dyspnoea, sustained tachyarrhythmias, exertional hypotension, or ischemic sinus tachycardia (ST)-T segment depression of at least 0.2 mV with a duration of 80 ms. Exercise was considered inadequate when the physical validity of the patient was less than 80% of the predicted validity (workload) in the absence of angina or an ischemic ST depression. Pharmacological stress with 0.14mg/kg/min adenosine during 6 minutes was used in 27 patients (47%) who were not able to exercise adequately. All these patients withheld caffeine-containing beverages for 12 hours before the test. A dose of 300 µg/kg dobutamine in 15 minutes was used in 7 patients (12%) who where not able to exercise adequately and who also had a contraindication to the use of adenosine. Before and every minute during stress, 12-lead electrocardiography (ECG) was performed. In case of ST-T-segment abnormalities, registration of the stress ECG was continued until normalization of the electrocardiogram was seen.

Exercise versus pharmacological stress

To assess the influence of different stress modalities on the change in LVEF, LVEDV, and LVESV, we analyzed baseline and post-stress LVEF, LVEDV and LVESV both in the patients who received pharmacological stress agents and the patients who underwent ergometry stress. For the purpose of this study, we only compared adenosine stress with conventional exercise.

Image acquisition protocol

A dose of 500 MBq (13.5mCi) technetium-99m tetrofosmin (Myoview, Cygne-Amersham) was administered 45 to 60 minutes before rest image acquisition and 30 minutes before to stress image acquisition. Imaging was performed with the patient in prone position with a Toshiba GC-9300 triple-head camera equipped with high-resolution collimators and connected to a

Toshiba GMS 5500 computer. A 360-degree rotation with a noncircular orbit as close to the patient as possible was obtained with 90 steps of 4 degrees, 30 seconds per step, and a 64-by-64 matrix size. A 20% symmetric energy window centered on the 140 keV peak was used. Sixteen frames per cardiac cycle were gated. The data were prefiltered with a Butterworth filter power 9, order 8, and a cut-off frequency of 0.32, and they were reconstructed with the filtered back-projected algorithm and a Ramp filter. The data were reoriented to obtain oblique-angle tomograms parallel to the long axis and short axis of the left ventricle. The reconstructed data were projected as tomographic slices in short, vertical, and horizontal axis views in a side-by-side display. In addition, the images were displayed as polar plots (bull's-eye maps). Numerical values of LV volumes and LVEF were calculated by using a commercially available software package (QGS), yielding a dynamic 3-dimensional LV image developed by Germano et al. [2-4,15,16]

Static image analysis

On the static perfusion images, semiquantitative analysis of myocardial perfusion was performed for 18 LV segments. There were 6 segments on a preapical and mid-short-axis slice, 4 segments on the basal short-axis slice, (the septal part was left out because of the presence of the membranous part of the interventricular septum), and 2 apical segments on the vertical long-axis slice. This segment scheme is a modification of the scheme used by Germano et al.[3]. The analysis was done in both rest and stress perfusion images. All segments were scored using a 4-point scale: no uptake; less than 30% of normal perfusion (score 0), severely diminished uptake; 30% to 55% of normal perfusion (score 1), slightly diminished uptake; 56% to 80% of normal perfusion (score 2); and 80% to 100% of normal perfusion (score 3), normal uptake. The percentages were judged by using a hot-metal square color scale. The scoring was done by 2 experienced observers in consensus (CB, MS). Defects were characterized as fixed or reversible. A defect was considered to be fixed when there was no change between the stress and the rest image. A defect was considered to be reversible when there was an improvement in tracer uptake of at least 1 grade between stress and rest images. A perfusion defect severity score was calculated by summing the scores of 18 segments in the rest study. A lower score implies a more extensive perfusion defect. The severity of the reversibility was judged by calculating the numerical difference in perfusion score between the rest and stress study. Based on the stress-rest images, patients were divided into groups: patients with only fixed defects (n=42) and patients with additional reversible defects (n=16). Additional ischemia was defined as reversible ischemia in 2 or more LV segments in addition to the fixed perfusion defect.

Coronary Angiography

Coronary angiography was performed according to the standard Judkins technique. An obstruction of 50% or more in 1 or more of the major 3 coronary arteries seen by means of a visual examination was considered to be significant.

Statistical analysis

To determine interobserver variability, 3 technicians reconstructed the raw data of 19 patients to analyze LVEF. The standard deviation (SD) of the LVEF was expressed in LVEF units. The intraobserver variability was determined by 1 technician reconstructing the raw data twice,

with an 11 day-interval between processing instances in all 19 patients. The outside limits for variability of the measurements were determined to be 2 SD beyond the mean value. Significant differences of changes in LVEF, LVESV, and LVEDV between patients with and without reversible ischemia was tested by using the unpaired Student's *t* test. The same test was applied as a means of calculating the significance of differences in differences in changes of LVEF, LVEDV and LVESV between patients undergoing adenosine and ergometry stress. The paired Student *t* test was used as a means of calculating the significance in change between post-stress and rest of LVEF, LVESV, and LVEDV within patients and control subjects. Analysis of variance (ANOVA) was applied as a means of analyzing the influence of reversible ischemia on the changes in LVEF, LVESV, and LVEDV post-stress versus rest in the whole group. ANOVA was also used as a means of determining the influence of the amount of stenosed vessels on changes in LVEF, LVEDV, and LVESV post-stress versus rest. Covariance analysis was used as a means of adjusting the confounding effects of age and gender. Values are shown as the mean plus or minus SD, unless indicated otherwise. A p value of 0.05 or less was considered to be significant.

RESULTS

Serial reproducibility

For the interobserver variability, a SD of the mean LVEF of 0.77% was found (range 0.5 to 1%) expressed in LVEF units. For the intraobserver (P.D.) variability, a SD of 0.89% was found. The limits for serial reproducibility of the measurements were thus determined to be 2x0.89=1.8%. The Bland Altman plot showed that the differences in LVEF measurements between 2 technologists in this reproducibility study were independent of the LVEF level. Because the QGS only provides integer values for LVEF, we used a cutoff value of 2% to distinguish real LVEF changes from LVEF changes that might be caused by imperfect reproducibility.

Control group

The resting LVEF, LVESV, and LVEDV are shown in table 2. The mean LVEF, LVESV, and LVEDV in the group of patients with a low likelihood of coronary artery disease were not significantly different between post-stress and resting condition (Table 3).

Table 2. Rest LVEF, LVESV and LVEDV in the control group (n=23) and in 58 patients with an earlier myocardial infarction.

		LVEF (%)	LVEDV (ml)	LVESV (ml)
Controls	(n=23)	54.8 ± 4.5	99.7 ± 17.6	45.3 ± 10.9
All patients	(n=58)	39.5 ± 12.4*	158.2 ± 57.2*	101.2 ± 54.0*
Isch +	(n=16)	35.6 ± 14.8	160.3 ± 60.0	109.7 ± 60.0
Isch -	(n=42)	41.0 ± 11.2	157.4 ± 56.9	98.0 ± 51.7

LVEF: Left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; Isch+: reversible ischemia in addition to a fixed defect; Isch-: only a fixed defect. Values represent mean ± SD. *p<0.001, difference in rest LVEF, LVEDV, and LVESV between controls subjects and patients. p= not significant between patients with and without reversible ischemia. P value obtained with the unpaired Student's t test.

Table 3. Changes in LVEF, LVESV and LVEDV post-stress compared with rest in the 23 control patients and in patients with previous myocardial infarction.

	ΔLVEF (%)	ΔLVEDV (ml)	ΔLVESV (ml)
Control patients (n=23)	0.04 ± 3.2*	-1.3 ± 7.6*	-0.7 ± 5.1*
Patients with earlier MI (n=58)	-1.9 ± 4.2[a]	7.9 ± 17.6[b]	6.5 ±18.7[c]

Δ: Difference post-stress compared with rest; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MI: myocardial infarction. Values represent mean +/- SD. *: p=not significant; Patients: [a] p=0.002 for ΔLVEF; [b] p= 0.001 for Δ LVEDV and [c] p=0.002 for ΔLVESV. P values obtained with the paired Student's t-test.

Myocardial infarction group

The mean resting LVEF, LVEDV and LVESV in patients with an earlier myocardial infarction are listed in Table 2. There was a significant difference in rest LVEF, LVEDV, and LVESV between the patient and control group (Table 2). In contrast, there were no significant differences in rest LV parameters between patients with and without reversible ischemia (Table 2). Within the total group of 58, we found a significant average change in LVEF, LVEDV and LVESV post-stress versus the resting condition (Table 3). Conversely, the difference in change of LVEF, LVESV and LVEDV between the rest and the stress acquisition was not different between patients with and patients without reversible ischemia [LVEF(%), 0.94 ±1.1 (p=0.5), LVEDV(ml), -4.7 ±4.6 (p=0.4); LVESV(ml), -4.4 ±4.2 (p=0.4)]. Thus, it was demonstrated by means of ANOVA that the presence of reversible ischemia, which occurred in 16 patients (28%), did not influence the differences in LVEF, LVEDV and LVESV post-stress, as compared with the resting condition (p=0.4). By using the cutoff value of 2% to define a true change, we found a decrease (≥2%) in LVEF in 33 patients (57%), an increase (≥2%) in LVEF in 12 patients (22%), and no change in LVEF in 13 patients (21%; Figure 1). The amount and severity of the perfusion defects were not predictive of changes in LVEF post-stress compared with rest LVEF (r=0.05).

Figure 1. Percentage of patients with myocardial infarction with 1: decrease (> 2%), 2: unchanged (–2%<x<2%) or 3: increase (>2%) of left ventricular ejection fraction post-stress compared to rest. SEE for 1: 6.5%, SEE for 2: 5.3% and SEE for 3: 5.4%.

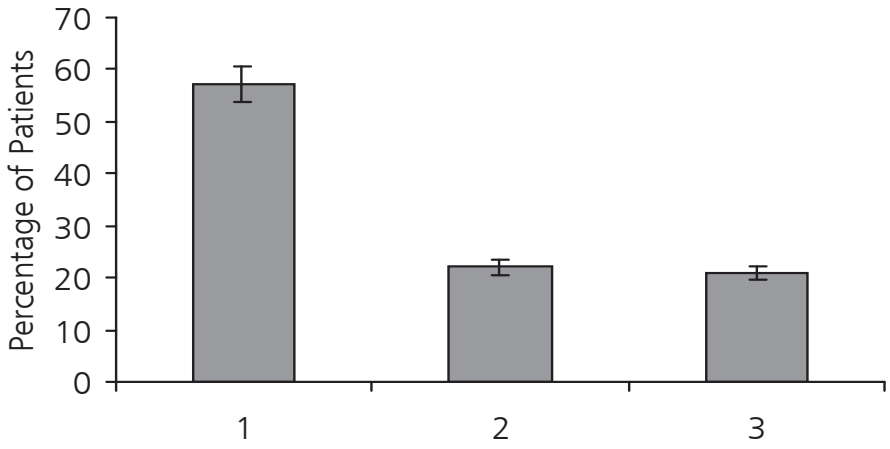

Table 4. Influence of the number of stenosed vessels on changes in LV functional parameters post-stress compared with rest. In 43 of 58 patients (74%), a coronary angiogram was available.

	1-vessel disease (n=17, LAD 12, RCA 4, LCX 1)	2-vessel disease (n= 14, LAD 12, RCA 6, LCX 10)	3-vessel disease (n=12)	P value by means of ANOVA
Rest LVEDV (ml)	163.1 ± 59.5	145.7 ± 62.5	173.1 ± 43.6	NS
Rest LVESV (ml)	102.3 ± 57.0	94.8 ± 58.8	114.8 ± 46.0	NS
Rest LVEF (%)	40.8 ± 13.2	39.3 ± 14.8	36 ± 11.8	NS
ΔLVEDV (ml)	7.5 ± 20.8	4.36 ± 14.8	5.6 ± 18.9	NS
ΔLVESV (ml)	8.6 ± 14.8	4.9 ± 15.5	8.25 ± 21.9	NS
ΔLVEF (%)	-2.1 ± 3.9	-1.3 ± 3.3	-1.9 ± 5.5	NS

LAD: Left coronary artery; RCA: right coronary artery; LCX: left circumflex artery; ΔLVEF: change in left ventricular ejection fraction post-stress compared with rest; ΔLVEDV: change in left ventricular end-diastolic volume post-stress compared with rest; ΔLVESV: change in left ventricular end-systolic volume post-stress compared with rest; NS: not significant. ANOVA, analysis of variance.

Coronary Angiography

In 43 patients (74%), coronary angiography data were available. The changes in LVEF, LVEDV, and LVESV post-stress between patients with 1, 2, or 3 stenosed vessels were not statistically significant (Table 4).

Stress modality

In the group of patients with an earlier myocardial infarction, there were no significant differences in resting LV function between the patients who underwent adenosine stress and the patients who underwent conventional exercise (Table 5). Also the changes in LVEF and LVESV post-stress compared with those at rest were not significantly different between groups. There was a marginally significant increase in LVEDV for the adenosine group (p=0.04). However, when applying the Bonferroni correction, the differences in change of LVEDV between both stress modalities were no longer statistically significant (p=0.08; Table 5).

Table 5. Mean LV function parameters in patients with different stress modalities. Because there were only 7 patients with dobutamine stress, we only calculated the P values between adenosine and conventional exercise.

	Ergometry (n=24)	Adenosine (n=27)	P Ergometry vs Adenosine
Rest LVEDV (ml)	169.4 ± 110.7	150.0 ± 51.6	NS
Rest LVESV (ml)	110.7 ± 57.8	92.0 ± 48.0	NS
Rest LVEF (%)	37.6 ± 11.5	41.8 ± 12.1	NS
ΔLVEF (%)	-1.2 ± 4.6	-2.6 ± 4.2	NS
ΔLVEDV (ml)	1.0 ± 18.4	11.9 ± 17.9	0.04, Bonferroni: 0.08
ΔLVESV (ml)	4.1 ± 20.4	11.7 ± 15.6	NS

LVEDV: Rest left ventricular end-diastolic volume; LVESV: rest left ventricular end-systolic volume; LVEF: rest left ventricular ejection fraction; ΔLVEF: change in left ventricular ejection fraction post-stress compared to rest; ΔLVEDV: change in left ventricular end-diastolic volume post-stress compared to rest; ΔLVESV: change in left ventricular end-systolic volume post-stress compared to rest; NS: not significant. Values represent mean ± SD.

Discussion

Gated SPECT myocardial imaging is routinely performed in many nuclear imaging departments. Because of logistics, the gating may be done during the acquisition of either the rest or the stress study. Several studies have shown a transient deterioration of LV function in patients with exercise-induced ischemia that persists long after cessation of exercise [5,6,8,17]. Therefore, when gated acquisition is only done during the acquisition of the stress perfusion study, LV function 30 minutes post-stress may not represent true LV function at rest. However, it is not known beforehand which category of patients will show reversible ischemia. Therefore, it is not possible to decide ahead of time whether the gated acquisition has to be done at rest. In our study, taking into concern the interobserver and intraobserver variability, we calculated a decrease of 2 or more LVEF points to be significant. The average decrease in LVEF for the whole patient group with a myocardial infarction was 1.9%, which was statistically significant. The highest LVEF decrease in this study was 13%. Although an average decrease of 1.9 LVEF points post-stress compared with rest is not clinically important, it is not fully known which patient will show a clinically significant or insignificant change when the rest study is non- gated. In our study we found that 33 of 58 patients (57%) with a previously sustained myocardial infarction showed a statistically significant deterioration of LV function ($\geq$2%) that persisted as long as 30 minutes after stress, even in patients without concomitant reversible ischemia. This finding allows the stratification of patients before starting the gated SPECT study. In all patients with definitive evidence of a previously sustained myocardial infarction, gating should be performed during the acquisition of the resting study to determine the true LV function at rest. Subsequently, in these patients, we found a similar change of LV function between post-stress and rest for patients who had adenosine stress and patients who underwent bicycle exercise.

Previous studies

Several studies have shown a transient deterioration of LV function in patients with exercise-induced ischemia that persisted long after cessation of exercise [5,6,8,17,18]. This phenomenon may be attributed to myocardial stunning, which has been defined as spontaneous reversible post-ischemic dysfunction in the presence of normalized perfusion [19]. This implies that patients with ischemia shown by means of the perfusion image may have a decreased LV function when gating is done during the post-stress study. Several pathophysiological mechanisms of myocardial stunning have been put forward, such as the oxygen-radical hypothesis and the calcium-overload hypothesis [19-22].

To date, only a few articles have been published on the evaluation of LV function at least 30 minutes post-stress analyzed with ^{99m}Tc labeled agents in combination with the QGS program [7,17,18]. Johnson et al.[7] analyzed 22 patients in whom a significant decrease in LVEF post-stress was shown. All 22 patients had reversible ischemia, and 10 of the patients (50%) had a history of myocardial infarction. In another group of patients (n=20), in whom only a fixed defect was shown, the average change in LVEF post-stress was not significant. In this group, 14 patients (70%) had sustained an earlier myocardial infarction. Because 6 of the patients (30%) were not known to have an earlier myocardial infarction, these results are not comparable with our results. Our findings are discordant with the findings of Paul et al.[17] who could not find a deterioration in LV function in 18 patients with a myocardial infarction. However, these patients were defined by means of the presence of fixed perfusion defects,

without additional historical or enzymatic evidence of earlier myocardial infarction. Because a fixed perfusion defect may be caused by an attenuation artifact, the perfusion abnormality might not necessarily represent infarcted tissue. In a recent study by Hashimoto et al.[18], a significant depression of post-stress LVEF relative to resting LVEF was shown in 11 patients with severe reversible ischemia. However, the authors did not explicitly describe whether their patient population (n=47) consisted of patients with an earlier myocardial infarction. As a result, it is not possible to compare their findings with ours.

Theoretical explanation

An explanation for the prolonged dysfunction after exercise in patients with myocardial infarction is the relative imbalance between oxygen supply and demand. In the presence of a flow-limiting coronary artery stenosis, exercise results in an alteration of the transmural distribution of myocardial perfusion in a manner such that flow is distributed preferentially to the subepicardium, while the subendocardium is most severely hypoperfused [23,24]. Moreover, it is known that the oxygen consumption per gram of tissue is usually higher in the subendocardium than in the subepicardium, and transmural thickening occurs primarily in the endocardial layer [25]. During stress, a relative high imbalance between oxygen supply and demand in the subendocardial layers subtended by stenosed vessels may develop without significant changes in overall blood supply. This may, in turn, lead to stunning and, hence, a decrease in LV function without signs of reversible ischemia on the myocardial perfusion images. In the QGS software program, an asymmetric Gaussian is fitted to each profile, and the inner and outer standard deviations of the Gaussian are noted [2]. A thinner perfused myocardium would decrease the count activity in the myocardial wall (partial volume effect), but probably would not shrink the width of the Gaussian count distribution across the wall much. Thus, in our opinion, a technical factor such as endocardial count loss is not an explanation for the fall in LVEF post-stress. Another factor leading to a relative high need for oxygen is the higher wall stress which occurs in large ventricles subjected to a previous myocardial infarction. This high oxygen need is further augmented during stress. When the blood supply is not adequate, this may also result in a relative deprivation of oxygen and, hence, may lead to myocardial stunning.

It is known that neurons are more sensitive to ischemia than myocytes. Therefore, LV dysfunction post-stress leading to a fall in LVEF could also be caused by neuronal dysfunction that is exaggerated during stress because of ischemia [26-28]. Because imaging with iodine-123-metaiodobenzylguanidine (a radio labeled norepinephrine analogue reflecting cardiac sympathetic activity) was not performed in our studied population, this neuronal involvement is only hypothetical.

Influence of the amount of stenosed vessels

We found no statistically significant differences between patients with 1-vessel, 2-vessel or 3-vessel coronary artery disease in the post-stress changes in LV function. This implies that there is probably no linear relationship between the extent of stenosed vessels and the level of LV function 30 minutes post-stress. The infracted myocardium is probably the major determinant of global LV function. Although the number of patients in the 3 groups was not high (n=17, n=14,n=12) our findings were confirmed by Johnson et al.[7] who found that the number of diseased vessels was not a dependent variable that correlated significantly with LVEF

changes. In addition, Marcassa et al.[29] found that the extent of coronary artery disease was similar among patients with and without transient LV dilatation post-stress. Conversely, several studies have reported that the degree of LV dysfunction is related to angiographically assessed severity of coronary artery disease [12,13]. However, these studies are not comparable with our study, because dypiridamole radionuclide angiography was used as a means of assessing LV function, and thallium-201 dipyridamole images were used as a means of measuring the LV cavity. In addition, functional information was obtained during stress and not 30 minutes post-stress [12,13].

Influence of the severity of the perfusion defect

There was no significant correlation between the severity of the fixed perfusion defects and the change of LVEF post-stress, compared with rest. This could be explained by the extent of damaged neurons, which exceeds the extent of tissue necrosis defined by means of rest blood flow abnormalities. Because neurons are more sensitive to ischemia than myocytes [26-28], we tentatively conclude that the damaged tissue may be more extensive than one would judge from the number of perfusion defects.

Influence of stress modality on post-stress LV function

In our group, 47% of the patients had adenosine as stress modality, 41% of the patients had ergometry, and 12% of the patients had dobutamine. The resting LV functional parameters and the change in LVEF and LVESV post-stress were not different between the patients who had adenosine stress and the patients who underwent conventional exercise. In the adenosine group, there was a marginally significant higher difference in change in EDV post-stress, compared with rest. However, when we applied the Bonferroni correction, this significance did not hold. Moreover, because the number of patients in the subgroups (adenosine, n=27; conventional exercise, n=24) was relative low, we think it is preferable to conclude that there was a trend towards a higher change in LVEDV in the adenosine group than that in the conventional exercise and not a significant difference in increase of LVEDV between both stress modalities. In accordance with our study, Nallamothu et al.[30] found more patients with LV cavity dilatation in the adenosine group than patient who underwent bicycle exercise, although no explanation was provided. Several studies reported a significant increase in pulmonary capillary wedge pressure in patients with coronary artery disease, compared with healthy subjects, when adenosine was used [11,31,32]. The increase in pulmonary wedge pressure is probably initiated by a change in vascular loading, higher LVED pressure, or diastolic dysfunction, which in turn leads to a higher EDV. In our opinion, it is not unlikely that this phenomenon may persist long after cessation of the infusion.

Controversial opinions exist about the influence of adenosine or dipyridamole on LV function [9,13,29]. Pennell et al.[9] found that the site of wall motion deterioration found by using magnetic resonance imaging was always the site of a reversible thallium-201 defect. In a later study analyzing the influence of dobutamine on LV function by using magnetic resonance imaging, Pennell et al.[10] suggested that dobutamine is more effective in eliciting wall motion abnormalities in patients with coronary artery disease than dipyridamole. Ogilby et al.[11], who used adenosine in patients with coronary artery disease, observed perfusion defects without a decrease in global and regional systolic function. Conversely, the authors found a higher pulmonary capillary wedge pressure, probably caused by diastolic left ventricular dysfunction.

Takeishi et al.[12] stated that dilatation of the LV cavity on dipyridamole Tl-201 imaging reflected relative subendocardial hypoperfusion induced by dipyridamole, rather than actual chamber enlargement. The cavity area increased, but the ventricular area did not change. In contrast, Klein et al.[13] concluded that dipyridamole induces ischemia that is sufficiently significant to be detected by means of radionuclide ventriculography such as LV dilatation and dysfunction. Marcassa et al.[29], who studied 234 patients, 130 of whom sustained a previous myocardial infarction, reported a similar incidence of transient LV dilatation after exercise and during pharmacologic stress testing (37% and 36%, respectively). However, the authors found LV dilatation in 86 patients (37%) of whom only 19 (22%) showed epicardial transient dilation. The remaining 67 patients showed endocardial transient dilation without concomitant epicardial dilation, probably caused by diffuse subendocardial hypoperfusion simulating an increase in LV cavity dimension. None of these studies used a QGS program similar to that applied in the present study, which could lead to different results.

Study limitations

Johnson et al.[7] analyzed the reproducibility of the test by applying the same gated SPECT approach as used in this study in 15 patients 24 hours later. They found a reproducibility of 5.2%. Because it was not allowed because of ethics in our institution to repeat the total myocardial perfusion test 1 day later, we tested the reproducibility of LVEF measurements by analyzing the interobserver and intraobserver variability by reconstructing the raw data. The reproducibility showed a mean standard deviation of 0.89%. Patients were studied in prone position during the acquisition of both the rest and stress study, eliminating the variability of LVEF caused by a difference in positioning [33]. In our study, only patient studies without gating problems or acquisition problems were used. Furthermore, the same technologist reconstructed the acquisition data for the rest and the stress study in 1 patient according to a standard protocol. Although a circumstantial variation cannot be excluded, we do not assume that the reproducibility would have been less accurate.

CONCLUSIONS

Most patients with an earlier myocardial infarction who undergo gated SPECT show a significant decrease in LVEF lasting at least until 30 minutes post-stress. This phenomenon occurs irrespective of the presence of demonstrable reversible ischemia or the stress modality used. To obtain true LVEF and LV volumes at rest in patients with an earlier myocardial infarction, it is preferable to perform the gating during the rest acquisition.

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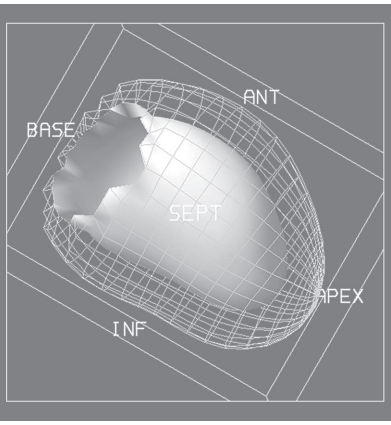
Chapter 4



Prognostic value of gated SPECT in patients with a left bundle branch block

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ABSTRACT

Background. The aim of this study was to assess the prognostic value of technetium-99m tetrofosmin gated SPECT imaging in patients with left bundle branch block (LBBB) using quantitative gated single photon emission computed tomography (SPECT) imaging.

Methods and Results. We followed 101 consecutive patients with LBBB using technetium-99m tetrofosmin gated SPECT imaging. Average follow-up was 1.24 years (max. 2.48). Hard endpoints were all-cause death and acute myocardial infarction. Event-free survival curves were obtained. Optimal cut-off points for LV volumes and LVEF to predict outcome were determined by ROC curve analysis. Of the patients, 94 had an abnormal study**.** Fifteen hard events occurred (13 deaths). Perfusion abnormalities were similar for patients with or without events. For LV function parameters the survival curves were maximally separated when we used cutoff values of 160 ml or greater for end-diastolic volume (p=0.019 and hazard ratio [HR] of 1.04 for hard events, p=0.024 and HR 1.04 for all-cause death), 100 ml or greater for end-systolic volume (p=0.043 and HR of 1.04 for hard events, p=0.062 and HR of 1.04 for all-cause death), and lower than 35% for LVEF (p=0.013 and HR of 0.81 for hard events, p=0.047 and HR of 0.81 for all-cause death).

Conclusion. By use of quantitative gated SPECT imaging, LBBB patients with an end-diastolic volume of 160 ml or greater, end-systolic volume of 100 ml or greater, or LVEF lower than 35% are at increased risk for subsequent cardiac events.

INTRODUCTION

A left bundle branch block (LBBB) pattern on the electrocardiogram (ECG) severely reduces the diagnostic accuracy of treadmill or bicycle exercise testing for the detection of coronary artery disease (CAD) [1-3]. Myocardial perfusion scintigraphy has a high sensitivity but decreased specificity for detecting ischemic heart disease in patients with LBBB [1,3,4]. The addition of regional left ventricular (LV) function parameters by gated SPECT improved the diagnostic accuracy and prognostic value of perfusion imaging, whereby LV function parameters have incremental prognostic value over perfusion data alone [5-11].
At present, few data exist on the prognostic value of gated SPECT in patients with LBBB. In this category of patients, no data are available on the value of LV function parameters to potentially improve risk stratification. Accordingly, the aim of the study was to assess the incremental prognostic value of technetium-99m tetrofosmin gated SPECT imaging in patients with LBBB.

METHODS

Study Population

We studied 101 consecutive patients (67% men, mean age 65±8.4 years) with known LBBB who underwent rest/stress technetium-99m tetrofosmin myocardial perfusion gated SPECT imaging between October 1, 1999, and January 1, 2002 at the Leiden University Medical Center were included. Patients were followed up until the fixed census date April 1, 2002. Patients with known non-ischemic dilated cardiomyopathy or valvular heart disease were excluded. According to the WHO/ ISFC definition, non ischemic dilated cardiomyopathy was defined as dilatation and impaired contraction of the left ventricle (or both ventricles) not associated with cardiovascular disease in which the degree of myocardial dysfunction is explained by the extent of ischemic damage [12]. Dilated cardiomyopathy was defined as: 1. a LVEF less than 45% and/or fractional shortening less than 25%, as ascertained by echocardiography. 2. a left ventricular end-diastolic diameter greater than 117% of the predicted value of corrected for age and body surface area [13].

Stress Myocardial Perfusion Protocol

All patients were instructed to refrain from caffeine-containing products for 24 hours before the test. Beta-blocking agents were discontinued at least 48 hours prior to SPECT imaging. All patients underwent a pharmacological stress test as described previously [14]. Vasodilatation was induced using intravenous administration of adenosine at a dose rate of 0.14 mg/kg/min for 6 minutes. Technetium-99m tetrofosmin (GE, Amersham, UK) was injected 4 minutes after start of infusion of the pharmacological agent.

Gated SPECT Acquisition Protocol

Both 1-day and 2-day imaging protocols were used [14]. A dose of 500 MBq technetium-99m tetrofosmin was given intravenously for the 2-day protocol stress study and 750 MBq for the 1-day protocol stress study. Dosages of 500 and 250 MBq, respectively, were given for the

rest study. All acquisitions took place 30-45 minutes (stress) or 45-60 minutes (rest) post-injection. Gating was performed under resting conditions during the myocardial perfusion SPECT acquisition following either the rest study (in the 2-day protocol) or the stress study (in the 1-day protocol). Imaging was performed with a triple-head 360° rotating gamma camera (Toshiba GC-9300 GMS, Japan). A total of 90 frames of 30» duration using a 64 x 64 pixel matrix were obtained at 4-degree intervals using a non-circular orbit. Sixteen bins per cardiac cycle were acquired. All studies were pre-filtered using a 9-order Butterworth filter at a cut-off frequency of 0.32 cycles/pixel (rest) [pixel size 6 mm] or 0.26 cycles/pixel (stress). All images were subject to quality control measures, including cinematic display for assessment of patient motion, corrections for field non-uniformity and center of rotation. No attenuation or scatter correction was used. The reconstructed data were projected as tomographic slices in short-axis and vertical/horizontal long-axis views. Myocardial perfusion data and quantitative LV volumes and LVEF were calculated using the commercially available Cedars-Sinai's Quantitative gated SPECT (QGS) software, version 2.0, revision A" [6,7]. When automatic reconstruction or reorientation failed, reconstruction limits and axes were assigned manually.

Semi-quantitative Visual Analysis of Myocardial Perfusion SPECT

Semi-quantitative visual interpretation of SPECT perfusion images used short-axis and vertical long-axis tomograms divided into 20 segments for each patient [15]. These segments were assigned to 6 evenly spaced regions in apical, mid-ventricular and basal slices of the short-axis views and two apical segments on the mid-ventricular vertical long-axis slice. Each segment was scored using a five-point scoring system (0=normal, 1= equivocal, 2=moderate, 3= severe reduction of radioisotope uptake, 4= absence of detectable radiotracer in a segment). Apparent perfusion defects presumably caused by soft tissue attenuation were assigned a score of 1. The observers were blinded to the patient's clinical history and results of stress testing.

Three global perfusion indices were employed to combine assessments of defect extent and severity [15]. A summed stress score (SSS) was obtained by adding the scores of the 20 segments of the stress perfusion images. A summed rest score (SRS) was obtained by adding the scores of the 20 segments of the rest perfusion images. The sum of differences between the stress and rest scores of each of the 20 segments was defined as the summed difference score (SDS) or reversibility score. All studies were evaluated by at 2 experienced observers in consensus readings. A perfusion study was considered normal when the SSS was ≤ 4 [16].

Patient Follow-up

Both medical records and the automated hospital information system were reviewed. If these data did not cover the entire period from recruitment until census date, the patient was sent a questionnaire. In case of no response, a second questionnaire was sent after 3 months. All cause mortality was noted; in addition hard events were defined as death to all causes (confirmed by certificate and hospital chart of physician's records) or nonfatal myocardial infarction. An acute myocardial infarction was documented by appropriate ECG findings (primary ST change: ST segment elevation of $\geq$1 mm in any leads concordant with [i.e., in the same direction as] the QRS complex; ST-segment depression of $\geq$ 1 mm in any lead from V1 toV3; or ST segment elevation of $\geq$ 5 mm in leads discordant with QRS complex [or any combination thereof]) accompanied by serum cardiac enzyme level changes or isolated cardiac enzyme level changes [17]. The cardiac enzymes levels tested were creatine kinase en troponin T.

Statistical Analysis

Continuous data were expressed as mean ± SD; differences in these variables between subgroups of patients were evaluated using unpaired Student *t* tests. Dichotomous data are presented as numbers and percentages, and differences between patient subgroups were evaluated by Chi-square tests or Fisher's exact tests, as appropriate.

We applied ROC curve analyses to determine the optimal cut-off values for LV volumes and LV ejection fraction to predict events during follow-up. Optimal cut-off values were defined as values resulting in the maximal sum of sensitivity and specificity. Event-free survival curves were obtained according to the method of Kaplan and Meier. Differences in event-free survival between patients at suspected low versus high risk (applying the cut-off value) were evaluated by log-rank tests. Univariable Cox proportional hazard regression analysis was used to further explore the relation between perfusion and functional data and the incidence of cardiac endpoints over time. We report hazard ratios and corresponding 95% confidence intervals (CI).

Annual event rates were calculated as the number of events divided by the sum of each individual follow-up period in years. For all analyses, a p value <0.05 was considered statistically significant. No correction was made to adjust for multiple comparisons unless stated otherwise.

RESULTS

Patient Characteristics

The patients' baseline characteristics are shown in Table 1. Of the patients, 68 patients were male (67%). The mean age was 65.0 ± 8.4 (range 44 -84 years). Of those, 74 (73%) patients had known coronary artery disease. Of those, 48 (47.5%) had sustained a myocardial infarction, 23 (22.7%) had undergone 1 or more revascularization procedures, and 10 (9.9%) had a history of cardiac arrest.

Perfusion and Function

Of the patients, 93% of the patients had an abnormal perfusion study. The average SSS was 34.4 ± 17.5 (range 0-67), the mean SRS was 33.1 ± 16.9 (range 0-65), and the mean SDS 3.7 ± 5.6 (range 0-34). Mean EDV was 194.2 ± 111.2 ml (range 55-657 ml), mean ESV 137.7 ± 106.4 ml (range 14-603 ml), and LVEF 36.9 ± 17.9 % (range 8-75%). Of note, in patients with EF $\leq$ 35 % (n= 51) the summed stress score (43.3± 15.7) and the summed rest score (40.9±16.3) were significantly higher than those in the total patient group ($p< 0.001$). Also the left ventricular volumes (EDV 260± 104.5 ml, ESV 203.9±98.8) were significantly larger ($p< 0.001$).

Outcome

In 93 patients (94.9%) follow-up was complete until census or death. The average follow-up for survivors was 1.24 years (maximum 2.48 years). Thirteen patients died (all of cardiac causes) during follow-up, on average after 0.72 years (range 3 days - 1.37 years). One patient experienced an acute myocardial infarction at 359 days and one patient needed cardiac resuscitation at 130 days. No hard events occurred during surgery or coronary intervention.

Table 1. Patient characteristics.

Total number of patients	101
Gender (M/F)	68/33
Age (yrs)	65.0 ± 8.4
Risk factors for CAD	
Family history CAD	53%
Hyperlipidemia	58%
Hypertension	49%
Diabetes	15%
Smoking	52%
Body Mass Index	24.1 ± 2.8
Body Mass Area (m^2)	1.9 ± 0.2
History	
Myocardial infarction	48 (48%)
Revascularization	23 (23%)
PCI	13 (13%)
CABG	13 (13%)
Cardiac resuscitation	10 (10%)
ICD	3 (3%)
Pharmaceuticals therapy	
ß- blockers	46 (46%)
Nitrates	51 (50%)
Ca- channel blockers	30 (30%)
ACE inhibitors	52 (52%)
Platelet aggregation inhibitors	32 (32%)
Statines	61 (60%)
Antithrombin	38 (38%)
Anti-arrhythmic therapy	24 (24%)
Digitalis	17 (17%)
Diuretics	42 (42%)

CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; ICD: internal cardiac defibrillator; PCI: percutaneous coronary intervention. Body Mass Index according to the Mosteller Formula.

Nine soft events were recorded: 5 patients underwent coronary bypass surgery on day 64, 154, 274 and 278, and in 4 patients PTCA was performed on day 14, 59, 75 and 266 days after the SPECT imaging study.

Patients with hard events were significantly older (63.9 ± 8.4 years vs 71.3±5.1 years $p<0.001$). The other baseline characteristics were not different between the 2 groups. Perfusion data was not significantly different between those patients with and those without hard events. The LV function data showed that patients with hard events had significantly larger LV volumes (EDV 185.1±109.2 ml vs 267.0±110.9 $p= 0.021$, ESV 129.0±104.0 vs 204.2±112.9 $p=0.023$) and lower LVEF (38.6±18.2 vs 26.8±12.1, $p<0.001$) as compared to patients with an event-free follow-up.

Survival

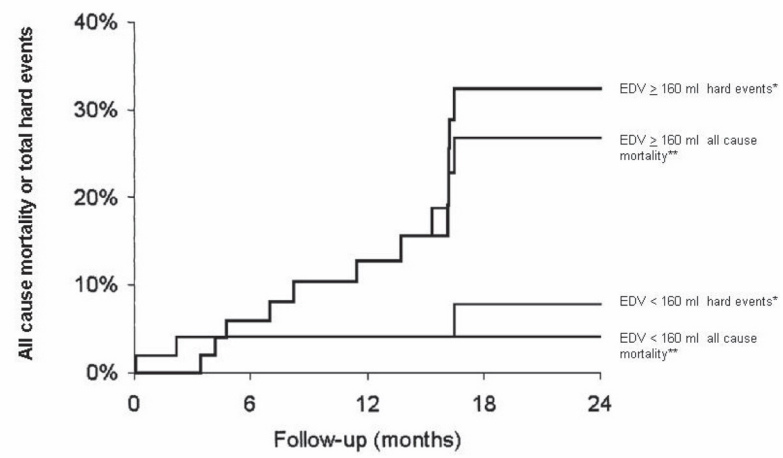
Results on the univariate analyses are listed in Table 2. ROC curve analysis was used to determine the optimal cut-off values for LV volumes and LVEF to predict outcome. Optimal cut-off values for these different parameters could be determined (LVEF 35% [sens 83%, spec. 53%, area under the curve {AUC} 0.67], EDV 160 ml [sens 83%, spec. 52% AUC 0.73] and

Table 2. Univariate analysis of the gated SPECT data to predict outcome.

	hazard ratio	95% CI	p-value
total mortality:			
EDV (ml)	1.04	1.01-1.08	0.02
ESV (ml)	1.04	1.01-1.08	0.03
LVEF (%)	0.81	0.66-1.01	0.06
SSS	1.01	0.97-1.05	0.67
SRS	1.02	0.98-1.06	0.32
SDS	0.93	0.80-1.08	0.36
hard events:			
EDV (ml)	1.04	1.04-1.00	0.03
ESV (ml)	1.04	1.00-1.08	0.04
LVEF (%)	0.81	0.66-0.99	0.04
SSS	1.00	0.97-1.04	0.92
SRS	1.01	0.98-1.05	0.51
SDS	0.92	0.79-1.08	0.31

Hard events = myocardial infarction, cardiac arrest, ventricular fibrillation and total mortality. EDV = end-diastolic volume; ESV = end-systolic volume; LVEF = left ventricular ejection fraction; SSS = summed stress score; SRS = summed rest score; SDS = summed difference score; CAD = coronary artery disease; CI = confidence interval

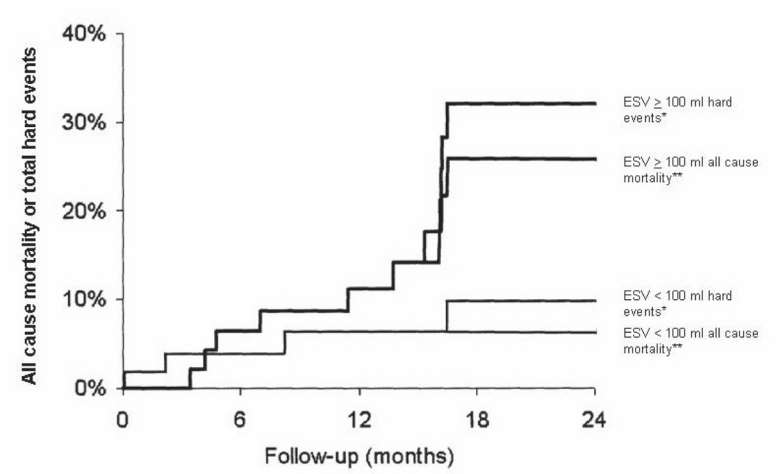
Figure 1. All cause mortality and hard endpoints according to the cut-off values for EDV.



EDV = end-diastolic volume * hard events log-rank P value = 0.019 ** all cause mortality log-rank P value = 0.024

ESV 100 ml [sens 75%, spec. 54%, AUC 0.74]). According to these cut-off values, patients could be divided into 2 groups (Figure 1-3). An EDV >160 ml was associated with a significantly higher risk of hard events (all cause death p=0.024, hard endpoint p=0.019). Patient with an EDV ≥160 ml had an annual hard event rate of 20% (13/64), whereas those with an EDV <160 ml had an annual hard event rate of 4.8 % (3/62) (p=0.01). For ESV, maximal separation could be found using a cut-off volume of 100 ml (p=0.043). The annual hard event rate for patients with an ESV ≥100 ml was 19.7% (12/61), whereas those with an ESV <100 ml had an annual hard event rate of 6.2% (4/64) (p=0.025). No significant differences in all cause mortality were observed between both groups. For LVEF, maximal separation was obtained using a cut-off value of 35% for both all cause mortality and hard events (p=0.047 and p=0.013 respectively). The annual hard event rates for patients with LVEF ≥35% and patients with a LVEF <35% were 19.4% (13/67) and 3.4% (2/58) respectively.

Figure 2. All cause mortality and hard endpoints according to the cut-off values for ESV.



ESV= end-systolic volume * hard events log-rank P value = 0.043 ** all cause mortality log-rank P value = 0.062

DISCUSSION

Our results show that LV volumes (ESV, EDV) and LVEF obtained by quantitative gated SPECT imaging have significant prognostic value in patients with LBBB. Using LV volumes and LVEF, patients with LBBB with increased risk of having subsequent serious cardiac events could be identified. Using ROC curve analysis, cut-off values for EDV of 160 ml for ESV of 100 ml and for LVEF 35% yielded the highest sensitivity/specificity (discriminative power) to predict increased cardiac risk. An EDV≥160 ml and an ESV≥100 ml or a LVEF of <35% were predictive for subsequent cardiac death. Presence or absence of myocardial perfusion abnormalities did not have any predictive power in our group of LBBB patients.

Prognostic Value of Perfusion Data

Our perfusion data extend previous findings that average defect size was largest in those patients who suffered a hard event [14,15,18]. In particular the summed stress score has

been shown to be a powerful independent predictor of cardiac events [19] However, these observations have been made in a wide spectrum of patients with suspected and known CAD, whereas our population was confined to patients with LBBB. In our well-defined LBBB patients we could not find an independent prognostic value for the perfusion data alone.
Bavelaar-Croon et al. [20] showed perfusion abnormalities in 37 LBBB patients both in the septal region as well as in other areas. These authors also showed that the severity of impaired septal perfusion was not directly associated with the severity of septal wall motion abnormalities and global LV function. Altehoefer et al. [21] found fixed defects outside the septal region in 7 of 22 patients with LBBB.
To summarize, although we found larger perfusion defects in patients with hard events, our perfusion indices (summed stress score, summed rest score, and summed difference score), did not allow adequate risk stratification in our population of LBBB patients.

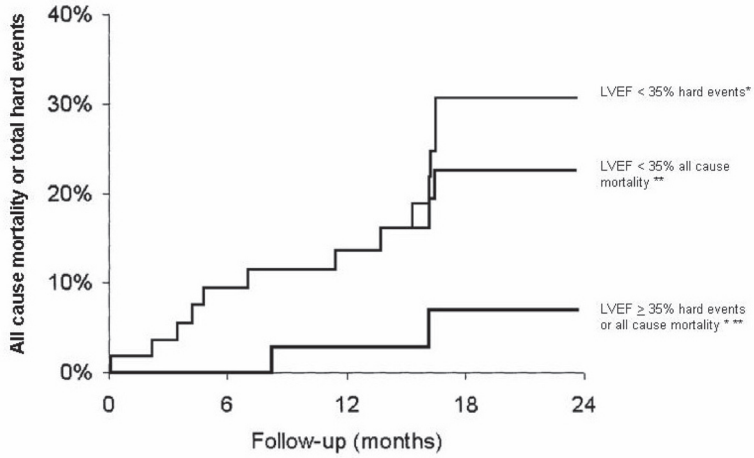
Prognostic Value of Functional Data

To the best of our knowledge, this is the first study that addresses the added prognostic value of LV function data obtained from technetium-99m tetrofosmin gated SPECT in patients with LBBB. We found that patients who died during follow-up had significantly increased LV volumes and a significantly lower LVEF. LBBB patients with an EDV ≥160 ml or an ESV ≥100 ml or a LVEF <35% were at increased risk of subsequent cardiac events.
Our results underscore previously published data on the prognostic value of gated SPECT imaging [22-26]. Sharir et al. [22] showed that perfusion variables and ESV were powerful markers in the prediction of total coronary events, whereas in the prediction of cardiac death, post-stress LVEF and ESV were independent predictors and had incremental value over perfusion data. According to their criteria, patients were at increased cardiac risk when they had a LVEF of less than 45% and an ESV greater than 70 ml. The study by Sharir et al [22] was performed in a very large cohort of 3200 patients, representing a heterogeneous population of patients with CAD in terms of LV function abnormalities. In our LBBB patients there was a large percentage of patients with known CAD and a history of sustained myocardial infarction. These differences might explain the finding of large fixed perfusion defects. These differences might also explain the increased LV volumes and a lower LVEF as cut-off points. Indirect evidence by others confirms the use of higher cut-off values in patients with LBBB. Bavelaar-Croon et al. [20] found that patients with LBBB without previous myocardial infarction had a significantly decreased LV function and increased LV volumes compared to those without LBBB. Compared to the data reported by Sharir et al. [22], the annual event rate in our group of LBBB patients with an EDV ≥160 ml or ESV ≥100 ml was similar to the annual event rate of a mixed population of patients with an ESV >70 ml.

Study Limitations

Recent guidelines recommend a 17-segment model for analyzing the left ventricle [27]. In our study we used a 20-segment model. Paeng et al. [28] showed significant differences between the 20-segment model and repartitioning the myocardium in 5 regions. The absolute differences between repeated measurements of the 20-segment model and the 5-segment model for wall motion and systolic thickening were 0.77 ± 0.62 mm, 7.2 %± 7.2 %, and 0.52 ± 0.49 mm, 4.5%±3.7%, respectively. Absolute differences between the groups were significant (t test P<0.001). However, in a 17-segment model the absolute differences will be more close

Figure 3. All cause mortality and hard endpoints according to the cut-off values for LVEF.



LVEF= left ventricular ejection fraction * hard events log-rank P value = 0.013 ** all cause mortality log-rank P value = 0.047

to the 20-segment model, and the use of 20-segment model will probably not have influenced our results.

In our study perfusion data did not predict events, but the study population was relatively small, the follow-up period was rather short, and the number of events was low. In addition to these factors, most patients predominantly had large fixed defects. In addition, one should realize that patients with LBBB and large defects are at high risk for events because even their low risk group is at high risk. The results of our patient group are in line with the results of the group described by Nallamothu et al [24], showing increased risk for patients with larger perfusion defects. In this group of patients risk stratification could be further done be using the functional data.

In our follow-up period (1.24 years), the prognosis is mainly determined by LV size and function.

CONCLUSION

In patients with LBBB, functional parameters derived from quantitative gated technetium-99m tetrofosmin SPECT imaging can adequately be used for cardiac risk assessment. By use of quantitative gated SPECT, LBBB patients with an EDV of 160 ml or greater, an ESV of 100 ml or greater, or a LVEF lower than 35% are at increased risk for subsequent cardiac events.

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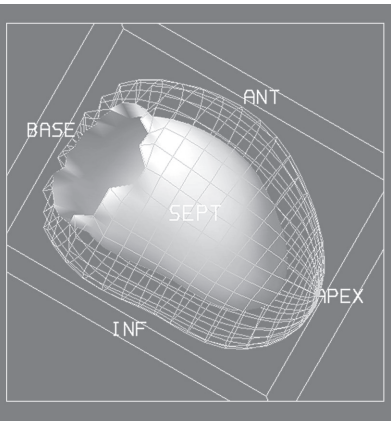
Chapter 5



The additive prognostic value of perfusion and functional data assessed by Quantitative Gated SPECT in women

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ABSTRACT

Background. The aim of this study was to assess the prognostic value of technetium-99m tetrofosmin gated SPECT imaging in women using quantitative gated single photon emission computed tomography (SPECT) imaging.

Methods. We followed 453 consecutive female patients. Average follow-up was 1.33 years (max. 2.55). Hard endpoints were cardiac death, acute myocardial infarction or documented ventricular fibrillation. Event-free survival curves were obtained. Optimal cut-off values for left ventricular (LV) volumes, LV ejection fraction (LVEF) and perfusion data to predict outcome were determined by ROC curve analysis.

Results. A total of 236 patients had an abnormal study, of whom 27 patients experienced hard events (16 deaths) and 47 patients soft events. For hard events summed stress score (SSS) and LVEF, and for any cardiac event SSS showed independent incremental prognostic value. The survival curves were maximally separated when using cut-off values for SSS of $\geq$ 22 and LVEF < 52% ($p<0.001$, HR 4.61 and $p<0.001$ HR 5.24 for SSS and LVEF resp.), and SSS $\geq$ 14 ($p<0.001$ HR 3.76) for any cardiac event.

Conclusion. In women, perfusion and functional parameters derived from quantitative gated technetium-99m tetrofosmin SPECT imaging can adequately be used for cardiac risk assessment. Using quantitative gated SPECT, female patients with an LVEF < 52% or an SSS $\geq$22 are at increased risk for subsequent hard events. Furthermore, patients with a SSS$\geq$14 are at increased risk for any cardiac events.

INTRODUCTION

Coronary artery disease (CAD) is the major cause of morbidity and mortality in the western countries. Increased mortality and reinfarction have been noted in women after myocardial infarction compared to men [1-3]. The large proportion of atypical symptoms, higher incidence of associated disease (e.g. hypertension, diabetes mellitus) and the higher age at presentation may account for the worse outcome [*3,*4]. Appropriate non-invasive diagnostic testing is important in the early diagnosis and the risk stratification of women with suspected CAD. Exercise ECG has a lower diagnostic and prognostic accuracy in women. It is influenced by multiple factors, i.e. exercise capacity and hormonal status [4,5]. The increased age at presentation is often associated with lower exercise capacity and an inability to attain maximal stress [4,5]. Myocardial perfusion imaging provides incremental prognostic information [4].
The addition of regional left ventricular (LV) function parameters by gated single photon emission computed tomography (SPECT) improved the diagnostic accuracy and prognostic value of perfusion imaging, whereby LV function parameters have incremental prognostic value over perfusion data alone [6-10]. Previous studies set normal functional data limits. However, some problems still have to be solved. First, most data on prognostic value of the parameters assessed by gated SPECT have been obtained in a mixed gender population and may not be applicable to women. Women often have smaller LV volumes. It has been shown that gender related differences in normal limits exist [11,12]. However, a multicenter phantom study showed a wide range of results in different standard end-systolic and end-diastolic volume combinations. Moreover, the LV ejection fraction (LVEF) was overestimated and both the end-systolic volume (ESV) and end-diastolic volume (EDV) were underestimated. Especially, this is the case for small volumes. Cutoff values for LV functional parameters should be validated in each center [13].
Second, most data on prognostic value of perfusion analyses by gated SPECT is obtained by a 20-segment model. However, recent guidelines on cardiac imaging suggest the use of a 17-segment model. Berman et al [14] showed that a 17-segment model provides a more accurate prognostic categorization of individual patients with small abnormalities of the distal short axil and apical portions of the LV.
At present, few data exist on the prognostic value of gated SPECT in women. In this category of patients, little data is available on the value of LV function parameters to potentially improve risk stratification. Accordingly, the aim of the study was to assess the incremental prognostic value of technetium-99m tetrofosmin (Tc^{99m}) gated SPECT imaging in women.

METHODS

Study Population

We studied 453 consecutive women (median age 62 years [53-70 years, 25^{th}-75^{th} percentiles]) who underwent rest/stress technetium-99m tetrofosmin myocardial perfusion gated SPECT imaging between October 1, 1999, and January 1, 2000 at the Leiden University Medical Center. Patients were followed up until the fixed census date May 1, 2000.

Stress Myocardial Perfusion Protocol

All patients were instructed to refrain from caffeine-containing products for 24 hours before the test. Beta-blocking agents, nitrates, calcium antagonists were discontinued at least 48 hours prior to SPECT imaging. A symptom-limited bicycle exercise stress test was performed. Technetium-99m tetrofosmin (GE, Amersham, UK) was injected at peak stress, and exercise was continued for an additional 60 seconds. The exercise stress protocol includes a stepwise increase in workload depending on gender, age, weight and height. This protocol is routinely applied in our institution. When the prespecified maximum workload (depending on gender, age, weight and height) is achieved, the physical validity is considered to be at least 100%. Exercise stress endpoints were severe angina, physical exhaustion, dyspnoea, sustained tachy-arrhythmias, exertional hypotension or ischemic ST-T segment-depression of at least 0.2 mV and a duration of 80 ms. Exercise was considered inadequate if the physical validity of the patient was less than 80% of the predicted validity (workload) in the absence of angina or an ischemic ST-depression. Patients who were unable to perform a physical stress test or patients with a left bundle branch block underwent a pharmacological stress test as described previously [15]. Vasodilatation was induced using intravenous administration of adenosine at a dose rate of 0.14 mg/kg/min for 6 minutes. Technetium-99m tetrofosmin was injected 3 minutes after start of infusion of the pharmacological agent. Dobutamine 0.3mg/kg infusion during 15 minutes was used in patients who where not able to exercise adequately and in whom the use of adenosine was contraindicated (except patients with LBBB). Horizontal or downsloping ST-segment depression of 1 mm or greater or upsloping of 1.5 mm or greater at 80 milliseconds after J point was considered positive for ischemia. In case of ST-T-segment abnormalities, registration of the stress ECG was continued until normalization of the ECG was seen.

Gated SPECT Acquisition Protocol

Both 1-day and 2-day imaging protocols were used [15]. A dose of 500 MBq technetium-99m tetrofosmin was given intravenously for the 2-day protocol stress study and 750 MBq for the 1-day protocol stress study. Dosages of 500 and 250 MBq, respectively, were given for the rest study. All acquisitions took place 30-45 minutes (stress) or 45-60 minutes (rest) post-injection. Gated SPECT acquisition protocol was performed post-stress. In case of 1-day protocol the rest study was done first. Imaging was performed with a triple-head 360° rotating gamma camera (Toshiba GC-9300 GMS, Japan). A total of 90 frames of 30" duration using a 64 x 64 pixel matrix were obtained at 4-degree intervals using a non-circular orbit. Sixteen bins per cardiac cycle were acquired. All studies were pre-filtered using a 9-order Butterworth filter at a cut-off frequency of 0.32 cycles/pixel (rest) [pixel size 6 mm] or 0.26 cycles/pixel (stress). All images were subject to quality control measures, including cinematic display for assessment of patient motion, corrections for field non-uniformity and center of rotation. No attenuation or scatter correction was used. The reconstructed data were projected as tomographic slices in short-axis and vertical/horizontal long-axis views. Myocardial perfusion data and quantitative LV volumes and LVEF were calculated using the commercially available Cedars-Sinai's Quantitative gated SPECT (QGS) software, version 2.0, revision A" [7,8]. When automatic reconstruction or reorientation failed, reconstruction limits and axes were assigned manually. End-systolic volume index (ESVi) and EDV index (EDVi), in millilitres per square meter, were derived by dividing ESV and EDV by body surface area (BSA), respectively.

Semi-quantitative Visual Analysis of Myocardial Perfusion SPECT

Semi-quantitative visual interpretation of SPECT perfusion images used short-axis and vertical long-axis tomograms divided into 17 segments for each patient [14]. These segments were assigned to 4 evenly spaced regions in apical, 6 mid-ventricular and 6 basal slices of the short-axis views and one apical segment on the mid-ventricular vertical long-axis slice. Each segment was scored using a five-point scoring system (0=normal, 1= equivocal, 2=moderate, 3= severe reduction of radioisotope uptake, 4= absence of detectable radiotracer in a segment). Apparent perfusion defects presumably caused by soft tissue attenuation were assigned a score of 1. The observers were blinded to the patient's clinical history and results of stress testing.

Three global perfusion indices were employed to combine assessments of defect extent and severity [16]. Summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS). These indices were converted to a percentage of the total myocardium involved with ischemic, or fixed defects [17-18]. All studies were evaluated by at 2 experienced observers in consensus readings.

Patient Follow-up and Endpoint Definitions

Both medical records and the automated hospital information system were reviewed. If these data did not cover the entire period from recruitment until census date, the patient was sent a questionnaire. In case of no response, a second questionnaire was sent after 3 months. Cardiac death (CD) was noted as death due to any cardiovascular cause, confirmed by certificate and hospital chart of physician's records; in addition, hard events were defined as cardiac death, nonfatal myocardial infarction (MI) or documented ventricular fibrillation. An acute MI was documented by appropriate ECG findings, accompanied with serum cardiac enzyme level changes or isolated cardiac enzyme level changes. The cardiac enzymes used were creatine kinase (CK) en troponin T. Soft events were defined as any late (> 60 days after MPI) revascularization procedure i.e. coronary artery bypass grafting (CABG) or percutanous transluminal coronary angioplasty (PTCA).

Statistical Analysis

Most continuous variables had non-normal distribution (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25th and 75th percentiles. Categorical data are summarised as frequencies and percentages. Differences in baseline characteristics between patients who reached the primary endpoint and those who did not were analysed using Wilcoxon-Mann-Whitney tests, Chi-square tests or Fisher's exact tests, as appropriate.

Univariable and multivariable Cox proportional hazard regression analyses were applied to study the relation between perfusion and functional data (based on gated SPECT imaging) and the incidence of study endpoints over time. We considered a broad range of potential confounders of these relations, including age, smoking, family history of CAD, hypertension, diabetes, hyperlipidemia, established CAD, resting heart rate, type of stressor (pharmacological or exercise), level of exercise, presenting symptom (angina pectoris), presence of ischemia on the exercise ECG. Cox models aiming at prediction should be used with a minimum of 10 events per predictor variable (EPV). Simulation studies showed increasing bias and variability, unreliable confidence interval coverage, and problems with model convergence as EPV declined below 10 [19,20]. However, Vittinghoff E and McCulloch. demonstrated that this

rule of thumb is too conservative in analyses of causal influences based on observational data, and control of confounding may require adjustment for more covariates than the rule of 10 EPV allows [21]. Discounting of statistically significant associations from models that are based on 5-9 EPV and that aim to adjust for confounding is not justified. Hence, multivariable models that are based on our dataset (with 27 events) could safely contain 3 to 5 variables. We performed stepwise regression according to the backward deletion approach, applying a p-value of 0.15 as threshold for variable removal, to adjust for as many covariables as is resonably allowed by the (limited) number of events. We report crude and adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI).

It was not our intention to formally build an outcome prediction model. Still, all the continuous variables were assessed for linearity by entering a transformed variable in addition to the variable of interest. The natural logarithm and square transformations were used. A significant change in the -2 log-likelihood was considered as a sign of non-linearity, otherwise the linearity assumption was accepted. All variables met the linearity assumption. To check the proportional hazard assumption, i.e. that the hazard ratio for two subjects with fixed predictors is constant over time, log(-log[survival probability]) for different categories was plotted against time to ensure that the curves were reasonably parallel. In general, all proportionality assumptions were appropriate.

It appears that SSS and LVEF were associated with the incidence of study endpoints over time. We applied receiver operator characteristic (ROC) curve analyses to determine the optimal cut-off values for these variables that can be used for event prediction in clinical practice. Optimal cut-off values were defined as values resulting in the maximal sum of sensitivity and specificity. Subsequently, event-free survival curves were obtained according to the method of Kaplan and Meier, separating patients with a value below or above the threshold. Differences in event-free survival between patients were evaluated by log-rank tests.

For all analyses, a p value <0.05 was considered statistically significant. No correction was made to adjust for multiple comparisons.

RESULTS

Patient Characteristics

Four-hundred and fifty-three patients were followed. The patient baseline characteristics are shown in Table 1. Median age was 62 (53-70 years [25^{th}-75^{th} percentiles]). One-hundred and fourteen (26%) patients had known CAD. Of those patients 67 (15%) patients had sustained a MI, 67 (15%) patients experienced one or more revascularization procedures, and no patient had a history of cardiac arrest.

Perfusion and Function

Perfusion and function data is shown in table 2. Two-hundred and thirty-five patients (48%) had an abnormal perfusion study. Of those, 105 patients (45 %) showed an ischemic perfusion study. The median SSS was 5 (25^{th}-75^{th} percentiles: 0-22), the median SRS was 3 (25^{th}-75^{th} percentiles: 0-17), and the median SDS 2 (25^{th}-75^{th} percentiles: 0-3), median EDV was 70 ml (25^{th}-75^{th} percentiles: 56-89.5 ml), median ESV 24 ml (25^{th}-75^{th} percentiles: 16-39.5 ml), and

Table 1. Patient characteristics

Total number of patients	453
Age (yrs)*	62 (53-70)
Risk factors for CAD	
Family history CAD	65%
Hyperlipidemia	61%
Hypertension	60%
Diabetes	18%
Smoking	43%
Body Mass Index *	26.9 (26.1-28.8)
Body Mass Area (m^2)*	1.8 (1.7-2.5)
History CAD	114 (26%)
Myocardial infarction	67 (15%)
Revascularization	67 (15%)

* median (25th-75th percentiles), CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; Body Mass Index according to the Mosteller Formula.

Table 2. Findings at gated SPECT imaging

	Median	25th – 75th percentile	range
A. Myocardial Perfusion			
Total patient group (n=453):			
SSS	5	0 - 22	0 - 67
SRS	3	0 - 17	0 - 65
SDS	2	0 - 3	0 – 34
B. Left Ventricular Function			
Total patient group (n=453)			
EDV (ml)	70	56 - 89.5	32 - 343
ESV (ml)	24	16 - 39.5	4 - 298
LVEF (%)	65.5	54 - 73	13 - 91
ESVi	13	9 - 22	2.0 - 156
EDVi	38	32 - 49	18 - 180

SSS = summed stress score, SRS = summed rest score, SDS = summed difference score, EDV = end-diastolic volume, ESV = end-systolic volume, LVEF = left ventricular ejection fraction, ESVi: end-systolic volume index., EDVi = end-diastolic volume index.

LVEF 65.5 % (25^{th}-75^{th} percentiles: 54-73%), The median EDVi was 38 (25^{th}-75^{th} percentiles: 32-49), and the median ESVi 13 (25^{th}-75^{th} percentiles: 9-22).

Outcome

In 422 patients (93.2%) follow-up was complete until census or death. The average follow-up was 1.33 years (maximum 2.55 years). Twenty-seven patients suffered a hard event during follow-up, on average after 1.06 years (range 1 day - 2.50 years). Sixteen patients died of cardiac cause during follow-up, with a mean follow-up of 0.72 years (range 1 day - 2.22 years).

Table 3. Outcome: Perfusion and functional data.

A	Hard events*	No hard event*	p-value
Myocardial perfusion:			
SSS	25 (0 - 46)	4 (0 – 21)	<0.01
SRS	18 (2 – 30)	2 (0 – 15)	<0.01
Myocardial function:			
EDV	85 (70 – 164)	69 (56 – 87)	<0.01
ESV	45 (23 – 91)	23 (16 – 37)	<0.01
LVEF	50 (31 – 64)	66 (55 – 73)	<0.01
ESVi	24 (12 – 49)	12 (8 – 21)	<0.01
EDVi	50 (37 – 84)	38 (32 – 47)	<0.01
B	Any Cardiac events*	No cardiac event*	p-value
Myocardial perfusion:			
SSS	23 (4 – 35)	3 (0 – 19)	<0.01
SRS	12 (2 – 24)	1 (0 – 14)	<0.01
SDS	3 (0 – 13)	0 (0 – 1)	<0.01
Myocardial function:			
EDV	77 (66 – 103)	68 (56 – 86)	0.01
ESV	34 (21 – 58)	22 (15 – 37)	<0.01
ESVi	17 (10 – 33)	12 (8 – 21)	<0.01
EDVi	42 (34 – 59)	38 (32 – 47)	0.01
LVEF	56 (44 – 68)	66 (56 – 73)	<0.01

* values of the median (25th – 75th percentile). Only parameters that showed significantly differences between the patient groups are mentioned. SSS = summed stress score, SRS = summed rest score, SDS = summed difference score, EDV = end-diastolic volume, ESV = end-systolic volume, LVEF = left ventricular ejection fraction. ESVi: end-systolic volume index. EDVi = end-diastolic volume index.

No hard events occurred during surgery or coronary intervention. Forty-seven soft events were recorded (mean follow-up 1.43 years; range 93 days – 2.52 years): 15 patients underwent coronary bypass surgery, and in 32 patients PTCA was performed.

Patients with hard events during follow up had significant larger LV volumes, larger perfusion defects and lower LVEF than those without hard events. Patients with any cardiac event during follow up had significant larger LV volumes, more extensive perfusion defects, lower LVEF's and larger reversible defects than those without [table 3].

Results based on univariate analysis are listed in Table 4. Summed stress score, SRS, all the function variables (EDV, ESV, EDVi, ESVi and LVEF) were predictive for CD and hard events. For hard events diabetes, smoking, presenting symptom (angina pectoris) and pharmacological stress test were also predictive. Age, diabetes, hyperlipedemia, smoking, history of MI, presenting symptom, pharmacological stress test, level of exercise and resting heart rate were predictive for any cardiac event. Also larger LV volumes (EDV and ESV), decreased LVEF, larger perfusion defects and ischemia were predictive for any cardiac event.

The variables entered in the initial multivariable model for hard events included age, diabetes, hypertension, family history, hyperlipedemia, smoking, presenting symptom, history of CAD, history of MI, history of revascularization, pharmacological stress test, level of exercise, SSS,

Table 4. Univariate and multivariate analysis of clinical data, perfusion and functional data assessed by gated SPECT.

Univariate analysis:	hazard ratio	95% CI	p-value
total mortality:			
Age	1.02	0.97-1.06	NS
Diabetes	2.58	0.75-8.80	NS
Hypertension	2.08	0.56-7.69	NS
Family history	0.79	0.22-2.79	NS
Lipid	0.39	0.12-1.22	NS
Smoke	1.23	0.55-2.75	NS
CAD	0.95	0.31-2.93	NS
Symptom (AP)	0.99	0.79-1.24	NS
History MI	1.93	0.62-6.00	NS
History revasc	0.00	0.00-0.00	NS
Pharmacological	1.37	0.97-1.93	NS
Resting HR	1.03	0.92-1.42	NS
level of exercise	0.90	0.85-1.00	NS
ECG ischemia	0.72	0.04-1.89	NS
SSS	1.04	1.01-1.07	0.01
SRS	1.04	1.01-1.07	0.01
SDS	1.05	0.98-1.13	NS
EDV (ml)	1.01	1.00-1.07	<0.001
ESV (ml)	1.01	1.01-1.02	<0.001
LVEF (%)	0.95	0.92-0.97	<0.001
EDVi	1.03	1.01-1.04	<0.001
ESVi	1.03	1.02-1.04	<0.001
hard events:			
Age	1.03	0.98-1.05	NS
Diabetes	1.03	1.24-7.44	0.02
Hypertension	0.91	0.40-2.11	NS
Family history	0.70	0.28-1.72	NS
Lipid	0.76	0.32-1.80	NS
Smoke	1.80	1.02-3.15	0.04
CAD	1.51	0.67-3.40	NS
Symptom (AP)	1.14	1.02-1.27	0.02
History MI	2.14	0.90-5.08	NS
History revasc	0.94	0.51-1.73	NS
Pharmacological	2.53	1.10-5.80	0.03
level of exercise	0.96	0.91-1.00	NS
Resting HR	0.99	0.96-1.02	NS
ECG ischemia	1.32	0.54-3.24	NS
SSS	1.05	1.03-1.07	<0.001
SRS	1.05	1.03-1.08	<0.001

Table 4: (Continued)

Univariate analysis:	hazard ratio	95% CI	p-value
SDS	1.05	0.99-1.11	NS
EDV (ml)	1.01	1.01-1.02	<0.001
ESV (ml)	1.01	1.01-1.02	<0.001
LVEF (%)	0.95	0.93-0.97	<0.001
EDVi	1.02	1.01-1.03	<0.001
ESVi	1.02	1.01-1.03	<0.001
Any cardiac events:			
Age	1.03	1.01-1.05	0.01
Diabetes	1.88	1.07-3.30	0.03
Hypertension	1.00	0.59-1.67	NS
Family history	1.21	0.69-2.11	NS
Lipid	2.03	1.13-3.64	0.02
Smoke	1.76	1.27-2.45	0.001
CAD	2.27	1.37-3.75	0.001
Symptom (AP)	1.11	1.04-1.20	0.004
History MI	2.36	1.35-4.12	0.003
History revasc	1.09	0.80-1.50	NS
Pharmacological	1.82	1.10-3.00	0.02
Resting HR	0.98	0.96-1.00	0.03
level of exercise	0.97	0.94-0.99	0.01
ECG ischemia	1.42	0.81-2.48	NS
SSS	1.05	1.03-1.06	<0.001
SRS	1.03	1.02-1.05	<0.001
SDS	1.11	1.08-1.14	<0.001
EDV (ml)	1.01	1.00-1.01	0.01
ESV (ml)	1.01	1.00-1.01	0.01
LVEF (%)	0.98	0.96-0.99	<0.001
EDVi	1.01	1.00-1.02	0.02
ESVi	1.01	1.00-1.02	0.01
Multivariate analysis			
hard events:			
LVEF (%)	0.97	0.94-1.00	0.03
SSS	1.03	1.01-1.06	0.02
Any cardiac events:			
SSS	1.06	1.03-1.08	<0.001

Hard events = myocardial infarction, cardiac arrest, ventricular fibrillation and total mortality. Any cardiac event= myocardial infarction, cardiac arrest, ventricular fibrillation and total mortality, revascularization procedure. Symptom (AP) = angina pectoris as presenting symptom. Pharmacological = pharmacological stress test. Resting HR= resting heart rate. Level of exercise = % of the target level of exercise adjusted for gender, age, length and weight. ECG ischemia = ischemia on stress ECG. EDV = end-diastolic volume. ESV = end-systolic volume. ESVi= end-systolic volume index. EDVi= end-diastolic volume index. LVEF = left ventricular ejection fraction. SSS = summed stress score. SRS = summed rest score. SDS = summed difference score. CAD = coronary artery disease. CI = confidence interval. MI= myocardial infarction

SRS and all the function variables (EDV, ESV, EDVi, ESVi and LVEF). For any cardiac events age, diabetes, hypertension, family history, hyperlipedemia, smoking, presenting symptom, known CAD, history of MI, history of revascularization, pharmacological stress test, resting heart rate, level of exercise, ischemia on stress ECG, SSS, SRS and all the function variables (EDV, ESV, EDVi, ESVi and LVEF) were entered in the model.
Multivariate analysis showed that summed stress score and LVEF provided independent and incremental prognostic value for hard events (beyond clinical data and/or perfusion variables respectively). Summed stress score provided independent and incremental prognostic value for any cardiac event (table 4).

Survival

The annual CD rate as function of percent stress defect for <5%, 10-20% and >20% hypoperfused myocardium was <0.7%/year, 1.6%/year and 4.6 %/years respectively. The annual hard event rate for these subgroups are 1.0%/year, 3.1%/year and 8.3%/year respectively. ROC curve analysis was used to determine the optimal cut-off values for LVEF and SSS to predict outcome. For hard events optimal cut-off values for these different parameters could be determined. According to these cut-off values, patients could be divided into 2 groups (Figure 1 and 2). An LVEF < 52% (area under the curve [AUC] 0.75) was associated with a significantly higher risk of hard events (p< 0.0001). Patients with a LVEF < 52% had an annual event rate of 11.6% with an annual CD rate of 6.6%, whereas those with an LVEF ≥ 52% had an annual hard event rate of 1.7%, and an annual CD rate of 0.6%. For SSS, maximal separation could be found using a cut-off score of 22 (AUC 0.84; p=0.0001). The annual hard event rate for patients with an SSS ≥ 22 was 10.5%, whereas those with an SSS <22 had an annual hard event rate of 2.5%.
For any cardiac event optimal cut-off value for SSS could be determined (figure 3). Maximal separation could be found using a cut-off score of 14 (AUC 0.81). The annual any cardiac event rate for patients with an SSS ≥ 14 was 20.8%, whereas those with an SSS <14 had an annual any cardiac event rate of 5.9% (p<0.0001).

Figure 1. Hard endpoints according to the cut-off values for SSS

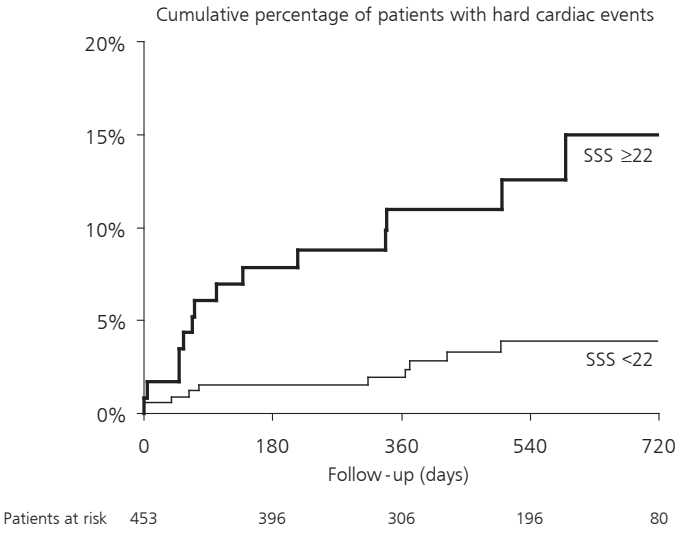


Figure 2. Hard endpoints according to the cut-off values for LVEF.

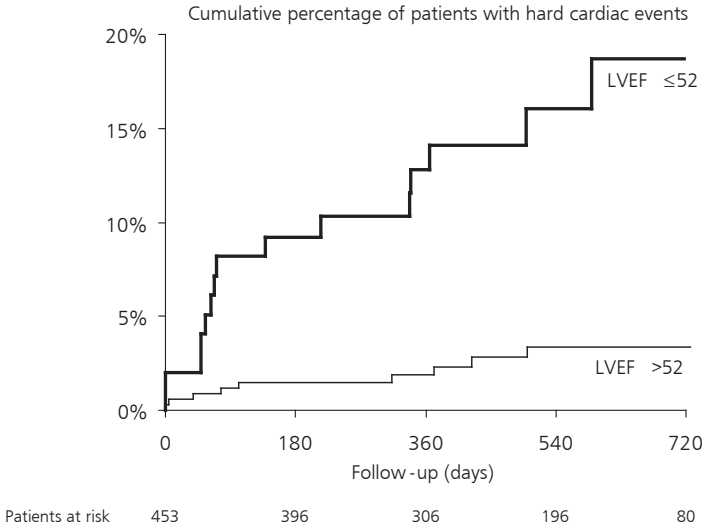
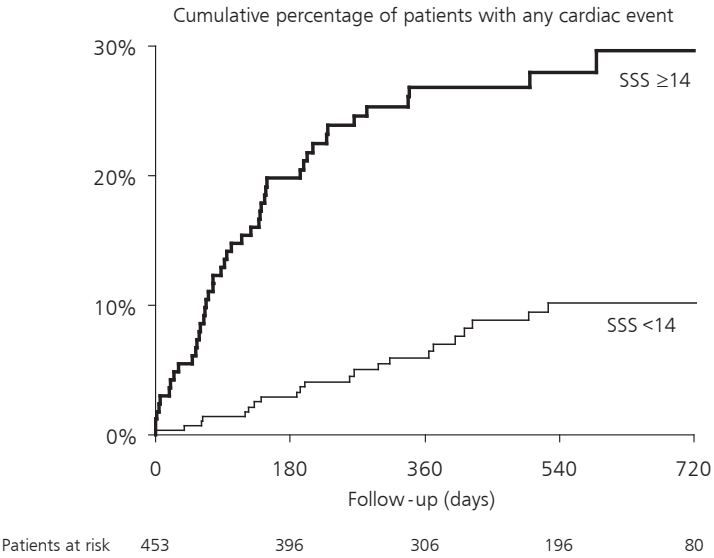


Figure 3. Any cardiac endpoint according to the the cut-off values for SSS.



DISCUSSION

Our results show that relatively young female patients with hard events had significant larger LV volumes, increased defect sizes and lower LVEF's than those without hard events. Also, patients with any cardiac event during follow up had significant larger LV volumes, increased defect sizes and lower LVEF's than those without any cardiac events. Moreover, patients with any cardiac event had significant larger ischemic defects. For hard events and cardiac death SSS, SRS and all the function variables (EDV, ESV, EDVi, ESVi and LVEF) were predictive. For

hard events diabetes, smoking, presenting symptom and pharmacological stress test were also predictive. Age, diabetes, hyperlipedemia, smoking, history of MI, presenting symptom, resting heart rate and pharmacological stress test were predictive for any cardiac event. Also larger LV volumes (EDV and ESV), decreased LVEF, larger perfusion defects and ischemia were predictive for any cardiac event. Summed stress score obtained by quantitative gated SPECT imaging had independent and incremental prognostic value for both hard events and any cardiac event in female patients beyond clinical data. For hard events also LVEF had independent and incremental prognostic value beyond clinical and perfusion data. Using these perfusion and functional data, female patients with increased risk of having subsequent serious cardiac events could be identified. Using ROC curve analysis, cut-off values for LVEF of 52% and SSS 22 for hard events and SSS of 14 for any cardiac event yielded the highest sensitivity/specificity (discriminative power) to predict increased cardiac risk. An SSS > 22 and a LVEF of <52% were predictive for subsequent hard events. An SSS> 14 was predictive for any cardiac event.

To our knowledge, this is the first study to show that large ischemic and mixed defects are not all at high risk of events. Only a combination of perfusion and function allows to effectively risk stratify this population and give an individualized risk estimates for this heterogeneous population. Therefore, perfusion data per se are definitely not enough to make individualized prognostic statements.

Prognostic Value of Perfusion Data

Our perfusion data extend previous findings that average defect size was largest in those patients who suffered a hard event. In particular the SSS has been shown to be a powerful independent predictor of cardiac events [10, 22-24].

However, most of the observations have been made in a mixed gender population [10, 22-24]. Sharir et al [11] showed that for CD and MI, perfusion data provided a larger proportion of the prognostic information for women than they did for men. We demonstrated that perfusion data has incremental value over clinical data, both for hard events and any cardiac event. In particular women with moderate to severe perfusion defects had a high annual hard event rate. Those with a normal perfusion image have very low annual event rate. Stress-induced ischemia was predictive in women who suffered any cardiac event but had no incremental prognostic value for predicting hard events. This is in line with previous findings that suggest that the extent of defect size and functional abnormalities are more predictive for hard events (CD and MI), whereas the extent of ischemia is more predictive for soft events and/or MI [10,25-27]. By using gated SPECT perfusion imaging, women at increased risk of having a cardiac event could be identified.

Most of the published data used a 20-segment approach. Berman et al [14] showed that in a 17-segment approach the apex and adjacent short-axis slice of the LV is less overweighed. There was a trend toward less frequent borderline scans with more normal and severely abnormal scans in the overall population. They found in the patients who shifted from abnormal scan by 20-segment model to normal scan in the 17-segment approach an equal cardiac death rate to other normal patients.

Berman et al [14] found a significantly higher annual CD rate for women compared to man in group of patients with moderately to severe perfusion defects. We found the same annual CD rates for the patients with normal images (stress defect <5% of the myocardium, 0.5% vs <0.7%). However, a smaller annual CD rate in the group of patients with severe perfusion

defects (4.6% versus 6.4%) was found. This may be explained by the fact that our population was 10 years younger. In a matched aged group, Groutars et al [24] found similar events rates compared to our study (0.4% vs 0.7% annual CD rate for normal perfusion, 2.1% vs 2.4% annual CD for moderately-severely abnormal images). Similar results were found for hard cardiac events. Our optimal cut-off value to identify patients at high risk for hard events was 22 (32% of the left ventricle). Patients with a SSS < 22 had the same annual hard event rate demonstrated by Zellweger et al [28] for mildly abnormal scans (2.5% vs 2.4%). Travin et al [10] reported similar annual hard event rates for patients with mildly abnormal perfusion images compared to patients with a SSS < 22 in our study (2.5% vs 3.0%). The cut-off value of SSS>22 suggests that the major part of the hard events occurs in patients with very large perfusion defects. Therefore, the group of female patients with severe perfusion defects is diverse with different outcome. In our group, using our cut-off values, it is possible to identify females at increased risk.

A few data is reported on any cardiac events. Groutars et al [29] reported good outcome in patients with normal perfusion studies. The annual event rate was 0.8% for any cardiac events. Schinkel et al [30] found that for all cardiac events an abnormal scan and SSS had independent prognostic value, which is in line with our results.

Prognostic Value of Functional Data

Our data showed that functional data obtained from technetium-99m tetrofosmin gated SPECT were predictive for cardiac events.

We found that patients who suffered a cardiac event (for subgroups: cardiac death, hard events and any cardiac event) during follow-up had significantly increased LV volumes and a significantly lower LVEF. Only for hard events functional data (LVEF) had independent incremental prognostic value. Our results underscore previously published data on the prognostic value of gated SPECT imaging [26-34].

Sharir et al. [9] showed that perfusion variables and ESV were powerful markers in the prediction of total coronary events, whereas in the prediction of CD, post-stress LVEF and ESV were independent predictors and had incremental value over perfusion data. According to their criteria, patients were at increased cardiac risk when they had a LVEF < 45% and an ESV >70 ml. The study by Sharir et al [9] was performed in a very large cohort of more than 1600 patients, representing a heterogeneous population of patients with CAD in terms of LV function abnormalities.

Recently, Sharir et al [11] showed lower limits of LVEF in women and men with a low likelihood of CAD. Fifty-one percent (mean-2 SDs) and 43% respectively. They also report upper limits for ESVi and EDVi for both genders (27 ml/m^2 and 60 ml/m^2 for women and 39 ml/m^2 and 75 ml/m^2 in men resp.).

Compared to the data reported by Sharir et al. [9], the annual event rate in our group of women with an LVEF ≥52% was similar to the annual event rate of a mixed population of patients with an LVEF≥45% (regardless of the degree of perfusion abnormality).

To summarize, functional data obtained from technetium-99m tetrofosmin gated SPECT can be used to identify women at increased cardiac risk. The cut-off value for LVEF used in a mixed gender population is not applicable to studies in women. Women at increased risk of major adverse cardiac events, those with an LVEF <52% and/or a SSS of > 22, may benefit from more

aggressive invasive therapy. However, further randomized prospective studies are needed to show better clinical outcome of aggressive therapy in these patients.

Study Limitations

It is known that in patients with small hearts LV volumes, especially ESV, measured by the QGS technique are often underestimated and LVEF is often overestimated. In general, this phenomenon occurs more in women than in men because women tends to have smaller LV's. However, previous studies [11] showed a significant correlation between ESV and EDV versus BSA. Another study [13] showed a systematically underestimation of volumes, more so for small volumes. As long as the QGS technique has a high reproducibility (for each individual center) [7,8, 35] the data on LV function can be used for risk stratification.

It would have been interesting to demonstrate whether LV volumes add prognostic information over LVEF. However, both variables are strongly interrelated, implying that LV volumes and LVEF cannot simultaneously be incorporated in a statistical model. Consequently, based on our data it is virtually impossible to decide whether LV volumes add incremental value to LVEF.

In the present study we included all female patients who underwent a myocardial perfusion study, without screening patients for pre-test likelihood of CAD. However, according to the used ESC guidelines, most patients have an intermediate likelihood of CAD. In the present study, ischemia did not show independent incremental prognostic value for predicting any cardiac events, but the study population was relatively small, the follow-up period was rather short and not for 100% complete (a total of < 5% lost to follow up), and the number of events was low. Future studies will be needed to further separate the group of patients with combined perfusion and functional high risk features.

CONCLUSION

In women, perfusion and functional parameters derived from quantitative gated technetium-99m tetrofosmin SPECT imaging can adequately be used for cardiac risk assessment. Using quantitative gated SPECT, female patients with an LVEF < 52% or an SSS ≥22 are at increased risk for subsequent hard events. Women with a SSS≥14 are at increased risk for any cardiac events.

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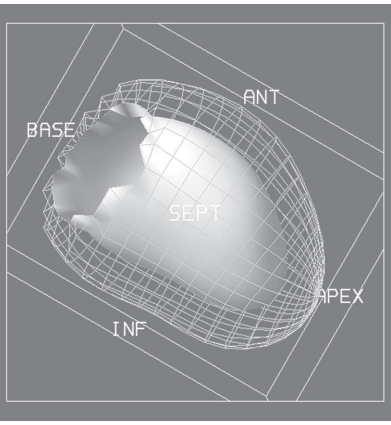
Chapter 6



Gated SPECT myocardial imaging: a valuable diagnostic and prognostic tool in clinical cardiology

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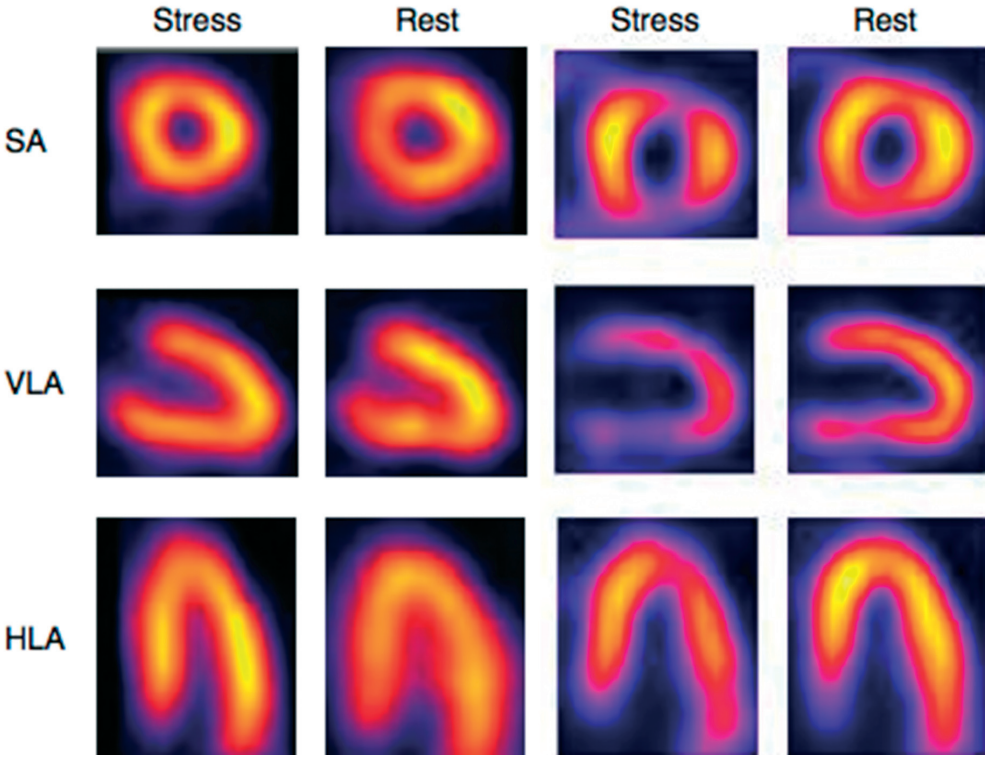
Submitted

INTRODUCTION

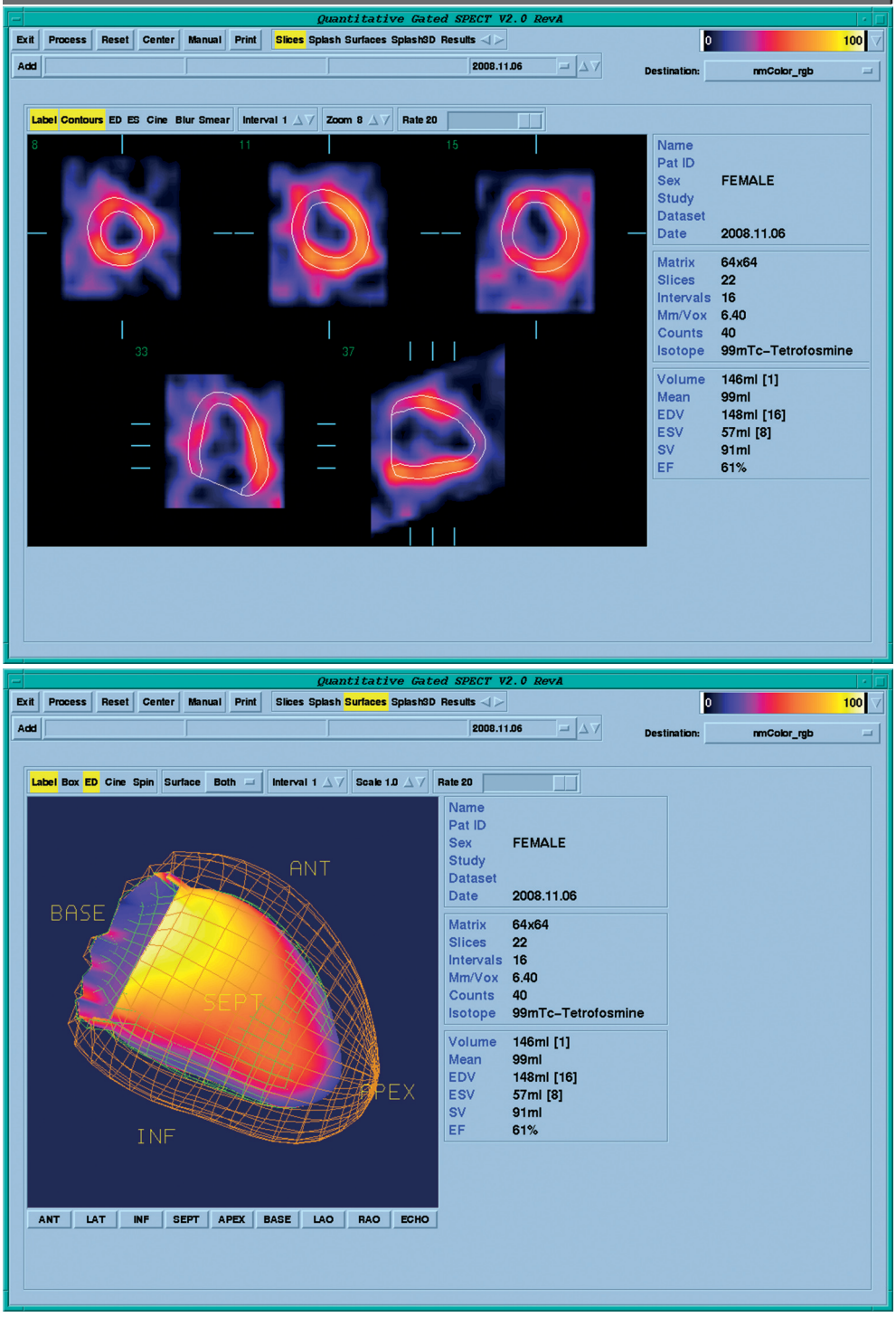
Coronary artery disease (CAD) is the major cause of morbidity and mortality in industrialized western countries. Early detection of CAD may decrease morbidity and mortality. Myocardial perfusion scintigraphy (MPI) is an important diagnostic tool both in patients with known and suspected coronary artery disease (figure 1). Moreover, MPI provides prognostic information and can therefore be used for optimal risk stratification. The improvement in survival after acute myocardial infarction has resulted in a markedly increased population of elderly patients with extensive cardiac disease, often associated with a diminished cardiac function. In this setting it becomes more important to go from a diagnosis of coronary artery disease towards the level of risk stratification. This need for risk stratification applies to patients with both acute and chronic CAD. Gated single photon emission computed tomography (SPECT) imaging provides beside regional perfusion data additional information on left ventricular (LV) wall motion, wall thickening, LV cavity volumes, and LV ejection fraction (LVEF). With the introduction of automated quantitative software programs in MPI, objectively defined abnormality thresholds can be set. This increases the diagnostic accuracy.

Figure 1. Examples of perfusion scintigraphic studies.



Left: normal perfusion study. Right: an anterior and lateral reversible and inferior fixed perfusion defect. SA= short axis, VLA= vertical long axis, HLA= horizontal long axis.

Figure 2. Left: Screen display with short and long axis images with overlaid endocardial and epicardial contours. Short axis images are used as input. Right: Four dimensional (three dimensional plus time) display screen utilized for the assessment of global and regional myocardial function. Gated short axis images are used as input.



The purpose of this educational paper is to give an outline of the additional value of automated gated SPECT in diagnosis and risk assessment of CAD.

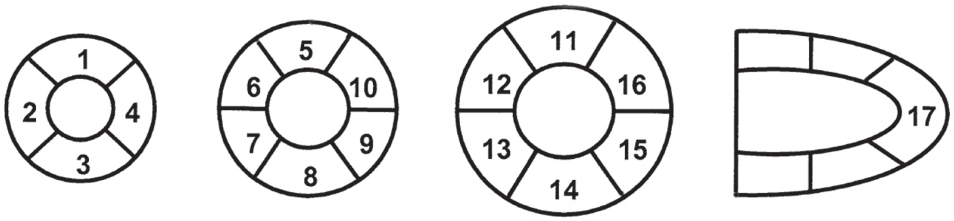
GATED SPECT

Gated SPECT takes full advantage of the properties of 99m-technetium (^{99m}Tc) perfusion agents, namely high count rates and stable myocardial distribution over time. Because the tracer distribution in the myocardium is stable, spatial and temporal changes in the myocardial tracer activity during the cardiac cycle reflect regional myocardial wall motion and wall thickening. The advantage of this technique is the assessment of both perfusion and function (LV wall motion and thickening, LV cavity volumes, LV cavity volumes, LVEF) during one single acquisition. Complete automatic quantitative algorithms have been developed [1]. Measurements of LV function from gated SPECT are implemented by fully exploiting the three-dimensional nature of the tomographic datasets (figure 2). Functional parameters assessed by gated SPECT have shown to have good to excellent concordance with well-known other imaging modalities [1].

DIAGNOSTIC VALUE OF GATED SPECT MYOCARDIAL PERFUSION IMAGING

The sensitivity of exercise perfusion imaging for detecting angiographicaly significant CAD ranges from 85-91% and the specificity ranges from 70-94% [2]. The addition of SPECT to exercise testing increases the diagnostic accuracy to detect CAD, with no significant differences between different tracers or between men and women [2]. Several factors can effect the diagnostic performance of MPI: referral bias -this means that of the patients with

Figure 3. 17-segment model for the quantitative segmental perfusion score (adapted from reference 10).



5-point scoring system:
- 0=normal,
- 1= equivocal,
- 2=moderate,
- 3= severe reduction of radioisotope uptake,
- 4= absence of detectable radiotracer in a segment.

Summed stress score (SSS).
Summed rest score (SRS).
Summed difference score (SDS): SRS - SSS

percentage abnormal perfusion of total myocardium: (score/68) x 100%

normal studies only those with a high suspicion of CAD are referred for coronary angiography-, reduced stress tolerance, anti-anginal medication and technical imaging problems such as tracer activity below diaphragm, photon attenuation and scatter, patient motion, low count statistics, reconstruction artifacts [2].

The addition of LV functional parameters assessed by gated SPECT has considerably improved the diagnostic value [1,2]. An attenuation artifact will usually show a fixed perfusion defect with concomitant preserved wall thickening and/or motion, whereas a region with a fixed perfusion defect due to myocardial infarction will show absence of wall thickening and or motion. Gated SPECT may show absence of wall thickening potentially indicating necrosis or stunning, and conversely, gated SPECT may show concomitant preserved wall thickening in the infarct region suggesting preserved viability.

Potential limitation of perfusion imaging is the measurement of relative myocardial blood flow rather than absolute blood flow. In patients with multivessel CAD, the degree of ischemia may be underestimated because of globally reduced perfusion of the LV. Overall sensitivity for identifying any SPECT abnormality of the combined perfusion/ function assessment in three-vessel disease is 80-95%, and for two or single vessel disease 92% and 86%, respectively, with an overall specificity of 72% [3].

Transient ischemic LV dilatation on myocardial perfusion scintigraphy indicates significant enlargement in LV size on the stress images compared with the rest images. Abnormal transient ischemic LV dilatation is related to a greater amount of ischemic burden as well as multivessel-type or LAD territory perfusion abnormality [4].

PROGNOSTIC VALUE OF (GATED) SPECT MYOCARDIAL PERFUSION SCINTIGRAPHY

The underlying risk in the population varies with a patient's pretest risk. A patient's pretest risk may be estimated as low, intermediate or high according to risk score models (eg, Framingham risk score). Selection of candidates for myocardial perfusion imaging is based on Bayesian theory. Post-test likelihood becomes a function of a patient's pretest risk. Intermediate-risk patients may shift posttest to low or high risk. Optimal candidates for imaging include patients at intermediate-risk for cardiac death or nonfatal myocardial infarction [2]. Intermediate-risk patients are those with an annualized event rate ranges from 1 to 3% per year. Numerous studies have shown the incremental prognostic value of myocardial perfusion imaging also after clinical assessment, exercise electrocardiography and coronary angiography. Important variables for risk stratifications are type of stress-test [2], extent and severity of inducible ischemia [5] and/or perfusion defect [6], increased lung uptake of thallium-201 (indicating elevated pulmonary capillary pressure) [7], transient ischemic LV dilatation [4] and LVEF [8, 9]. Calculation of the number of segments involved on a multislice tomographic evaluation of the SPECT study can be used to calculate both the extent and severity of the hypoperfused myocardium. Using sequential short axis slices, a polar map can be evaluated either visually or quantitatively to assess the total ischemic burden. The ischemic/hypo-perfused burden can be calculated by summed difference score (SDS) or summed stress score (SSS) (figure 3). These

indices can be converted to a percentage of the total myocardium involved with ischemic or fixed defects.

The normal perfusion scintigraphic study

A normal study is characterized by a SSS < 4 (in 17 segment model) or < 5% hypoperfused left ventricular myocardium. Patients with normal perfusion images have excellent survival rates with low annual event rates i.e. an annual cardiac death or myocardial infarction of 0.7%/year, similar to that of asymptomatic population even in the group of patients with known or suspected CAD [2]. However, a number of variables, including pharmacologic stress test, diabetes mellitus, advanced age are identified as markers of increased risk in which the annual event rate may exceed 1%/year. Overall, patients with a normal perfusion study are at low risk. Scintigraphic data provide incremental prognostic value compared to clinical and exercise data alone. No significant differences were seen for use of 201-thallium, 99m-Tc sestamibi or 99m-Tc tetrofosmin [2].

The abnormal perfusion image

Berman et al [10] reported a cut-off value of 5 % hypoperfused myocardium at stress as an optimal criterion for distinguishing images associated with a low (<1/y) risk on coronary death from those associated with a higher risk of cardiac death. The risk on major adverse cardiac events (MACE) increases logarithmically over patients with low-risk findings in the setting of moderately-severely abnormal studies [11]. High risk patients (annualized event rates 3% or higher [11]) are those with moderately to severely abnormal scans, multivessel perfusion abnormalities or a hypoperfused myocardium of > 10%. Patients with abnormal images have on average an annual event rate of 6.7% (cardiac death or myocardial infarction) [2]. Different studies have shown an annual cardiac death rate of 1.0-2.7% for mildly (5-10% of the myocardium), 2.1-4.0 moderately severe (10-15%) and > 4.2 % for severely (> 15%) post-stress perfusion abnormalities. For myocardial infarction, annual event rates of 0.8-2.5% for mildly abnormal, 2.3-4.0% for moderately and >2.9% severely perfusion abnormalities were reported [10,12,13] with higher rates of MACE for patients undergoing pharmacological stress versus exercise stress [12]. The extent of fixed defects provides a better estimation of cardiac death, whereas reversible defects often predict acute ischemic events [2].

It has been shown that resting or exercise LVEF determined by radionuclide angiography is a major determinant of long-term survival in patients with CAD. In patients with normal LV function, nonfatal infarction accounted for at least 50% of initial events, whereas in patients with severe LV dysfunction death was the predominant event [9].

With gated SPECT additional information on regional left ventricular function can be assessed. Sharir et al. [14] found that patients with severe perfusion abnormalities but an end-systolic volume <70 ml had very low cardiac death rates (0.4%/year), whereas patients with only mild/moderate perfusion defects but an endsystolic volume >70 ml had high cardiac death rates (8.2%/year). Even patients with preserved global LV function (LVEF>45%) but an end-systolic volume >70 ml had a relatively high death rate (2.6% versus 0.5%; P=0.02). Patients with an LVEF<45% and mild/moderate or severe perfusion abnormalities had high mortality rates (9.2% and 5.7% respectively), whereas patients with an LVEF >45% had a cardiac death rate <1%/year, regardless the degree of the perfusion abnormality (figure 4 and 5). Post-stress ^{99m}Tc-sestamibi gated SPECT in patients with known or suspected CAD provides incremental

Figure 4. Cardiac death rate as a function of perfusion abnormality and LVEF and ESV (adapted from reference 14).

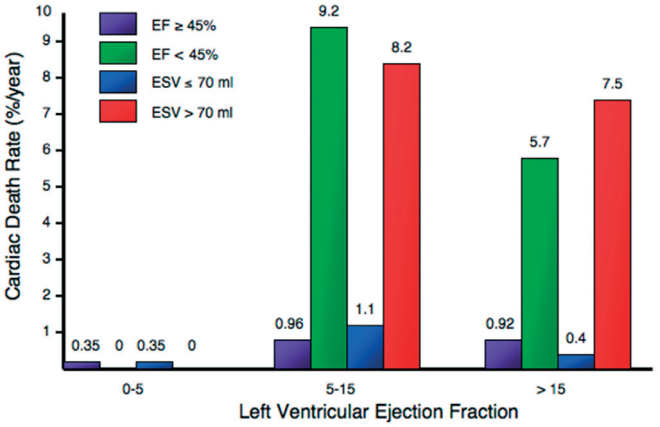


Figure 5. Cardiac Death rate as function of LVEF and ESV (adapted from reference 14).

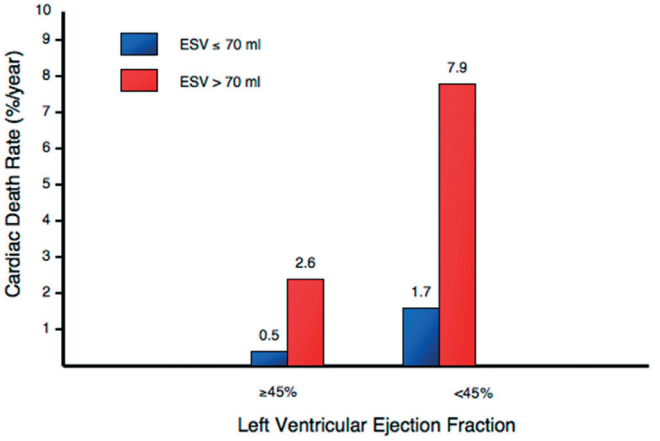
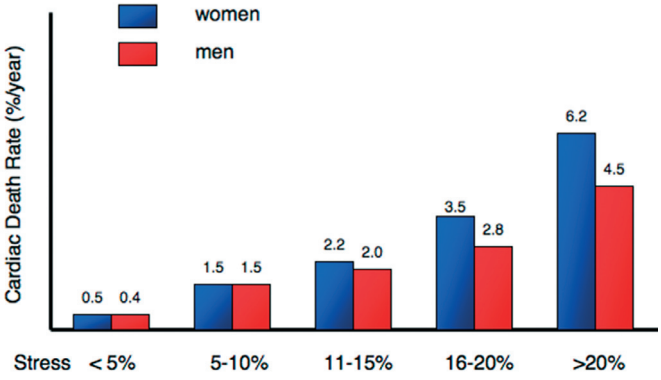


Figure 6. Annual cardiac death rate of men vs women as a function of percent stress defect (Adapted from reference 10).



- Stress percent Myocardium abnormal.

prognostic information over perfusion data alone [14]. The same authors studied the value of gated SPECT in the assessment of outcome-specific (nonfatal myocardial infarction vs cardiac death) independent predictors [8]. Post-stress LVEF is a good predictor for cardiac death, whereas the amount of ischemia is a very good predictor of nonfatal myocardial infarction. Integration of LVEF and SDS yielded effective stratification of patients into low- (<1%/year), intermediate- (2%-3%/year), and high-risk subgroups (>4%/year) of cardiac death. Patients with LVEF >50% and a large amount of ischemia were at intermediate risk whereas those with mild or moderate ischemia were at low risk. Patients with LVEF between 30% and 50% were at intermediate risk even in the presence of only mild or moderate ischemia. LVEF <30% was predictive of high risk, irrespective the amount of ischemia. Transient ischemic LV dilatation can be assessed by gated SPECT. Even in patients with normal myocardial perfusion study, transient ischemic LV dilatation has independent and incremental prognostic value [4]. High risk has been defined by a transient ischemic LV dilatation > 1.21, regardless the type of stress.

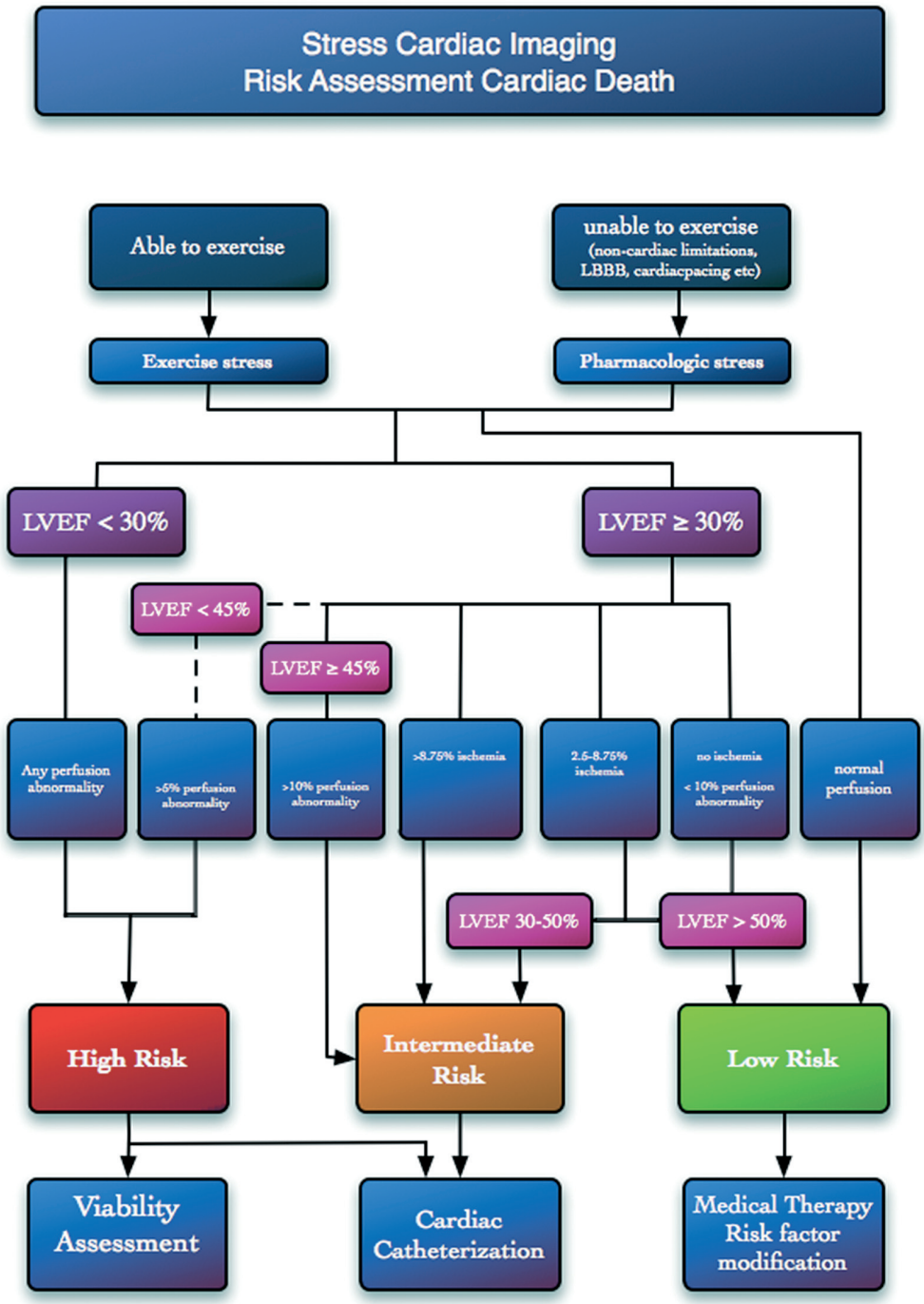
Risk assessment in women.

After myocardial infarction increased mortality and reinfarction have been observed in women after myocardial infarction compared to men. The large proportion of atypical symptoms, higher incidence of associated disease (e.g. hypertension, diabetes mellitus) and the higher age at presentation account for the worse outcome. Beside this, Exercise ECG has a lower diagnostic and prognostic accuracy in women. It is influenced by multiple factors, i.e. exercise capacity and hormonal status. The increased age at presentation is often associated with lower exercise capacity and an inability to attain maximal stress [15]. However, exercise stress SPECT yields independent and incremental prognostic information for both genders [10]. In fact, women with severe abnormalities may have a worse outcome than men with severe abnormalities (figure 6)[10,15]. Post-stress LVEF and ESV index (ESV/ body surface area = ml/m^2) by gated SPECT provide incremental prognostic information over perfusion in women and men [16]. In women perfusion variables add more prognostic information than function data whereas in men function variables are more powerful. Women and men with a low likelihood of CAD have different upper limits for ESV index (women: 27 ml/m^2 vs men: 39 ml/m^2) and EDV index (women: 60 ml/m^2 vs men: 75 ml/m^2), and different lower limits for LVEF (women: 51% vs men: 43%). Combination of severe ischemia and abnormal LVEF or ESV index identifies women at very high risk of MACE [16]. LVEF and SSS assessed by gated SPECT scintigraphy have incremental prognostic value, with a cut-off value for LVEF < 52% or an SSS ≥22 for women at increased risk for subsequent hard events (SSS≥14 are at increased risk for any cardiac events). Previous studies have shown that the annual event rate in women with an LVEF ≥52% was similar to the annual event rate of a mixed population of patients with an LVEF≥45% regardless of the degree of perfusion abnormality [14, 17]. Women with large ischemic and/ or mixed defects are not all at high risk of cardiac events. Only a combination of perfusion and function allows to effectively risk stratify this population and give an individualized risk estimates for this heterogeneous population [17].

Risk assessment before non-cardiac surgery.

Inducible ischemia on myocardial perfusion scintigraphy for perioperative death or infarction has an excellent negative predictive value (98.6%) [2]. The extent of reversible defects correlates with perioperative cardiac events, whereas the presence of fixed perfusion defects

Figure 7. Risk stratification by Myocardial Perfusion Scintigraphy for patients with suspected or known coronary artery disease based on stress percent abnormal myocardial perfusion or percent ischemia and post-stress left ventricular ejection fraction (based on references 2, 8,14 and 15).



- LVEF= left ventricular ejection fraction.

is a predictor of late cardiac events [18]. Addition of Gated SPECT functional variables allows further selection of low-risk patients [18]. Perioperative cardiac event rate increases with decreasing LVEF. The decision of nuclear testing should be made based upon urgency of the surgery and its cardiac risk, individual risk factor and exercise tolerance of the patient. Patients with intermediate risk or with low-risk and low exercise tolerance who have to undergo moderate-risk or high-risk surgery will need further investigation. Also patients at high clinical risk require further investigation even for low-risk surgery.

Risk assessment after acute myocardial infarction.

Recent studies in patients after acute myocardial infarction have shown that adenosine MPI is a reliable method for risk stratification and guidance for therapeutic decision early after hospital admission [19]. Total perfusion defect size has shown to be the most important independent risk predictor, followed by ischemic perfusion defect size and LVEF [19,20]. In this patient group a LVEF of < 40% is an independent predictor of cardiac death, acute myocardial infarction or hospitalization for unstable angina, congestive heart failure, or revascularization [20]. Low-risk patients (irrespective of age, gender, site of infarction, or clinical risk) have small perfusion defects, preserved LVEF and minimal residual ischemia. Such low-risk patients can be medically treated as alternative to an invasive evaluation, with a quite acceptable low overall event rate [19].

It is important to identify the myocardium at risk but with the potential to improve LV function after acute myocardial infarction. Therefore, accurate assessment of the extent of viable myocardium in the dyssynergic LV can play an important role in the early management of patients with acute myocardial infarction. Evaluation of contractile reserve by means of low-dose dobutamine (LDD) gated SPECT with Tl-201 has incremental value over perfusion assessment alone, in the prediction of function recovery in patients early after AMI (within 48 hours) [21]. Mean Tl-201 uptake score or ischemic area is associated with the recovery of wall motion. The number of segments with preserved uptake at rest and the number of akinetic or dyskinetic segments with preserved uptake and wall thickening are independent predictors of events (cardiac death or nonfatal myocardial infarction) [22].

Prognostic value in diabetic patients.

Patients with diabetes mellitus are at increased risk for CAD. In these patients CAD can develop on earlier age and might be more advanced at diagnosis, and have increased mortality and morbidity after myocardial infarction [23]. Early testing for CAD can aid in risk stratification. Multivariate analysis has shown that myocardial perfusion imaging abnormalities, retinopathy and duration of diabetes are independent predictors of cardiac events [24]. The prognostic value of MPI is equivalent in diabetes and nondiabetics. The SSS provides incremental prognostic information [25]. Diabetic women with mildly perfusion abnormalities have twice the annual mortality rate (3.3%) of diabetic men with the same abnormalities (1.6%) [26]. Nondiabetic women with normal, moderately abnormal, and severely abnormal scans have an annual MACE rate of 0.8%, 2.8%, and 6.1% respectively; the cardiac event rates increase to 1.6%, 4.1%, and 8.5 % in diabetic women [23].

Patient selection for revascularization therapy.

MPI can be used to identify patients who benefit from revascularization as opposed to medical treatment [27]. Although LVEF predicts cardiac death, only inducible ischemia identifies who will have a short-term benefit from revascularization [28]. Patients with small ischemic defects (5-10%) benefit from medical therapy. Patients with >10% ischemic myocardium have an increased survival benefit from revascularization. In these patients revascularization nearly neutralizes the prognostic impact of ischemia [27].

Viability-guided revascularization may reduce perioperative morbidity and mortality [28]. Patients with viable myocardium show improvement in function after revascularization [29]. On the other hand, patients with viable tissue treated medically had increased event rates [30]. Several methods have been established to differentiate patients with myocardial viability from patients without viable myocardium: 1) ^{201}Tl imaging to assess myocardial perfusion and cell membrane integrity, 2) dobutamine echocardiography to assess myocardial contractile reserve, 3) F-18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) imaging to assess the myocardial metabolic state, and 4) the use of 511 keV collimators to detect viable myocardium with FDG-SPECT. FDG/Tl-201 SPECT can predict regional ventricular functional recovery after revascularization [31]. In patients with CAD and severe LV dysfunction, information of perfusion and wall motion assessed by gated SPECT significantly improved the sensitivity and overall accuracy for determination of viability in comparison with perfusion alone [32,33]. ^{18}FDG SPECT demonstrated more evidence of myocardial viability than either gated ^{99m}Tc-sestamibi wall thickening or delayed ^{201}Tl SPECT [34].

GENERAL CONCLUSIONS

Gated SPECT allows the analysis of LV perfusion and function during the same acquisition. Gating provides a valuable adjunct to ^{99m}Tc-sestamibi or tetrofosmin SPECT in characterizing perfusion abnormalities and potentially improving test specificity. Gated SPECT is a valuable tool in risk stratification (figure 7) because it provides information of LV end systolic volume and LVEF, which are both important prognostic parameters and have incremental value over perfusion alone. Gated SPECT imaging may be used for stratification of candidates for revascularization as it allows the analysis of residual wall thickening in a region with a fixed perfusion defect or depressed wall motion in a region with a moderate or mild perfusion defect indicating hibernation. Gated SPECT provides important additional information beyond myocardial perfusion imaging alone and has major clinical implications for optimal patient management.

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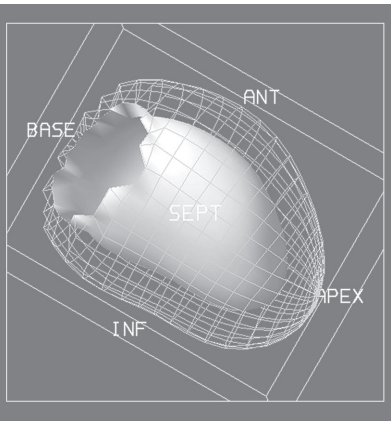
Chapter 7



Summary, general discussion and future perspectives

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Summary

In this PhD thesis we evaluated the added prognostic value of functional data assessed by quantitative gated single photon emission computed tomography (SPECT) in patients with (suspected) coronary artery disease. Substantial data has been reported on the prognostic value of myocardial perfusion imaging in mixed population. We evaluated the technique on subgroup level. Important perfusion or function predictors of worse outcome have been identified. Beyond this, multiple analysis have been done to maximally separate high risk patients from those without increased risk of major adverse cardiac events.

Techniques for automated quantitative approach of myocardial perfusion imaging have been developed to minimize inter- intra operator variability and increase reproducibility. With regard to the validation of the Cedars-Sinai's Quantitative SPECT (QGS) software, in cross-validations with other techniques, results have been evaluated on population level. Any failure in specific subgroups will be diluted by the large amount of successful analysis over the investigated population. The software used in the QGS technique is complex and, under certain conditions, falls back on alternative algorithms. This complexity makes cross-validations with other techniques difficult. In **Chapter 2** we evaluated the reliability of the quantitative assessment of the left ventricular volumes (end-diastolic and end-systolic), left ventricular ejection fraction and regional segmental wall motion and wall thickening based on a system analyses. In this approach we tried to identify conditions under which the algorithm becomes operator-dependent. We especially reviewed the algorithm for interfering clinical conditions. The operator-dependent factors contain only the reorientation that the operator has to perform after raw data acquisition. The rest of the data processing can easily kept constant and is assumed to be stable. We selected series of prototypes. The prototypes consisted of a) normal perfusion, b) perfusion defects in all perfusion regions, c) perfusion studies of patients with angiographic confirmed normal coronary arteries, proximal (≥70% luminal stenosis) single and multiple vessel disease, and d) spurious activity in close proximity. While defining and re-orienting the volume containing the left ventricle, the operator adjusted 8 variables/ degrees of freedom. The results were expressed as a coefficient of variation. Separate coefficients of variation were calculated per distinct degrees of freedom. A segment was considered not robust when the coefficient of variation did exceed 20% in a single degree of freedom, 15% in at least 2 degrees of freedom, or 10% in at least 3 degrees of freedom. Our results showed excellent reproducibility for left ventricular ejection fraction and volumes. Normal perfusion and the vessel disease prototypes showed an excellent coefficient of variation (for all re-orientation steps [33/prototype]) mostly below 5% for left ventricular functional parameters. However, regional wall motion and thickening became less reliable in the presence of large perfusion defects or artifacts. Therefore, we concluded that quantitative estimates for regional left ventricular functional data show excellent reproducibility using automated gated SPECT. However, there may be substantial operator dependency in the presence of large defects or spurious activity in close proximity. Gated acquisition of the stress myocardial perfusion images 30 minutes post-stress reflect myocardial perfusion at maximal stress whereas left ventricular function, which is evaluated 30-45 minutes post-stress, represents the resting situation. Several studies have shown that patients with stress-induced ischemia may develop post-stress left ventricular dysfunction, probably due to myocardial stunning, which may last

until 60 minutes post-stress or even longer. Before starting the gated SPECT study it is not known which patients will show stress-induced ischemia. Therefore, it is impossible to stratify patients who should be gated during the rest study acquisition beforehand in order to avoid the possibility of stunning which leads to a lower left ventricular ejection fraction compared to the rest left ventricular ejection fraction.

In **Chapter 3** the left ventricular function post-stress in patients with a previously sustained myocardial infarction were compared to the basal left ventricular function at rest. In this patient group we studied the influence of different stress modalities (pharmacological stress and conventional exercise stress) on change in left ventricular ejection fraction post-stress. We investigated 58 patients with a previous myocardial infarction. In all patients myocardial perfusion and left ventricular ejection fraction was determined from both the rest and post-stress acquisition. The reproducibility of the left ventricular ejection fraction was excellent within a margin of 2%. In 33 (57%) patients the left ventricular ejection fraction post-stress was ≥ 2% lower compared to the rest left ventricular ejection fraction. In a matched control group of 23 patients with a low likelihood of coronary artery disease there was no significant change in left ventricular ejection fraction post-stress compared to rest (0.04%± 3.2%, p=ns). Conversely, the patient group with a previous myocardial infarction showed a significant lower left ventricular ejection fraction post-stress compared to rest (-1.9%± 4.2%, p=0.002). The presence of reversible ischemia, which occurred in 16 (28%) patients, did not interact with the change in left ventricular ejection fraction post-stress compared to rest (p=ns). This finding implies that the presence of reversible ischemia is not a prerequisite for the development of myocardial stunning in patients with a previous myocardial infarction. Furthermore, the used stress modality (exercise test or adenosine) did not influence the results. From this study we concluded that in patients with a previous myocardial infarction, left ventricular function post-stress may not represent true resting left ventricular function. Left bundle branch block pattern on the electrocardiogram severely reduces the diagnostic and prognostic accuracy of myocardial perfusion scintigraphy. The addition of regional left ventricular (LV) function parameters by gated SPECT improved the diagnostic accuracy. In **Chapter 4**, we studied the incremental prognostic value of quantitative technetium-99m tetrofosmin gated SPECT imaging in patients with left bundle branch block. We followed 101 consecutive patients with a left bundle branch block using technetium-99m tetrofosmin gated SPECT imaging. The average follow-up was 1.24 years (max. 2.48). Hard endpoints were all-cause death and acute myocardial infarction. Event-free survival curves were obtained. Optimal cut-off points for left ventricular volumes and left ventricular ejection fraction to predict outcome were determined by receiver operating characteristic curve analysis. Ninety-four patients had an abnormal study, fifteen patients suffered a hard event (13 deaths). Perfusion abnormalities were similar for patients with or without events. For left ventricular function parameters the survival curves were maximally separated when using cut-off volumes for end-diastolic volume >160 ml (p=0.019, HR 1.04 for hard events, p=0.024 HR 1.04 for all-cause death), and for end-systolic volume >100 ml (p=0.043 HR 1.04 for hard events, p=0.062 HR 1.04 for all-cause death), for left ventricular ejection fraction <35% (hard events p=0.013, HR 0.81, all-cause death p=0.047, HR 0.81). Therefore, we concluded that quantitative gated SPECT imaging in patients with left bundle branch block can be used for risk stratification. Patients with an end-diastolic volume ≥160 ml or an end-systolic volume ≥100 ml or left ventricular ejection fraction < 35% are at increased risk for subsequent cardiac events.

An increased mortality and re-infarction have been noted in women after myocardial infarction compared to men. The large proportion of atypical symptoms, higher incidence of associated disease (e.g. hypertension, diabetes mellitus) and the higher age at presentation may account for the worse outcome. Exercise ECG has a lower diagnostic and prognostic accuracy in women. Appropriate non-invasive diagnostic testing is important in the early diagnosis and the risk stratification of women with suspected CAD. Most data on prognostic value of the parameters assessed by gated SPECT have been obtained in a mixed gender population and may not be applicable to women. It has been shown that gender related differences in normal limits exist.

In **Chapter 5** we evaluated the incremental prognostic value of quantitative gated SPECT imaging in female patients. We followed 453 consecutive female patients. Average follow-up was 1.33 years (max. 2.55). Hard endpoints were cardiac death, acute myocardial infarction or documented ventricular fibrillation. Event-free survival curves were obtained. Optimal cut-off values for left ventricular volumes, left ventricular ejection fraction and perfusion data to predict outcome were determined by receiver operating characteristic curve analysis. A total of 236 patients had an abnormal study, of whom 27 patients experienced hard events (16 deaths) and 47 patients soft events. For hard events summed stress score and left ventricular ejection fraction, and for any cardiac event summed stress score showed independent incremental prognostic value. The survival curves were maximally separated when using cut-off values for summed stress score of $\geq$ 22 and left ventricular ejection fraction < 52% ($p<0.001$, HR 4.61 and $p<0.001$ HR 5.24 for summed stress score and left ventricular ejection fraction resp.), and summed stress score $\geq$ 14 ($p< 0.001$ HR 3.76) for any cardiac event. We concluded that in female patients the perfusion and functional parameters derived from quantitative gated technetium-99m tetrofosmin SPECT imaging has incremental prognostic value and can adequately be used for cardiac risk assessment. Using quantitative gated SPECT, female patients with an left ventricular ejection fraction < 52% or an summed stress score $\geq$22 are at increased risk for subsequent hard events. Furthermore, patients with a summed stress score $\geq$14 are at increased risk for any cardiac events.

Gated SPECT myocardial perfusion imaging allows the analysis of left ventricular perfusion and function during a single acquisition. The addition of left ventricular functional parameters to perfusion improves test specificity in patients with known or suspected coronary artery disease and hence diminishes the amount of borderline diagnoses. As gated SPECT provides reliable information on regional wall motion and thickening, left ventricular ejection fraction and left ventricular volumes, it is also a valuable tool in risk stratification. The improvement in survival after acute myocardial infarction resulted in a markedly increased population of patients with more or less extensive cardiac disease. Patients tend to be older and to have a more severe extent of disease. In this setting it becomes more important to go beyond establishing a diagnosis of coronary artery disease, and toward the level of risk stratification. This need for risk stratification applies to patients with either acute or chronic coronary artery disease.

In **Chapter 6** we give a review of the relevant literature on the prognostic value of SPECT imaging. Numerous studies have shown the incremental prognostic value of myocardial perfusion imaging. Even after clinical assessment, exercise electrocardiography and coronary angiography. Especially, in patients at intermediate risk of CAD. Important variables for risk stratifications are type of stress-test, extent and severity of inducible ischemia and/

or perfusion defect, increased lung uptake of thallium, transient ischemic dilatation and left ventricular ejection fraction. Patients with a normal myocardial perfusion scan have an excellent prognosis with a very low annual cardiac death and myocardial infarction rate (< 1%/year). High-risk patients (annualized event rates 3% or higher) are those with moderately to severely abnormal scans, multivessel perfusion abnormalities or a SSS > 8 (hypoperfused myocardium of > 10%). Patients with abnormal scans have on average an annual event rate of 6.7% (CD or MI). Women with severe abnormalities may have worse outcome than men with severe abnormalities. The prognostic value of MPI is equivalent in DM and nondiabetic. Diabetic women with mildly perfusion abnormalities had twice the annual mortality rate (3.3%) of diabetic men with the same abnormalities (1.6%). Nondiabetic women with normal, moderately abnormal, and severely abnormal images have an annual major adverse cardiac events rate of 0.8%, 2.8%, and 6.1% respectively; the cardiac event rates increase to 1.6%, 4.1%, and 8.5 % in diabetic women. Gated SPECT imaging may be used for stratification of candidates for revascularization as it allows the analysis of residual wall thickening in a region with a fixed perfusion defect or depressed wall motion in a region with a moderate or mild perfusion defect indicating hibernation. Gated SPECT provides important additional information beyond myocardial perfusion imaging alone, which could have major clinical implications for optimal patient management.

General conclusions

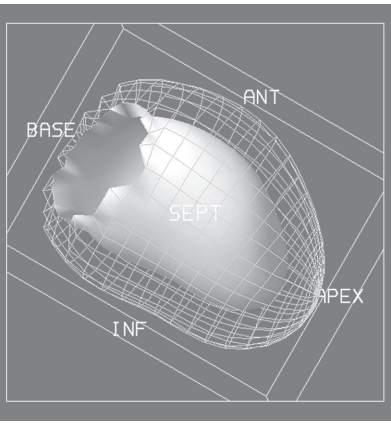
The software program (the QGS-software, version 2.0, revision A") of the automated regional quantitative gated SPECT is robust and shows excellent reproducibility. However, special care must be taken into account in the presence of large defects or spurious activity in close proximity. In patients with previous myocardial infarction assessment of left ventricular function must be done in rest, because left ventricular function post-stress may not represent true resting left ventricular function. Furthermore, the presence of reversible ischemia is not a prerequisite for the development of myocardial stunning in patients with a previous myocardial infarction. Quantitative gated single photon emission computed tomography provides additional information beyond myocardial perfusion alone in patients with (suspected) coronary artery disease. Especially, stress defect size and left ventricular function parameters assessed by gated SPECT show independent and incremental prognostic value in the different subgroups. At subgroup level we showed that gated SPECT can be used in risk stratification. It is possible to select those patients at increased risk of suffering a major adverse cardiac event. This will have major clinical implications for optimal patient management. Patients at increased risk could benefit from a more aggressive (invasive) therapy such as revascularization. Conersely, patients with smaller perfusion defects and/or normal left ventricular function benefit from a more conservative approach.

Future perspectives

In search of the ideal approach to diagnose and assess the prognosis of patients with (suspected) coronary artery disease new nuclear devices, attenuation correction, reconstruction and processing algorithms have been developed. Paralleling the advances in instrumentation are novel approaches in radiotracer design. Herewith, substantial reductions in acquisition time have been achieved without sacrificing diagnostic quality. New clinical devices include high-count sensitivity cardiac SPECT systems that do not use conventional collimation and

the introduction of diagnostic-quality hybrid SPECT/CT or PET/CT systems. These high-count sensitivity cardiac SPECT systems provide significantly higher count sensitivity and better spatial resolution than the conventional myocardial SPECT systems. Combined SPECT/ PET and CT systems have an improved attenuation correction, resulting from the more accurate and precise attenuation map that is associated with CT. Also anatomical information (presence of coronary artery calcium and the degree of coronary artery luminal narrowing) assessed by CT adds information to functional data assessed by SPECT or PET studies. A combined system ensures efficient access to both image sets and allows the operators better control of patient orientation. Another advantage is the ability to perform complementary diagnostic studies in the same setting, making both of these studies more efficient and convenient for the patient. Much emphasis is placed on the diagnosis and treatment of cardiovascular disease at its earliest stages. The therapeutic response to early detection of cardiovascular disease will lead to improved patient outcome. Molecular imaging exploits specific molecular targets, pathways, or cellular processes. This enables to study the pattern of gene expression, cellular protein structure and function, and small-molecule metabolite profile to identify more specific markers of disease presence and cellular therapeutic responses. For example, pre-clinical small animal Ultra-single Photon Emission Computed Tomography (U-SPECT) has been developed. It enables to exploit the high-resolution content of pinhole projection data. This system has pushed the limits of SPECT into the sub-millimeter range, making them valuable molecular imaging tools capable of providing information unavailable from other modalities. It has a volumetric resolution on the order of 0.1 μL. Radioactively filled capillaries as small as 0.5 mm and separated by 0.5 mm can be distinguished clearly in reconstructions. One can monitor myocardial perfusion in the left and right ventricular walls, even structures as small as the papillary muscles. The resolution is significantly better with U-SPECT than with traditional small animal SPECT and PET systems. The challenge for the future will be the translation of the research in small animals to application in the clinical era.

Chapter 7



Samenvatting, conclusie en toekomstperpectieven

SAMENVATTING, CONCLUSIE EN TOEKOMSTPERPECTIEVEN

Samenvatting

In dit proefschrift werd de toegevoegde prognostische waarde van de functionele data, verkregen met "quantitative gated single photon emission computed tomography (SPECT)", bij patiënten met (verdenking op) coronairlijden geëvalueerd. Veel studies zijn verricht om de prognostische waarde van myocardperfusiescintigrafie in een gemengde (niet geselecteerde) populatie te evalueren. De techniek werd op subgroepniveau geëvalueerd. Belangrijke perfusie dan wel functionele voorspellers voor een slechte cardiale uitkomst werden gedefinieerd. Hiernaast, werden verschillende analyses verricht om een optimale scheiding te realiseren tussen patiënten met een sterk verhoogd cardiaal risico en patiënten zonder verhoogd risico.
Verschillende technieken voor automatische kwantitatieve benadering van myocardperfusie-scintigrafie zijn ontwikkeld om de bedieningsafhankelijkheid te minimaliseren en de reproduceerbaarheid te verhogen. Met betrekking tot de validatie van de Cedars-Sinai's Quantitative SPECT (QGS) software, is de kruislinkse validatie met andere technieken op populatieniveau verricht. Elk falen bij bepaalde specifieke subgroepen zal verwateren door de grote hoeveelheid succesvolle analyses in de onderzochte gegeneraliseerde groep. De software van de QGS techniek is complex en valt in bepaalde gevallen terug op alternatieve algoritmen. Deze complexiteit maakt het moeilijk om kruislinkse validatie met andere technieken te verrichten. In **hoofdstuk 2** werd op basis van systeem analyse de betrouwbaarheid van de kwantitatieve bepaling van linker ventrikel volumina (einddiastolische en eindsystolische), linker ventrikel ejectie fractie (LVEF) en de regionale segmentele linker ventrikel wandbeweging en wandverdikking geëvalueerd. Met deze benadering werd het algoritme werd op interfererende klinische condities geëvalueerd. De bedieningsafhankelijke factor van het algoritme bestond alleen uit de re-oriëntatie die de gebruiker van de software moet uitvoeren na de acquisitie van de ruwe data. De verdere verwerking van de data kan gemakkelijk constant worden gehouden. Een serie prototypen werd geselecteerd. De prototypen bestonden uit: a) normale perfusie, b) perfusie defecten in alle verschillende perfusie regio's, c) perfusie scintigrafische studies bij patiënten met angiografisch bevestigde normale coronairarteriën, proximale (≥ 70% luminale stenose) 1 vat en meervats coronairlijden, en d) radiofarmacon "omgevingsactiviteit". Bij het definiëren en re-oriënteren van de *region-of-interest* die het linker ventrikel moet bevatten moet de gebruiker 8 variabelen/ vrijheidsgraden aanpassen. De resultaten werden weergeven in variatie-coëfficiënten. Voor iedere vrijheidsgraad werd de variatie-coëfficiënt berekend. Een segment was niet robuust indien de variatie-coëfficiënt groter was dan 20% in 1 vrijheidsgraad, 15% in tenminste 2 vrijheidsgraden, of 10% in tenminste 3 vrijheidsgraden. De resultaten toonden een uitstekende reproduceerbaarheid aan wat betreft de LVEF en linker ventrikel volumina. Een normaal perfusie scintigrafisch onderzoek en de verschillende prototypen coronairlijden toonden een uitstekende variatie-coëfficiënt (voor alle re-oriëntatie stappen [33/prototype]). Meestal < 5% voor linker ventrikel functie parameters. Echter, regionale linker ventrikel wandbeweging en wandverdikking werden minder betrouwbaar in geval van grote perfusie defecten of radiofarmacon "omgevingsactiviteit" in de buurt van het myocard (bijvoorbeeld darmactiviteit). Geconcludeerd werd dat de kwantitatieve automatische gated SPECT software (QGS) een uitstekende reproduceerbaarheid heeft. Gated acquisities van de inspanningsmyocardperfusie scintigrafische beelden, verkregen 30 minuten post-stress, tonen de perfusie ten tijde van maximale inspanning. De linker ventrikelfunctie data, welke 30-45

minuten post-stress verkregen werden, geven de rust (post-stress) situatie weer. Meerdere studies toonden aan dat inspanningsgeïnduceerde ischemie post-stress linker ventrikel dysfunctie kan veroorzaken, waarschijnlijk op basis van stunning. Deze kan 60 minuten of zelfs langer aanhouden. Voor aanvang van een gated SPECT onderzoek is niet bekend welke patiënten inspanningsgeïnduceerde ischemie tonen. Daarom is het niet mogelijk om vooraf patiënten te selecteren die een gated studie in rust (i.p.v. post-stress) moeten ondergaan om de mogelijkheid van stunning (een lagere LVEF t.o.v. de rust situatie) te voorkomen.

In **hoofdstuk 3** werd bij patiënten met een doorgemaakt myocardinfarct de linker ventrikel post-stress functie vergeleken met linker ventrikel functie in rust. Daarnaast werd in deze patiëntengroep de invloed van de verschillende stress technieken (farmacologische stress t.o.v. conventionele inspanning) op de linker ventrikel functie bepaald. Achtenvijftig patiënten met een doorgemaakt myocardinfarct werden onderzochten. Bij alle patiënten werd de perfusie en LVEF bij de rust en post-stress acquisitie bepaald. De bepaling van de LVEF was uitstekend reproduceerbaar, binnen een marge van 2%. In 33 patiënten (57%) was de LVEF post-stress ≥ 2% lager dan de rust LVEF. De "matched control group", bestaande uit 23 patiënten met een lage verdenking op coronairlijden, toonde geen significante verschillen in LVEF tussen post-stress en rust (0.04%± 3.2%, p=ns). Echter, de patiënten met een doorgemaakt myocardinfarct toonden een significant lagere LVEF post-stress t.o.v. de rust (-1.9%± 4.2%, p=0.002). De aanwezigheid van ischemie, welke bij 16 patiënten (28%) voorkwam, had geen invloed op de verandering in LVEF post-stress t.o.v. rust (p=ns). Deze bevinding betekent dat de aanwezigheid van reversibele ischemie geen voorwaarde is voor het ontstaan van stunning bij patiënten met een doorgemaakt myocardinfarct. Verder heeft de soort inspanning (conventionele inspanningstest of adenosine) geen invloed op de resultaten. Hieruit werd geconcludeerd dat bij patiënten met een doorgemaakt myocardinfarct, de linker ventrikel functie post-stress niet de ware rust linker ventrikel functie weerspiegelt.

Een linker bundeltakblok (LBTB) patroon op het elektrocardiogram vermindert de diagnostische en prognostische waarde van myocardperfusiescintigrafie.

In **hoofdstuk 4** werd de toegevoegde prognostische waarde van kwantitatieve technetium-99m tetrofosmin gated SPECT scintigrafie bij patiënten met een LBTB bestudeerd. De gemiddelde duur van follow-up was 1.24 jaar (max. 2.48). Harde eindpunten waren "all-cause" mortaliteit en acuut myocardinfarct. Overlevingsgrafieken werden verkregen. Optimale afkappunten voor linker ventrikel volumina en LVEF voor risicostratificatie werden verkregen met behulp van receiver operating characteristic (ROC) curve analyse. Bij 94 patiënten toonde het scintigram perfusie afwijkingen, 15 patiënten bereikten een hard eindpunt (13 sterfgevallen). Patiënten met en zonder harde eindpunten toonden significante verschillen in perfusiedefecten. Ten aanzien van de linker ventrikel functie parameters konden de overlevingsgrafieken maximaal worden gescheiden indien voor einddiastolisch volume 160 ml (p=0.019, HR 1.04 voor harde eindpunten, p=0.024 HR 1.04 voor all-cause mortaliteit), voor eindsystolisch volume 100 ml (p=0.043 HR 1.04 voor harde eindpunten, p=0.062 HR 1.04 voor all-cause mortaliteit), voor LVEF 35% (harde eindpunten p=0.013, HR 0.81, all-cause mortaliteit p=0.047, HR 0.81) als afkappunten werd genomen. Hieruit werd geconcludeerd dat kwantitatieve gated SPECT scintigrafie gebruikt kan worden voor risicostratificatie bij patiënten met een LBTB. Patiënten met een einddiastolisch volume ≥160 ml of een eindsystolisch volume ≥100 ml of linker ventrikel ejectie fractie < 35% hebben een sterk verhoogd cardiaal risico.

Vrouwen met een doorgemaakt myocardinfarct tonen een hoger mortaliteitsrisico en grotere aantallen re-infarcten t.o.v. mannelijke patiënten. Het grote aandeel presentaties met atypische klachten, hogere incidentie van geassocieerde ziekten (b.v. hypertensie, diabetes mellitus) en de hogere leeftijd bij presentatie hebben een aandeel in de slechtere prognose. Een inspannings-ECG bij vrouwen heeft een lagere diagnostische en prognostische waarde. Adequate niet-invasieve diagnostische onderzoeken zijn belangrijk voor de vroege diagnostiek en risicostratificatie bij vrouwen met verdenking op coronairlijden. De meeste data over de prognostische waarde van de met gated SPECT verkregen linker ventrikel parameters werden verkregen in een gemengde (mannen en vrouwen) populatie en kunnen daarom niet zonder meer worden betrokken op de vrouwelijke patiënt. Het is bekend dat er geslachtsgebonden normaalwaarden bestaan. In **hoofdstuk 5** werd de toegevoegde prognostische waarde van kwantitatieve gated SPECT scintigrafie bij de vrouwelijke patiënt onderzocht. Er werden 453 opeenvolgende vrouwelijke patiënten gevolgd. De gemiddelde follow-up was 1.33 jaar (max. 2.55). Harde eindpunten waren cardiale sterfte, acuut myocardinfarct of gedocumenteerd ventrikelfibrilleren. Overlevingsgrafieken werden vervaardigd. Ten aanzien van het voorspellen van eindpunten werden optimale grenzen voor linker ventrikel volumina, LVEF en perfusiedata berekend m.b.v. ROC analyse. In totaal toonden 236 patiënten een abnormale studie, waarvan 27 patiënten een hard eindpunt (16 doden) en 47 patiënten en zacht eindpunt (revascularisatie procedure) bereikten. De totale " summed stress score" en LVEF toonden een onafhankelijke toegevoegde prognostische waarde t.a.v. harde eindpunten. De summed stress score toonde ook een onafhankelijke toegevoegde prognostische waarde t.a.v. zachte eindpunt. De overlevingsgrafieken werden maximaal gescheiden indien voor harde eindpunten een summed stress score van 22 en voor LVEF 52% als grens werd aangehouden ($p<0.001$, HR 4.61 en $p<0.001$ HR 5.24 voor summed stress score en linker ventrikel ejectie fractie respectievelijk). Voor alle eindpunt samen werd een summed stress score van 14 ($p<0.001$ HR 3.76) als grens genomen. Geconcludeerd kon worden dat bij de vrouwelijke patiënt de met kwantitatieve gated technetium-99m tetrofosmin verkregen linker ventrikel perfusie- en functiedata toegevoegde prognostische waarde heeft. Het kan derhalve gebruikt worden voor een adequate risicostratificatie. Vrouwen met een LVEF van < 52% of een summed stress score van ≥22 hebben een sterk verhoogd risico op een hard eindpunt. Verder, vrouwelijke patiënten met een summed stress score van ≥14 hebben een verhoogd risico op enig cardiaal eindpunt.

Met gated SPECT myocardperfusiescintigrafie kan de linker ventrikel perfusie- en functiedata tijdens een enkele acquisitie worden verkregen. Het toevoegen van linker ventrikel functie parameters, bovenop perfusie, verbetert de specificiteit van de test bij patiënten met (verdenking op) coronairlijden en het vermindert het aantal diagnostische "grensgevallen". Naast het feit dat gated SPECT betrouwbare informatie levert over regionale wandbeweging en wandverdikking, LVEF en linker ventrikel volumina, is het ook een waardevol instrument voor risicostratificatie. Verbeterde overlevingskansen na een doorgemaakt myocardinfarct resulteerde in een aanmerkelijk grotere populatie patiënten met min of meer uitgebreid cardiaallijden. De patiënt wordt ouder en heeft vaak een uitgebreide vorm van hart- en vaatziekte. Dit in achtnemend wordt het interessant om verder te gaan dan alleen het stellen van de diagnose coronairlijden en te streven naar een beleid dat gebaseerd is op risicostratificatie. De behoefte aan risicostratificatie heeft betrekking op patiënten met zowel acuut als chronisch coronairlijden.

In **hoofdstuk 6** werd in een overzicht gegeven over de huidige beschikbare relevante literatuur t.a.v. de prognostische waarde van myocard SPECT scintigrafie. Meerdere studies hebben een toegevoegde prognostische waarde van myocardperfusiescintigrafie beschreven. Zelfs na stratificatie op basis van klinische data, inspanningselektrocardiogram en coronair angiografie. Vooral bij patiënten met een "intermediate" risico op coronairlijden. Belangrijke variabelen voor risicostratificatie zijn type inspanningsonderzoek, uitgebreidheid en ernst van de ischemie en/of perfusie defect, verhoogde thallium opname in de longen, ischemisch gemedieerde linker ventrikel dilatatie en LVEF. Patiënten met een normaal perfusie scintigrafisch onderzoek hebben een uitstekende prognose met een zeer lage jaarlijkse incidentie myocardinfarct en/of mortaliteits (< 1%/jaar). Hoog risico patiënten (jaarlijks 3% of hoger kans op myocardinfarct en/of overlijden) zijn degenen met een matig tot ernstig afwijkend perfusiescintigram, met een persfusiepatroon passend bij meervatslijden of een summed stress score > 8 (verminderde perfusie in > 10% van het linker ventrikel). Het gemiddelde risico op een hard eindpunt (cardiale sterfte of myocardinfarct) bij een patiënt met een afwijkend myocardperfusiescintigram bedraagt 6.7%. Vrouwen met ernstige perfusiedefecten hebben een slechtere prognose dan mannen met ernstige perfusiedefecten. De prognostische waarde van myocardperfusiescintigrafie is hetzelfde bij patiënten met of zonder diabetes mellitus (DM). Echter, vrouwen met DM en kleine perfusiedefecten hebben een tweemaal zo groot mortaliteitsrisico (3.3% jaarlijks) t.o.v. diabetische mannen met dezelfde afwijkingen (1.6%). Niet-diabetische vrouwen met een normaal scintigram, gematigd afwijkend perfusie scintigram (10-15% van totale linker ventrikel) en ernstige perfusie afwijkingen (> 15% van de totale linker ventrikel) hebben een kans op ernstige cardiale gebeurtenissen (cardiale sterfte of myocardinfarct) van respectievelijk 0,8%/jaar, 2,8%/jaar en 6,1%/jaar; De incidentie stijgt naar 1,6%, 4,1% en 8,5% bij diabetisch vrouwen. Gated SPECT scintigrafie kan worden gebruikt bij patiënten die in aanmerking komen voor revascularisatie. Behouden wandverdikking in een gebied met een persisterend perfusiedefect of verminderde wandbeweging in een gebied met milde of gematigde perfusiedefecten toont aan dat er sprake is van hibernatie in het betreffende gebied. Gated SPECT verschaft toegevoegde informatie bovenop myocardperfusiescintigrafie alleen, welke belangrijke klinische gevolgen kan hebben voor het patiëntenbeleid.

Conclusies

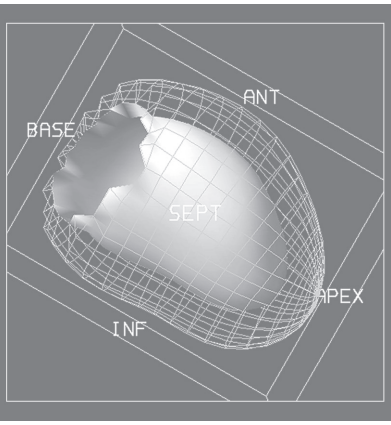
Het software programma (de QGS software, version 2.0, revisor A") van de automatisch regionale kwantitatieve gated SPECT is robuust en heeft een uitstekende reproduceerbaarheid. Echter, speciale aandacht is vereist bij aanwezigheid van grote perfusiedefecten of activiteit van het radiofarmacon in de nabije omgeving van het myocard. Bij patiënten met een myocardinfarct in de voorgeschiedenis zal analyse van de linker ventrikel functie moeten worden verricht in rust, gezien het feit dat bepaling van post-stress linker ventrikel functie niet de ware rust situatie kan weergeven. Verder, de aanwezigheid van reversibele ischemie is geen vereiste voor de ontwikkeling van myocard stunning bij patiënten met een doorgemaakt myocardinfarct. Kwantitatieve gated single photon emission computed tomografie verschaft bij patiënten met (verdenking op) coronairlijden additionele informatie bovenop informatie over myocardperfusie. Vooral de met gated SPECT verkregen inspanningsgerelateerde defectgrootte en de LVEF parameters tonen onafhankelijke en toegevoegde prognostische waarde bij de verschillende subgroepen. Dit proefschrift toont aan dat op subgroepniveau gated SPECT gebruikt kan worden voor risicostratificatie. Het is mogelijk om de patiënten met

een sterk verhoogd cardiaal risico te selecteren. Dit heeft grote klinische betekenis voor optimale patiëntmanagement. Patiënten met een verhoogd cardiaal risico kunnen profijt hebben bij een agressieve (invasieve) therapie zoals revascularisatie. In tegenstelling tot patiënten met kleine perfusiedefecten en/of een normale linker ventrikel functie. Deze patiënten hebben profijt bij een meer conservatieve aanpak.

Toekomst perspectieven

In de zoektocht naar de ideale strategie voor het stellen van de diagnose en bepaling van de prognose bij patiënten met (verdenking op) coronairlijden zijn nieuwe nucleaire technieken, attenuatie correctie, reconstructie en proces algoritmen ontwikkeld. Parallel hieraan is de nieuwe aanpak in radiofarmaca design. Hierdoor is een substantiële reductie in acquisitieduur bereikt zonder negatieve gevolgen voor de diagnostische kwaliteit. Nieuwe klinische technieken betreffen o.a. high-count sensitivity cardiale SPECT systemen die geen gebruik maken van conventionele collimatoren en de introductie van hybride SPECT/CT of PET/CT. Deze high-count sensitivity cardiale SPECT systemen zorgen voor een significante hogere *count* sensitiviteit en een betere spatiële resolutie dan de conventionele myocardiale SPECT systemen. Gecombineerde SPECT/PET en CT systemen verbeterden de attenuatie correctie, die voortkomen uit de accurate en precieze attenuatie weergave van de CT. Ook anatomische informatie (aanwezigheid van calcium in coronair arteriën en de ernst van coronair arterie luminal vernauwing) verkregen met CT voegt belangrijke informatie toe aan functionele data verkregen met SPECT of PET studies. Een ander voordeel is de mogelijkheid om aanvullende diagnostische studies te verrichten in de zelfde onderzoekstijd, waardoor deze studies efficiënter en gebruiksvriendelijker zijn voor de patiënt.

Veel belangstelling is er voor diagnostiek en behandeling van de hart- en vaatziekten in haar vroegste fase. De therapeutische respons op vroege detectie van hart- en vaatziekte verbetert de prognose van de patiënt. Molecular imaging exploreert specifieke moleculaire doelen of cellulaire processen. Dit maakt het mogelijk om patronen van genexpressie, proteïne structuur en functie, en molecuul metabolietprofielen te bestuderen en om specifieke ziekte- en cellulaire therapeutische activiteitsmarkers te identificeren. Bijvoorbeeld met het pre-klinische Ultra-single Photon Emission Computed Tomography (U-SPECT). Dit systeem heeft een volumetrische resolutie van 0,1 µL. Het is mogelijk om myocardperfusie van de linker en rechter ventrikel wanden bij b.v de muis weer te geven, met zelfs structuren zo groot als de papillairspieren. De resolutie is significant beter met U-SPECT dan met traditionele kleine dierenmodel SPECT en PET systemen. De uitdaging voor de toekomst zal zijn om de omslag te maken van diermodel naar de klinische toepassing.



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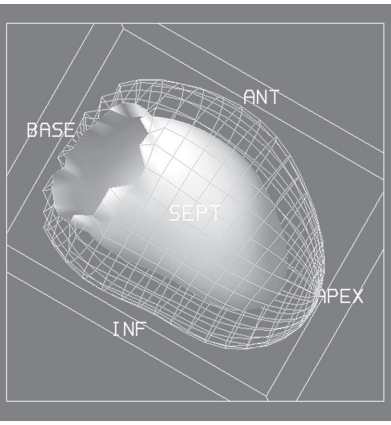

Curriculum Vitae

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 23 april 1970, in Amstenrade. In 1991 behaalde hij zijn eindexamen Atheneum B aan het Serviam Lyceum in Sittard, waarna hij een jaar economische wetenschappen studeerde aan de Universiteit Maastricht. Hij begon de studie Geneeskunde aan de Universiteit Maastricht in 1992. In de laatste periode van zijn doctoraalfase heeft hij gedurende 1 jaar een student-assistentschap klinische pathologie gedaan, o.l.v. dr. W.S. Kwee, in het Laurentius Ziekenhuis te Roermond. Hierop volgend heeft hij gedurende 6 maanden onderzoek gedaan op de afdeling Nucleair Cardiologie, o.l.v. prof. dr. M.S. Verani, aan de Baylor College of Medicine, the Methodist Hospital te Houston (USA). Aansluitend werd in september 1996 het doctoraal examen behaald. Tussen 1996 en de zomer van 1999 doorliep hij zijn co-assistentschappen. Waarvan de laatste 9 maanden (research) keuze co-schap nucleaire cardiologie (afdeling Cardiologie en afdeling Radiologie, divisie Nucleaire Geneeskunde, Leids Universitair Medisch Centrum [LUMC]). Van juli 1999 tot en met juli 2002 werkte hij als researchfellow op de afdeling Cardiologie en afdeling Radiologie, divisie Nucleaire Geneeskunde van het LUMC. In deze periode werd ook een aanvang gemaakt met het promotieonderzoek op de afdeling Cardiologie van het LUMC (prof. dr. E.E. van der Wall en prof. dr. J.J. Bax). Op 1 juli 2002 startte hij met de opleiding tot cardioloog in het kader waarvan hij respectievelijk werkzaam was in het Groene Hart ziekenhuis in Gouda (dr. M. Van Hessen), Kennemer Gasthuis in Haarlem (Interne Geneeskunde, prof. dr. R.W. Ten Kate) en het Leids Universitair Medisch Centrum (prof. dr. E.E. van der Wall). Sinds juli 2009 is hij werkzaam als cardioloog/ fellow niet-invasieve cardiale beeldvorming in het Universitair Medisch Centrum Utrecht.