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

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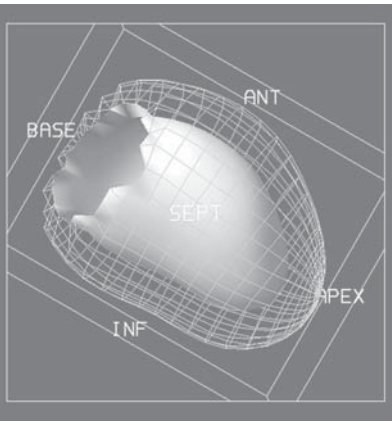
Chapter 6



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

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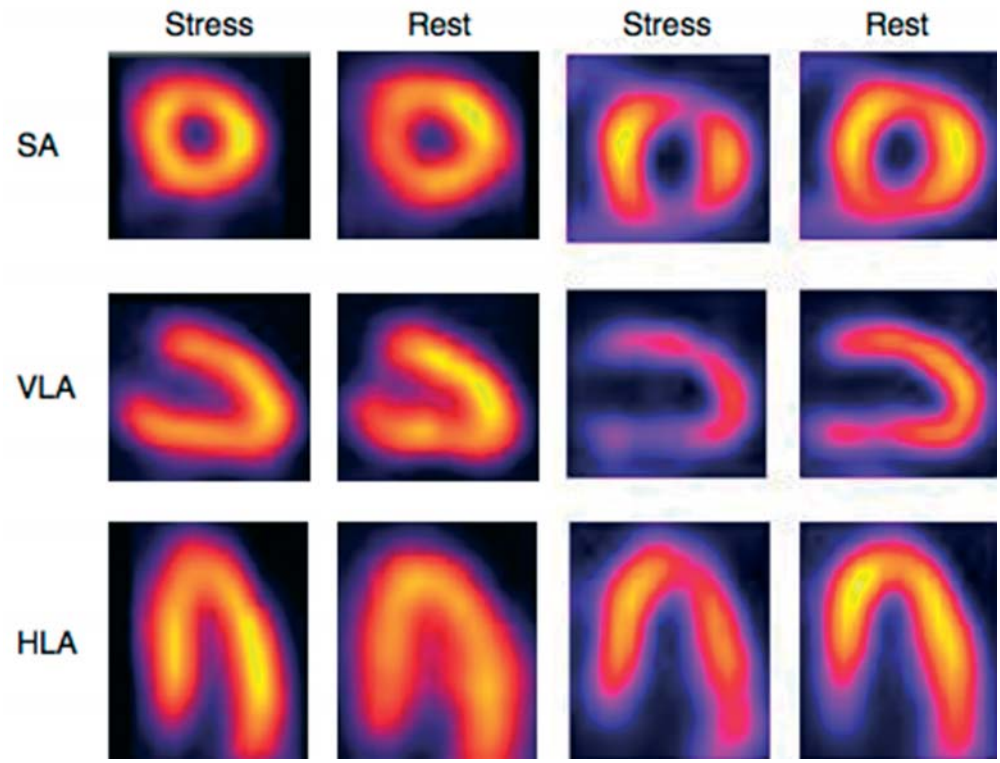
Submitted

INTRODUCTION

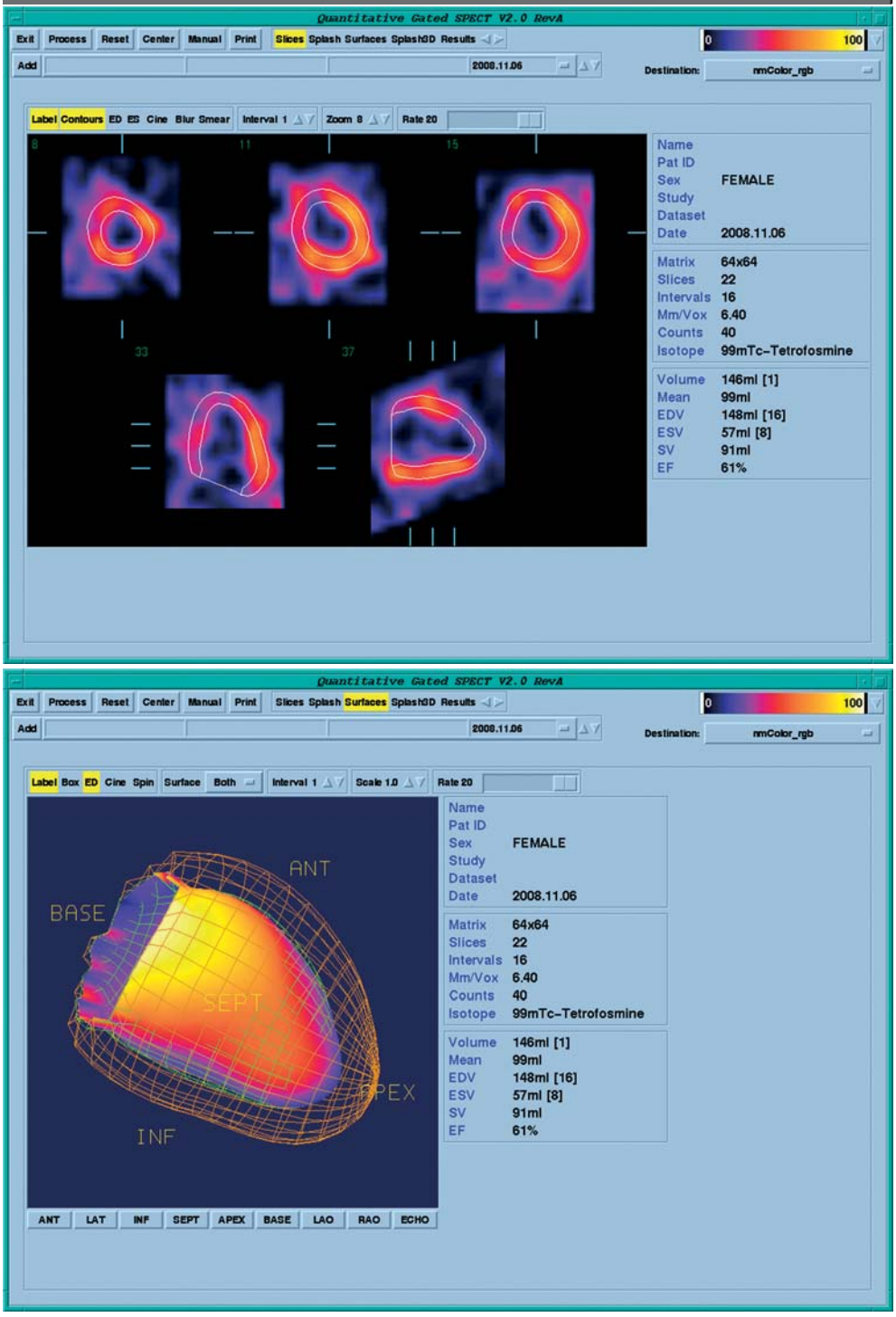
Coronary artery disease (CAD) is the major cause of morbidity and mortality in industrialized western countries. Early detection of CAD may decrease morbidity and mortality. Myocardial perfusion scintigraphy (MPI) is an important diagnostic tool both in patients with known and suspected coronary artery 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.

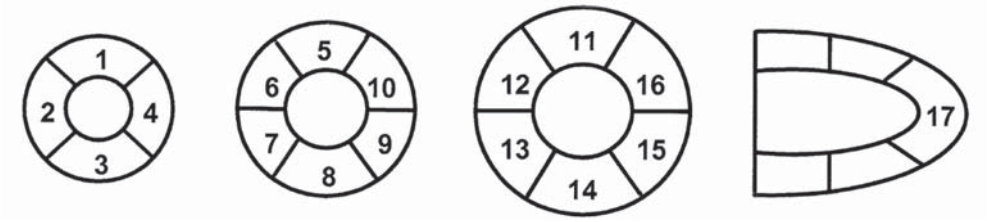
GATED SPECT

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).

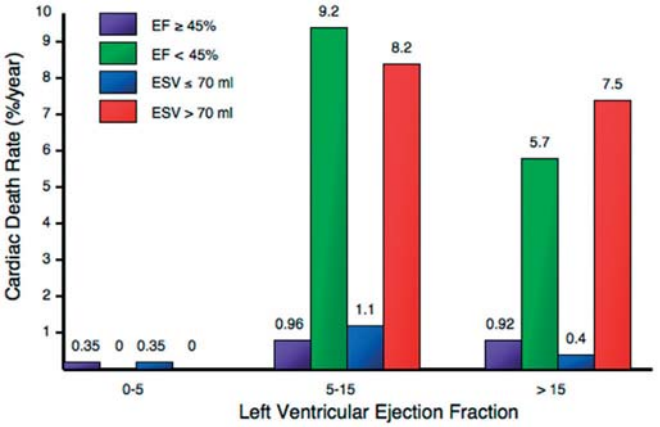


Figure 5. Cardiac Death rate as function of LVEF and ESV (adapted from reference 14).

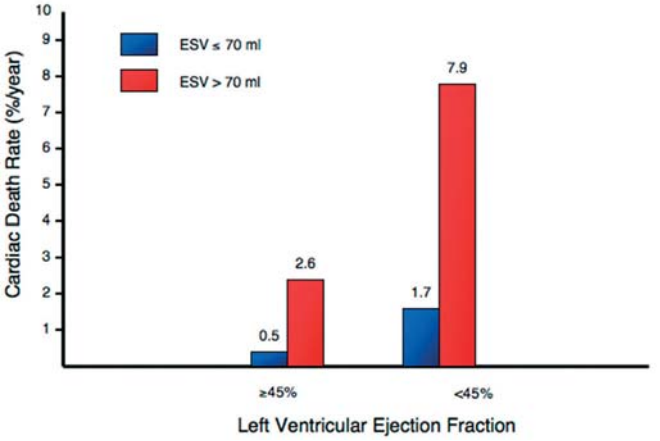
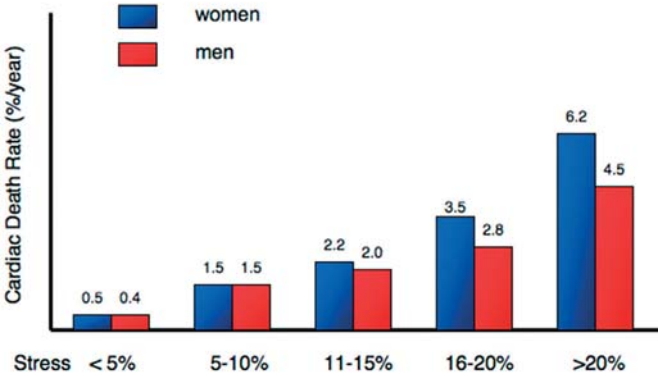


Figure 6. Annual cardiac death rate of men vs women as a function of percent stress defect (Adapted from reference 10).



- 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.

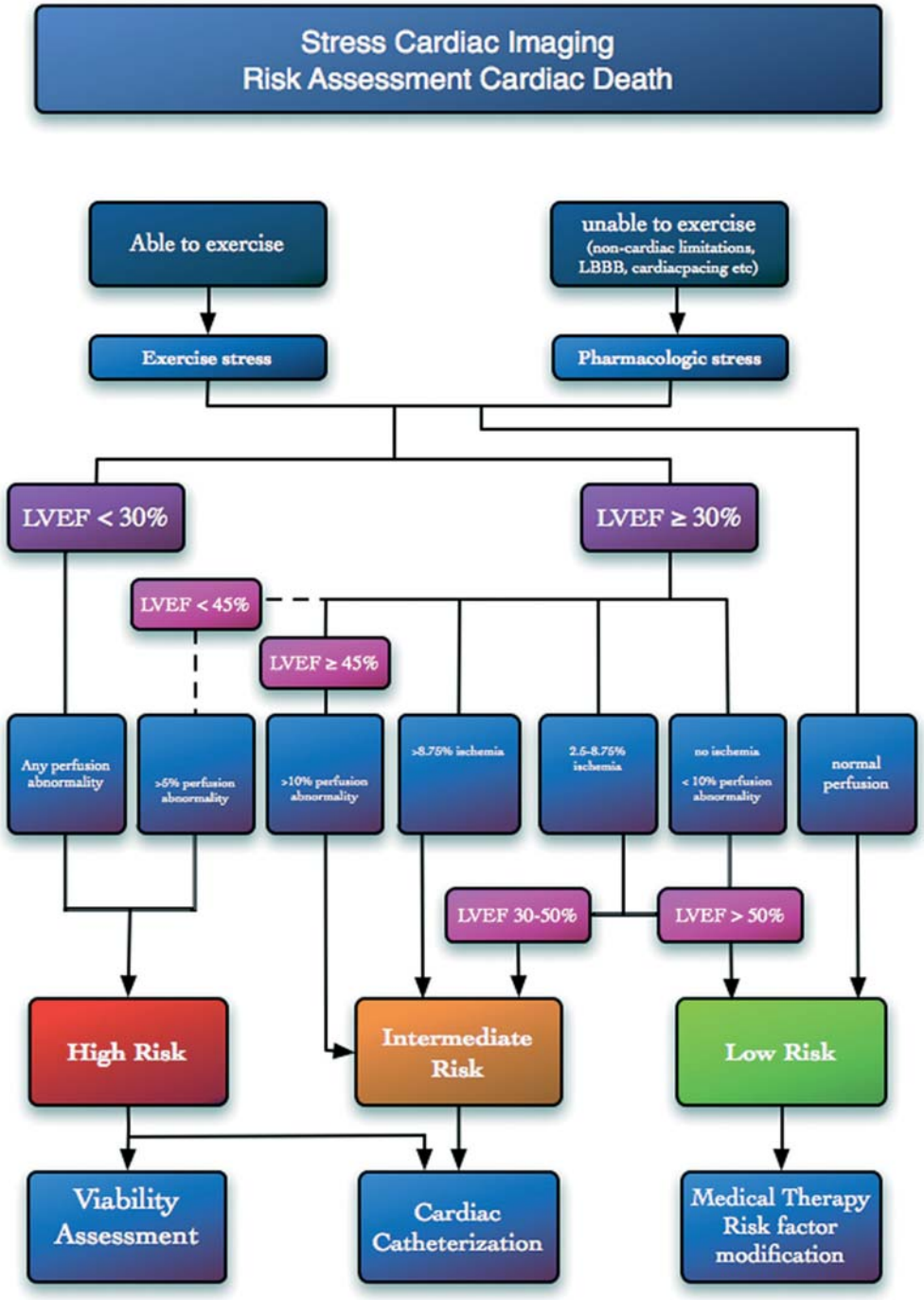
Risk assessment in women.

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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