ORIGINAL ARTICLE

The additive prognostic value of perfusion and functional data assessed by quantitative gated SPECT in women

Yves G. C. J. America, MD,[a] Jeroen J. Bax, MD, PhD,[a] Eric Boersma, MSc, PhD,[b] Marcel Stokkel, MD, PhD,[c] and Ernst E. van der Wall, MD, PhD[a]

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 cutoff 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 cutoff values for SSS of ≥22 and LVEF < 52% ($P < 0.001$, HR 4.61 and $P < 0.001$ HR 5.24 for SSS and LVEF resp.), and SSS ≥ 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 ≥ 22 are at increased risk for subsequent hard events. Furthermore, patients with an SSS ≥ 14 are at increased risk for any cardiac events. (J Nucl Cardiol 2009;16:10–9)

Key Words: Women · gated single photon emission computed tomography · prognosis

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 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 (Tc^{99m}) gated SPECT imaging in women.

METHODS

Study Population

We studied 453 consecutive women (median age 62 years [53 to 70 years, 25th to 75th 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, dyspnea, sustained tachy-arrhythmias, exertional hypotension, or ischemic ST-T

segment-depression of at least 0.2 mV and a duration of 80 milliseconds. 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 0.3 mg/kg infusion during 15 minutes was used in patients who were 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 to 45 minutes (stress) or 45 to 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 64×64 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 cutoff 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 milliliters 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 four evenly spaced regions in apical, six mid-ventricular, and six 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] namely 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 two 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) and troponin T. Soft events were defined as any late (>60 days after MPI) revascularization procedure, i.e., coronary artery bypass grafting (CABG) or percutaneous 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 summarized as frequencies and percentages. Differences in baseline characteristics between patients who reached the primary endpoint and those who did not were analyzed 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 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 to 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 reasonably 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 cutoff values for these variables that can be used for event prediction in clinical practice. Optimal cutoff 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 to 70 years [25th to 75th percentiles]). One-hundred and fourteen (26%) patients had known CAD. Of those patients 67 (15%)

Table 1. Patient characteristics

Total number of patients	453
Age (years)*	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.

had sustained a MI, 67 (15%) experienced one or more revascularization procedures, and none had a history of cardiac arrest.

Perfusion and Function

Perfusion and function data are 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 (25th to 75th percentiles: 0 to 22), the median SRS was 3 (25th to 75th percentiles: 0 to 17), and the median SDS was 2 (25th to 75th percentiles: 0 to 3); median

Table 2. Findings at gated SPECT imaging

	Median	25th–75th percentile	Range
Total patient group (n = 453)			
Myocardial perfusion			
SSS	5	0–22	0–67
SRS	3	0–17	0–65
SDS	2	0–3	0–34
Left ventricular function			
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.

EDV was 70 mL (25th to 75th percentiles: 56 to 89.5 mL), median ESV 24 mL (25th to 75th percentiles: 16 to 39.5 mL), and median LVEF 65.5% (25th to 75th percentiles: 54% to 73%). The median EDVi was 38 (25th to 75th percentiles: 32 to 49) and the median ESVi 13 (25th to 75th percentiles: 9 to 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 to 2.50 years). Sixteen patients died of cardiac cause during follow-up, with a mean follow-up of 0.72 years (range 1 day to 2.22 years). No hard events occurred during surgery or coronary intervention. Forty-seven soft events were recorded (mean follow-up 1.43 years; range 93 days to 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 significantly larger LV volumes, more extensive perfusion defects, lower LVEFs, 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, 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.

Table 3. Outcome: perfusion and functional data

	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
	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 to 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.

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 to 20, and >20% hypoperfused myocardium was <0.7, 1.6, and 4.6%/years, respectively. The annual hard event rate for these subgroups are 1.0, 3.1, and 8.3%/year, respectively. ROC curve analysis was used to determine the optimal cutoff values for LVEF and SSS to predict outcome. For hard events optimal cutoff values for these different parameters could be determined. According to these cutoff values,

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

	Hazard ratio	95% CI	P-value
Univariate analysis			
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	1.02	0.98-1.05	NS
Diabetes	3.04	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
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

Table 4 continued

|	Hazard ratio	95% CI	P-value
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.

patients could be divided into two groups (Figures 1 and 2). An LVEF < 52% (area under the curve [AUC] 0.75) was associated with a significantly higher risk of hard
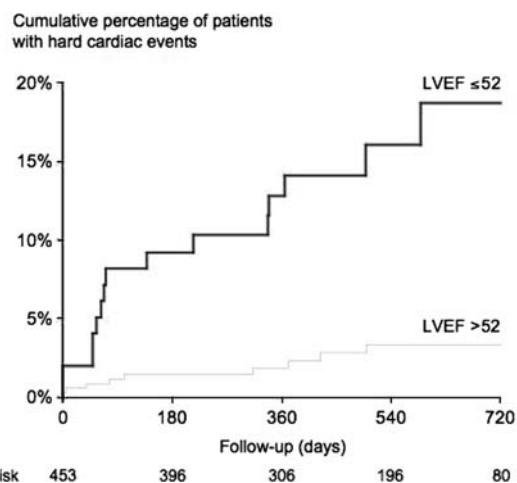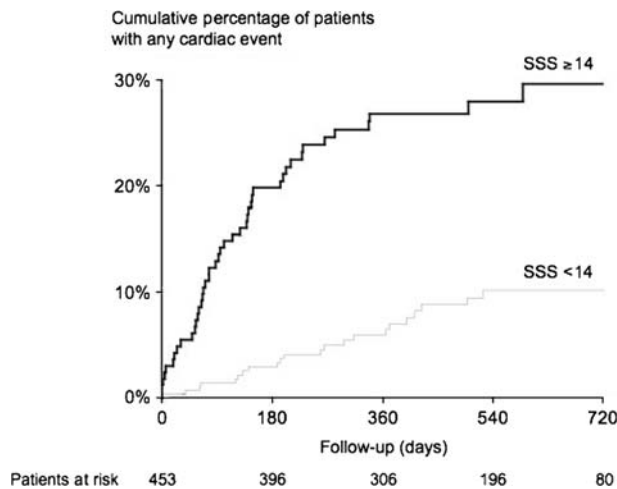

Figure 1. Hard endpoints according to the cutoff values for LVEF.
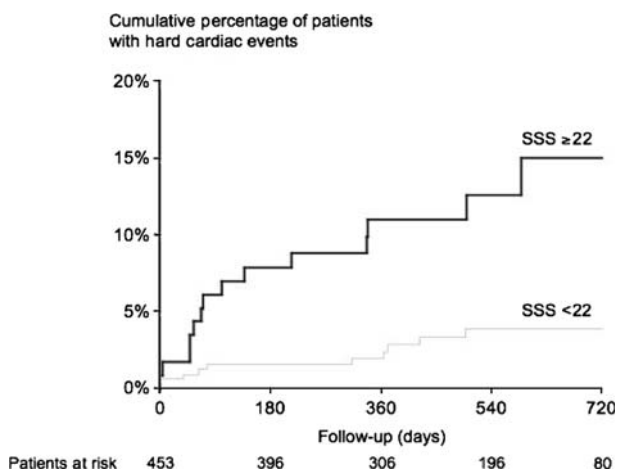
Figure 2. Hard endpoints according to the cutoff values for SSS.

events (P < 0.0001). Patients with an 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 cutoff 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 cutoff value for SSS could be determined (Figure 3). Maximal separation could be found using a cutoff 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 3. Any cardiac endpoint according to the cutoff values for SSS.

DISCUSSION

Our results show that relatively young female patients with hard events had significantly larger LV volumes, increased defect sizes, and lower LVEFs than those without hard events. Also, patients with any cardiac event during follow-up had significantly larger LV volumes, increased defect sizes, and lower LVEFs than those without any cardiac events. Moreover, patients with any cardiac event had significantly 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, cutoff 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 an 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 have 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 men 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% vs 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 event rates compared to our study (0.4% vs 0.7% annual CD rate for normal perfusion, 2.1% vs 2.4% annual CD for moderate to severely abnormal images). Similar results were found for hard cardiac events. Our optimal cutoff 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 an SSS < 22 in our study (2.5% vs 3.0%). The cutoff 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 outcomes. In our group, using our cutoff values, it is possible to identify females at increased risk.

A few data are 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 an LVEF < 45% and an ESV > 70 mL. The study by Sharir et al[9] was performed in a very large cohort of more than 1,600 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—51% (mean-2 SDs) and 43%, respectively. They also report upper limits for ESVi and EDVi for both genders (27 and 60 mL/m^2 for women and 39 and 75 mL/m^2 in men, respectively).

Compared to the data reported by Sharir et al,[9] the annual event rate in our group of women with an LVEF $\geq$ 52% was similar to the annual event rate of a mixed population of patients with an LVEF $\geq$ 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 cutoff 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 an 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 tend to have smaller LVs. However, previous studies[11] showed a significant correlation between ESV and EDV vs BSA. Another study[13] showed a systematic 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 an SSS ≥ 14 are at increased risk for any cardiac events.

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