Incidence and predictors of heart failure during long-term follow-up after stress Tc-99m sestamibi tomography in patients with suspected coronary artery disease

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Background. **Heart failure is a major cause of morbidity and death in patients with coronary artery disease (CAD). The aim of this study was to define the incidence and predictors of heart failure during long-term follow-up in patients with suspected CAD referred for stress myocardial perfusion imaging.**

Methods and Results. **We studied 787 patients (mean age, 57 ± 12 years; 470 men) with suspected CAD who had no history of previous myocardial infarction or heart failure with exercise (n = 508) or dobutamine (n = 279) stress technetium 99m sestamibi single photon emission computed tomography. Patients were followed up for the occurrence of heart failure, nonfatal myocardial infarction, and death. An abnormal perfusion scan (reversible or fixed perfusion defect) was detected in 341 patients (43%). During a mean follow-up of 6.7 ± 2.3 years, heart failure occurred in 46 patients (6%), 170 patients (22%) died, and 52 patients (7%) had nonfatal myocardial infarction. Patients in whom heart failure developed were older (mean age, 60 ± 12 years vs 56 ± 12 years; *P* = .01) and were more likely to be men (34 [74%] vs 436 [59%], *P* = .01) and to have an abnormal scan (32 [70%] vs 309 [42%], *P* = .0002) compared with patients without heart failure. Nonfatal myocardial infarction occurred before the onset of heart failure in only 3 patients (7%). By multivariate analysis, predictors of heart failure were age (risk ratio [RR], 1.04 [95% CI, 1.01-1.08]), male gender (RR, 2 [95% CI, 1.3-4.5]), resting heart rate (RR, 1.1 [95% CI, 1.05-1.2]), and abnormal scan (RR, 2.3 [95% CI, 1.4-3.9]). The annual mortality rate was 15% after the diagnosis of heart failure.**

Conclusion. **In patients with suspected CAD and no history of myocardial infarction, late heart failure is predicted by age, gender, resting heart rate, and abnormal perfusion, and it is associated with a substantial mortality rate. The majority of heart failure events are heralded by perfusion abnormalities on sestamibi single photon emission computed tomography but not by an earlier myocardial infarction. (J Nucl Cardiol 2004;11:527-33.)**

Key Words: Heart failure • stress test • myocardial perfusion • technetium 99m sestamibi • prognosis

Congestive heart failure is a major cause of morbidity and death in patients with coronary artery disease (CAD).[1-4] Previous studies have shown that after acute myocardial infarction, the extent of left ventricular dysfunction and other parameters of myocardial damage predict the occurrence of heart failure.[1,5] The incidence of heart failure in the general population has been studied.[6-11] However, little is known about the incidence and predictors of heart failure among patients with suspected CAD who have no history of myocardial infarction. In particular, it is not known whether the occurrence of heart failure in these patients is heralded by the presence of abnormalities on images obtained by current stress imaging techniques or the occurrence of a manifest myocardial infarction before the onset of heart failure.

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Stress myocardial perfusion imaging is a widely used technique for the diagnosis and risk stratification of CAD. Numerous studies have shown an association of myocardial perfusion abnormalities with the risk of cardiac death and nonfatal myocardial infarction.[12-16] However, the association of perfusion abnormalities with late-onset heart failure in patients without previous myocardial infarction has not been previously studied. The aims of this study were (1) to define the incidence and predictors of heart failure in patients with suspected CAD referred for stress myocardial perfusion imaging and (2) to assess the prognostic implications of heart failure in these patients.

METHODS

Patient Selection

The study population consisted of consecutive patients with suspected CAD and no history of myocardial infarction or pathologic Q waves on baseline electrocardiogram, who underwent stress technetium 99m sestamibi single photon emission computed tomography (SPECT) in our laboratory between 1990 and 1995. Exclusion criteria were known cardiomyopathy, exertional dyspnea, heart failure, previous myocardial revascularization, and significant valvular heart disease. Inclusion criteria were fulfilled in 790 patients. Follow-up was successful in 787 patients (99%). The data from these patients are reported. The choice of stress test was based on ability to exercise. Patients with limited exercise capacity underwent dobutamine stress testing. All patients gave informed consent before the test. The Hospital Ethics Committee of University Hospital, Rotterdam, approved the protocol. A structured interview and clinical history were acquired and cardiac risk factors were assessed before nuclear testing. Hypertension was defined as repeated blood pressure measurements greater than 140/90 mm Hg or intake of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of 7.8 mmol/L or greater or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol level of 6.4 mmol/L or greater or treatment with lipid-lowering medication. The pretest probability of CAD was determined by use of the criteria of Diamond and Forrester.[17]

Exercise Protocol

Exercise stress was performed in 508 patients by use of a symptom-limited upright bicycle ergometry test with a stepwise increment of 20 W every minute.[18] Three electrocardiographic leads were continuously monitored. Cuff blood pressure measurements and 12-lead electrocardiograms were recorded at rest and every minute during exercise and recovery.

Dobutamine Stress Protocol

Dobutamine-atropine stress testing was performed in 279 patients. Dobutamine was injected intravenously, first at a dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 minutes, increasing by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 3 minutes up to a maximum dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[15] If the test endpoint was not reached at a dobutamine dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, atropine (up to 1 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were continuously monitored. The test endpoints were as follows: achievement of target heart rate (85% of maximum age-predicted heart rate), horizontal or downsloping ST-segment depression greater than 2 mm at an interval of 80 milliseconds after the J point compared with baseline, severe angina, systolic blood pressure decrease of greater than 40 mm Hg, blood pressure greater than 240/120 mm Hg, or significant cardiac arrhythmia. Metoprolol was available to reverse the (side) effects of dobutamine/atropine if these did not revert spontaneously. Significant ST-segment depression was defined as a horizontal or downsloping ST-segment depression of 1 mm or greater occurring at 80 milliseconds after the J point.

Tc-99m Sestamibi SPECT Imaging

An intravenous dose of 370 MBq Tc-99m sestamibi (Cardiolite; Bristol-Myers Squibb Medical Imaging, Inc, New York, NY) was administered approximately 1 minute before the termination of the dobutamine or exercise test. For resting studies, 370 MBq sestamibi was injected at least 24 hours after the exercise study. Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp, Iselin, NJ). Thirty-two projections were obtained, from the left posterior oblique to the right anterior oblique over 180°. For each study, 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices from the septum to the lateral wall were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The septal part of the 2 basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. Consequently, a total of 47 segments were identified (3 long-axis and 44 short-axis segments). Interpretation of the scan was semiquantitatively performed by visual analysis assisted by circumferential profiles analysis.[15,18] Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical data. A reversible perfusion defect was defined as a perfusion defect on the exercise images that partially or completely resolved at rest in 2 or more contiguous segments or slices in the 47-segment model. A fixed perfusion defect was defined as a perfusion defect on exercise images in 2 or more contiguous segments or slices that persisted on rest images in the 47-segment model. To assess the severity of perfusion abnormalities, the left ventricular myocardium was divided into 6 segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical. Each of the 6 major left ventricular segments was scored by use of a 4-point scoring method (0, normal; 1, slightly reduced; 2, moderately reduced; and 3, severely reduced or absent uptake). The summed stress score was calculated to estimate the extent and severity of perfusion defects on stress scans as previously described.[15,19,20]

Follow-up

Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. Endpoints were the occurrence of heart failure, nonfatal myocardial infarction, and death. Heart failure was diagnosed by use of the Framingham Heart Study criteria.[2,3] Accordingly, hospital admission for treatment of heart failure was not required for patients to be categorized as having heart failure. Patients were not censored at the occurrence of heart failure and were subsequently followed up with regard to other endpoints to study the prognostic implication of heart failure. Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death. Nonfatal myocardial infarction was defined by cardiac enzyme levels and electrocardiographic changes. Myocardial revascularization procedures were also noted during follow-up. Follow-up data collection and categorization of patients with regard to endpoints were performed by an investigator who was unaware of scan results.

Statistical Analysis

Continuous data were expressed as mean ± SD. The Student *t* test was used to analyze continuous data. Differences between proportions were compared by use of the χ^2 test. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc, Los Angeles, Calif) were used to identify predictors of heart failure. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of .05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% CI. Variables considered for multivariate analysis were those that were significant in the univariate analysis. The probability of event-free survival was calculated by use of the Kaplan-Meier method, and survival curves were compared between different groups by use of the log-rank test. $P < .05$ was considered statistically significant.

RESULTS

Clinical Data

The patients' mean age was 57 ± 12 years. There were 470 men (60%). Symptoms before the stress test were typical angina in 208 patients (26%) and atypical chest pain in 307 (39%). Risk factors for CAD were hypertension in 337 patients (43%), diabetes mellitus in 68 (9%), hypercholesterolemia in 193 (25%), and smoking in 197 (25%).

Stress Data

There was a significant increase in heart rate (from 80 ± 20 beats/min to 140 ± 22 beats/min) and systolic blood pressure (from 143 ± 21 mm Hg to 174 ± 33 mm Hg) from rest to peak stress (both $P < .001$). The mean achieved workload with exercise was 143 ± 38 W. The mean maximal dobutamine dose was 38 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Atropine was administered in 105 patients (38%). No patient had a myocardial infarction or sustained ventricular tachycardia. Short runs of ventricular tachycardia occurred in 16 patients (2%), and short runs of supraventricular tachycardia occurred in 9 patients (1%). During stress, angina occurred in 145 patients (18%) and ST-segment depression occurred in 70 patients (9%).

SPECT Results

Stress myocardial perfusion abnormalities were detected in 341 patients (43%). Abnormalities were fixed in 104 patients (13%) and partially or completely reversible in 237 patients (30%).

Follow-up Events

During a mean follow-up of 6.7 ± 2.3 years, heart failure occurred in 46 patients (6%), with an annual incidence rate of 1%. Clinical data from patients with and without heart failure during follow-up are shown in Table 1. Scintigraphic data are presented in Table 2. Of the patients, 170 (22%) died; of these, 62 (36%) died as a result of cardiac causes. Nonfatal myocardial infarction occurred in 52 patients (7%), and 130 patients (16.5%) underwent coronary revascularization. The incidence of follow-up events in patients with heart failure as compared with patients without heart failure during follow-up is provided in Table 2. The incidence of death was significantly higher in patients with heart failure than in those without heart failure. The annual mortality rate was 15% after onset of heart failure. There was no significant difference between patients with and without subsequent heart failure with regard to rate or type of revascularization (Table 2). Myocardial revascularization was performed in 20% of patients with reversible defects who had subsequent heart failure and in 25% of patients with reversible defects who had no heart failure during follow-up.

The mean time to onset of heart failure was 3.8 years (range, 0.4-8 years) after the stress test. The patients' mean age at presentation was 64 ± 14 years. Nonfatal myocardial infarction occurred before the onset of heart failure in 3 patients. The cause of heart failure was CAD (defined as prior myocardial infarction, segmental wall motion abnormalities on echocardiogram, or angiographic CAD) in 28 patients (61%), severe valvular heart disease in 2 (4%), high output as a result of arteriovenous fistula in 1 (2%), dilated cardiomyopathy in 2 (4%), and hypertensive heart disease in 7 (15%). In 6 patients (13%) the cause of heart failure could not be determined. Among these patients, 2 had

Table 1. Clinical and stress test data of study patients with and without heart failure during follow-up

Parameter	Heart failure		*P* value
	Yes (n = 46)	No (n = 741)	
Age (y)	60 ± 12	56 ± 12	.01
Men	34 (74%)	436 (59%)	.01
Angina before stress test	10 (22%)	198 (27%)	NS
Atypical chest pain	11 (24%)	296 (40%)	.01
Systemic hypertension	19 (41%)	318 (43%)	NS
Diabetes mellitus	6 (13%)	62 (8%)	.1
Smoker	7 (15%)	190 (26%)	.04
Hypercholesterolemia	8 (17%)	185 (25%)	.07
β-Blockers	12 (26%)	260 (35%)	NS
ACE inhibitors	9 (20%)	90 (12%)	NS
Pretest probability of CAD			NS
Low	4 (9%)	66 (9%)	
Intermediate	28 (61%)	406 (55%)	
High	14 (30%)	269 (36%)	
Exercise/dobutamine stress (patients)	32/14	476/265	NS
Resting systolic blood pressure (mm Hg)	134 ± 19	141 ± 21	.07
Stress systolic blood pressure (mm Hg)	161 ± 33	176 ± 32	.01
Resting heart rate (beats/min)	86 ± 21	78 ± 17	.01
Stress heart rate (beats/min)	134 ± 19	141 ± 22	.1
Workload (W)	139 ± 34	144 ± 39	NS
ST-segment depression	3 (7%)	67 (9%)	NS
Angina during stress	6 (13%)	139 (19%)	NS

ACE, Angiotensin-converting enzyme; *NS,* not significant.

normal left and right ventricular systolic function and no valvular heart disease on echocardiogram and the diagnosis of diastolic heart failure was assumed.

Predictors of Heart Failure

Table 3 presents the univariate and multivariate predictors of heart failure. Independent predictors were age, male gender, higher resting heart rate, and abnormal scan. Survival curves with freedom from heart failure in patients with abnormal scans as compared with patients with normal scans are shown in Figure 1. To generate these curves, patients were censored at the time of occurrence of heart failure or death. Figure 2 presents survival curves for the combined endpoint of cardiac death and heart failure in patients with normal versus abnormal scans. Independent predictors of the endpoint of cardiac death were age (risk ratio [RR], 1.05 [95% CI, 1.01-1.1]; $P = .02$), male gender (RR, 2.3 [95% CI, 1.5-6.5]; $P = .01$), and abnormal scan (RR, 3.1 [95% CI, 1.9-5.8]; $P \leq .005$).

Perfusion abnormalities were more frequent in patients with heart failure considered to be due to CAD as compared with patients with heart failure considered to be due to other causes or due to unknown etiology (22/28 [79%] vs 10/16 [63%], $P = .09$). When heart failure due to CAD was considered as the endpoint, an abnormal scan was associated with a relatively larger risk ratio for heart failure prediction in the multivariate analysis (RR, 2.9 [95% CI, 1.3-4.5]).

DISCUSSION

In this study we assessed the incidence, predictors, and prognostic implications of heart failure in patients with suspected CAD who underwent stress Tc-99m sestamibi SPECT. Patients had no history of myocardial infarction or heart failure before stress testing. During long-term follow-up (mean, 6.7 years), heart failure occurred in 46 patients (6%). Predictors of heart failure were age, male gender, higher resting heart rate, and abnormal perfusion scan. A normal perfusion study was associated with a relatively low annual incidence of heart failure (0.5% vs 1.7% of patients with abnormal perfusion). Heart failure was associated with adverse outcomes, with an annual

Table 2. Scintigraphic and outcome data in patients with and without heart failure during follow-up

Parameter	Heart Failure		*P* value
	Yes (n = 46)	No (n = 741)	
Scan results			.001
Normal	14 (30%)	432 (58%)	
Reversible defect	23 (50%)	214 (29%)	
Fixed defect	9 (20%)	95 (12%)	
Summed stress score	2.7 ± 2.6	1.7 ± 2.8	.01
Events			
Overall deaths	26 (57%)	144 (19%)	.0001
Cardiac death	14 (30%)	48 (6%)	.001
Nonfatal myocardial infarction	5 (11%)	47 (6%)	.2
Myocardial revascularization	7 (15%)	123 (17%)	NS
Early	2 (4%)	21 (3%)	NS
Late	5 (11%)	102 (14%)	NS
Coronary artery bypass/percutaneous coronary intervention	2/5	50/73	NS
Complete/incomplete revascularization	5/2	102/21	NS

NS, Not significant.

Table 3. Predictors of heart failure by Cox models

Parameter	Univariate		Multivariate	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Age	1.1 (1.08–1.2)	.01	1.04 (1.01–1.08)	.03
Male gender	1.5 (1.2–5)	.01	2 (1.3–4.5)	.02
Stress systolic blood pressure	1.2 (1.05–1.3)	.03		
Resting heart rate	1.2 (1.04–1.25)	.02	1.1 (1.05–1.2)	.02
Abnormal scan	2.8 (1.3–4)	.005	2.3 (1.4–3.9)	.01

mortality rate of 15% after the diagnosis. Only 7% of patients with heart failure had a documented myocardial infarction before the onset of heart failure. It is possible that some of the patients without documented myocardial infarction had sustained a silent myocardial infarction. Another contributing mechanism would be the presence of severe myocardial hibernation and/or stunning, resulting in heart failure symptoms. It has been demonstrated in the CHRIST-MAS trial (Carvedilol Hibernation Reversible Ischaemia Trial) that many patients with heart failure symptoms have inducible ischemia and myocardial hibernation.[21]

The association of abnormal perfusion with an increased incidence of heart failure can be explained by many mechanisms. These include worsening of left ventricular function due to silent or manifest myocardial infarction or due to severe ischemia resulting in myocardial hibernation, stunning, mitral regurgitation, and diastolic dysfunction.

The association of advanced age and gender with the incidence of heart failure is consistent with previous studies in elderly persons and in community populations.[6-11] The association of higher heart rate at rest and incidence of heart failure may be related to the onset of autonomic dysfunction before clinical presentation of heart failure or an early compensatory mechanism with incipient heart failure. Some authors have suggested that sympathetic overactivity could be the common factor acting on cholesterol, heart rate, pulse pressure, and arterial stiffness,[22-25] with a subsequent increase in cardiac workload. A higher resting heart rate has been associated with an increased mortality rate after acute myocardial infarction.[26]

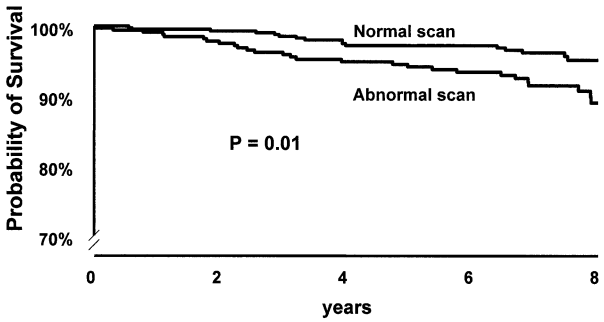

Figure 1. Kaplan-Meier survival curves with freedom from heart failure in patients with normal stress sestamibi SPECT scans and in those with abnormal scans.

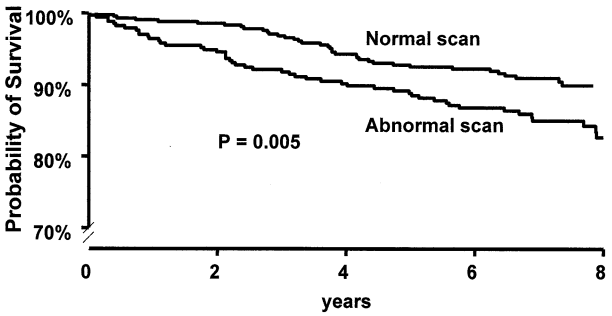

Figure 2. Kaplan-Meier survival curves for the combined endpoint of cardiac death and heart failure in patients with normal stress sestamibi SPECT scans and in those with abnormal scans.

Previous Studies

Previous studies of the incidence and predictors of heart failure focused primarily on patients with previous myocardial infarction or community populations. To our knowledge, there are no previous reports in patients with suspected CAD who had no previous myocardial infarction. Furthermore, the association of abnormalities on images obtained by current imaging techniques with the incidence of heart failure has not been previously studied.

Johansson et al[27] reported an annual incidence of heart failure in the general population of 0.44% in men and 0.39% in women. The incidence increased steeply with age in both sexes. Smoking, hypertension, diabetes, and obesity were independently associated with heart failure. CAD was the most common cause of heart failure, with a greater relative prevalence in men than women. Zannad et al[6] studied the incidence of heart failure in a community of 1,592,263 persons (mean age, 65 years; 26% with diabetes mellitus and 44% with hypertension) and reported a crude incidence rate of 225 per million. Forty-six percent had a coronary heart disease. The 1-year mortality rate was 35%, and the rate of mortality and/or readmission to the hospital was 81%. Cowie et al[9] reported the incidence of new cases of heart failure in a population of 151,000 persons in West London, England. The prevalence of risk factors in this population was not reported. The crude incidence rate of cases was 0.13% per 1,000 persons per year for those aged 25 years or over. New cases of heart failure largely occurred in the elderly, and the incidence was higher in men than in women. The single most common etiology was coronary heart disease, but in a third of cases the etiology could not be determined. The incidence rate among individuals aged 55 to 64 years (matching the ages of patients in our study) was 0.12%.

An incidence for heart failure of 1.7% in patients with abnormal scans in our study reflects a major increase in the incidence of heart failure in this age group, as compared with studies in the general population. Nevertheless, normal perfusion in patients with suspected CAD was still associated with a relatively higher incidence of heart failure compared with the incidence reported in the previous studies conducted in a general population. This may be explained by the inclusion of a largely symptomatic population in our study as compared with epidemiologic studies, which included patients with and without symptoms.

Study Limitations

Left ventricular function was not evaluated at the time of stress testing, and therefore it is not known whether these patients had occult cardiac dysfunction at that time. Although none of the study patients had a history of myocardial infarction or pathologic Q waves at the time of stress testing, the occurrence of a silent previous myocardial infarction or early cardiomyopathy cannot be ruled out.[28] We used two different methods of stress testing, and the functional capacity could not be evaluated by dobutamine stress. Some of these patients may have had very low physical activity and therefore did not experience heart failure symptoms. Nevertheless, each patient had basically served as a control for himself or herself, as all patients had no heart failure symptoms at the time of the stress test. Finally, the 6-segment model used in this study is different from the commonly used 20- or 17-segment model used in other centers. However, our method was shown to be useful in predicting outcome.[15,20] Our conclusion that an abnormal scan is associated with a late onset of heart failure should not be influenced by the segmental model. The size of the perfusion abnormality was not a better predictor of heart failure than simply an abnormal scan. Although this finding may have been related to the segmental model used in our study, further studies are needed to determine whether the

extent of perfusion abnormality is a better predictor of heart failure.

Summary and Conclusion

In patients with suspected CAD and no history of previous myocardial infarction, late onset of heart failure is predicted by age, gender, resting heart rate, and abnormal perfusion scan, and it is associated with a substantial mortality rate. The majority of late heart failure events are heralded by perfusion abnormalities on stress sestamibi scans but not by an earlier myocardial infarction. A normal stress sestamibi study is associated with a relatively low incidence of heart failure during long-term follow-up in these patients.

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