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# Prognostic Stratification of Obese Patients by Stress $^{99m}\text{Tc}$ -Tetrofosmin Myocardial Perfusion Imaging

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Obesity is a major health problem associated with increased cardiovascular mortality. There are currently no data to support a role for stress imaging techniques in the risk stratification of obese patients. The aim of this study was to assess the independent value of stress  $^{99m}\text{Tc}$ -tetrofosmin SPECT in predicting mortality and hard cardiac events in obese patients. **Methods:** We studied 265 patients with a body mass index greater than 30 kg/m<sup>2</sup> by exercise or dobutamine stress  $^{99m}\text{Tc}$ -tetrofosmin myocardial perfusion tomography. Endpoints during follow-up were cardiac death and death of any cause. **Results:** The mean patient age ( $\pm$ SD) was 59  $\pm$  10 y, and 110 of the patients were men (42%). The mean body mass index was 37  $\pm$  7 kg/m<sup>2</sup>. Scan findings were normal in 113 patients (43%). Myocardial perfusion abnormalities were fixed in 62 patients (23%) and reversible in 90 patients (34%). During a mean follow-up period of 5.5  $\pm$  2 y, 41 patients (15%) died. Death was considered cardiac in 22 patients (8%). Nonfatal myocardial infarction occurred in 20 patients (7.5%). The annual cardiac death rate was 0.6% in patients with normal perfusion and 3.3% in patients with abnormal perfusion. Patients with a multiple-vessel distribution of abnormalities had a higher cardiac death rate than did patients with a single-vessel distribution (4.1% vs. 2.5%,  $P < 0.05$ ). The annual mortality rate was 1.3% in patients with normal perfusion and 4.2% in patients with abnormal perfusion. In a multivariate analysis, perfusion abnormalities were independently predictive of cardiac mortality (risk ratio, 3.2; 95% confidence interval, 1.5–6.7) and overall mortality (risk ratio, 2.7; 95% confidence interval, 1.4–4.3). **Conclusion:** Stress  $^{99m}\text{Tc}$ -tetrofosmin myocardial perfusion imaging is a useful tool for predicting cardiac and overall mortality in obese patients.

**Key Words:** obesity; radionuclide imaging; coronary artery disease; prognosis

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**O**besity predisposes to cardiac complications such as coronary artery disease (CAD), heart failure, and sudden death (1–3). The impact of obesity on the use of health services and on medical costs is tremendous (2). Although coronary angiography remains the standard technique for the diagnosis of CAD, its routine use is prevented by the associated risk, which is particularly higher in obese patients (4). Therefore, identification of an accurate method for risk stratification of obese patients is of the ultimate importance to limit invasive procedures for high-risk patients.

Stress myocardial perfusion imaging (MPI) is an established technique for diagnosis and risk stratification of CAD (5–8). Earlier studies with thallium imaging in obese patients have shown that imaging may be limited by attenuation artifacts, most commonly resulting from attenuation by the diaphragm or the breast (9,10). Although the accuracy of MPI may be improved with  $^{99m}\text{Tc}$ -labeled agents (11), there are currently scarce data regarding the use of stress MPI as a prognostic tool in obese patients. Because of the independent risk associated with obesity and the high prevalence of other risk factors, it is not known whether obese patients with normal MPI results are at low risk of cardiac events. The aims of this study were to assess the value of stress  $^{99m}\text{Tc}$ -tetrofosmin MPI in predicting mortality and cardiac events in obese patients and to assess the outcome after a perfusion study showing normal findings in these patients.

## MATERIALS AND METHODS

### Patients

The study population consisted of 267 consecutive obese patients who were referred to our laboratory between January 1996 and December 2002 for stress  $^{99m}\text{Tc}$ -tetrofosmin SPECT because of cardiac symptoms or multiple risk factors. Body mass index was calculated as the body weight divided by the squared height. Patients were considered obese if they had a body mass index greater than 30 kg/m<sup>2</sup>, according to the criterion of the National Institutes of Health and the World Health Organization (1). The choice of stress test was based on ability to exercise.

Follow-up was successful in 265 patients (99.5%). All patients gave informed consent before the test. The Ethics Committee of the University Hospital Rotterdam approved the protocol. Clinical history was recorded and cardiac risk factors assessed before nuclear testing. Diabetes mellitus was defined as a fasting glucose level of at least 140 mg/dL or the need for insulin or oral hypoglycemic agents. Impaired glucose tolerance was defined as a fasting glucose level of between 110 and 139 mg/dL. Hypercholesterolemia was defined as a total cholesterol level of at least 200 mg/dL or treatment with lipid-lowering medications. Hypertriglyceridemia was defined as a fasting triglyceride level of at least 150 mg/dL. Hypertension was defined as blood pressure of at least 140/90 mm Hg or the use of antihypertensive medication.

### Stress Test Protocols

Patients discontinued  $\beta$ -blockers at least 24 h before the stress test whenever applicable. Other medications were not routinely discontinued. Exercise stress testing was performed on 70 patients using a symptom-limited upright bicycle ergometer with a stepwise increment of 20 W every minute (8). Dobutamine-atropine stress testing was performed on 195 patients. Dobutamine was infused intravenously, starting at a dose of 10  $\mu\text{g}/\text{kg}/\text{min}$  for 3 min and increasing by 10  $\mu\text{g}/\text{kg}/\text{min}$  every 3 min up to a maximum dose of 40  $\mu\text{g}/\text{kg}/\text{min}$ . If the test endpoint was not reached at a dobutamine dose of 40  $\mu\text{g}/\text{kg}/\text{min}$ , atropine (up to 1 mg) was given intravenously. The test endpoints were achievement of target heart rate (85% of maximum age-predicted heart rate), horizontal or downsloping ST-segment depression of more than 2 mm (compared with baseline) occurring 80 ms after the J point, severe angina, a fall in systolic blood pressure of more than 40 mm Hg, blood pressure greater than 240/120 mm Hg, and significant cardiac arrhythmia. Metoprolol was available to reverse the side effects of dobutamine or atropine if these did not revert spontaneously. Computer averaging of the electrocardiographic complexes was performed for both stress tests. Significant ST-segment depression was defined as a horizontal or downsloping ST-segment depression of more than 1 mm occurring 80 ms after the J point.

### $^{99\text{m}}\text{Tc}$ -Tetrofosmin SPECT Imaging

An intravenous dose of 370 MBq of  $^{99\text{m}}\text{Tc}$ -tetrofosmin (Myoview; Amersham) was administered approximately 1 min before the termination of the dobutamine or exercise test (8,12). For resting studies, 370 MBq of tetrofosmin were injected at least 24 h after the exercise study. Images were acquired without attenuation or scatter correction with a triple-head  $\gamma$ -camera system (Prism 3000 XP; Picker) fitted with a low-energy all-purpose collimator. Thirty-two projections were obtained over a 180° arc from left posterior oblique to right anterior oblique, with an acquisition time of 45 s per projection. Data were collected in a 64  $\times$  64 matrix, and images were reconstructed using a filtered backprojection algorithm and a ramp reconstruction filter. From the 3-dimensional data, oblique (short-axis) and sagittal (vertical long-axis) images obtained perpendicular and parallel, respectively, to the long axis were reconstructed. For each study, 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices 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, 47 segments in total were identi-

fied (3 long-axis and 44 short-axis). The scan was interpreted semiquantitatively by visual analysis. Images were positioned side by side for review by an experienced observer who was unaware of the clinical data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in at least 2 contiguous segments and slices in the 47-segment model. A fixed perfusion defect was defined as one appearing on 2 or more contiguous segments and slices on stress images and persisting on rest images. Study findings were considered abnormal if a fixed or reversible perfusion defect was seen. The impact of the extent of perfusion abnormalities on outcome was evaluated by estimating the number of coronary artery territories showing perfusion abnormalities on stress images, as previously described (12).

### Follow-up

Follow-up was performed by contacting the patient's general practitioner and by reviewing the hospital records. In addition, vital status was verified through the civil data registry. Endpoints were death from any cause, cardiac death, and hard cardiac events (cardiac death and nonfatal myocardial infarction, defined by cardiac enzyme levels and electrocardiographic changes). Death was considered cardiac if it was caused by an acute myocardial infarction, significant arrhythmias, or heart failure. Sudden unexpected death occurring without another explanation was included as cardiac death. Myocardial revascularization procedures were also noted. Patients who underwent revascularization within 3 mo of the stress test were censored at the time of revascularization.

### Statistical Analysis

Continuous data are expressed as mean value  $\pm$  SD. The Student *t* test was used to analyze continuous data. Differences between proportions were compared using the  $\chi^2$  test. Univariate and multivariate Cox proportional hazards regression models (BMDP Statistical Software Inc.) were used to identify independent predictors of events. Parameters considered for multivariate analysis were those with a *P* value of less than 0.05 in the univariate analysis. Variables were selected in a forward, stepwise manner, with entry and retention set at a significance level of 0.05. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test.

## RESULTS

Clinical and stress test data are presented in Table 1. The mean body mass index was  $37 \pm 7 \text{ kg}/\text{m}^2$  (range, 30.5–61  $\text{kg}/\text{m}^2$ ), and the mean weight was  $101 \pm 16 \text{ kg}$ .

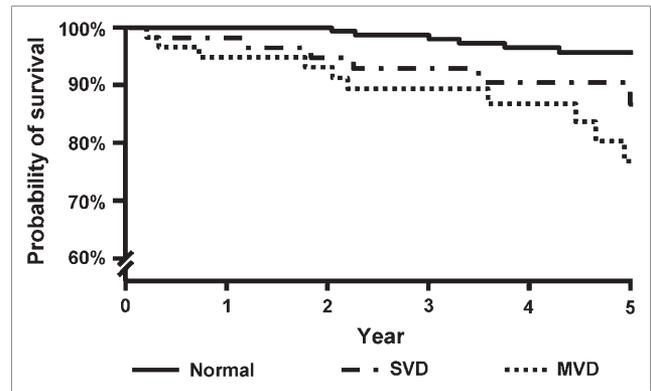
Image quality was considered suboptimal in 6 patients (2%). Breast attenuation was noted in 28 patients (11%), and diaphragmatic attenuation was noted in 12 patients (5%). Scan findings were normal in 113 patients (43%). Myocardial perfusion abnormalities were fixed in 62 patients (23%) and reversible in 90 patients (34%). Among patients with reversible defects, 34 had completely reversible defects and 56 had resting perfusion defects as well. Among the 62 patients with a fixed defect (without reversibility), 35 had no history of previous myocardial infarction. Perfusion abnormalities had a single-vessel distribution in 72 patients and a multiple-vessel distribution in 80 patients. During a mean follow-up of  $5.5 \pm 2 \text{ y}$ , 41 patients (15%) died. Death was cardiac in 22

**TABLE 1**  
Clinical and Stress Test Data

Parameter	Data
Age (y)	59 ± 10
Men	110 (42)
Hypertension	156 (59)
Diabetes mellitus	46 (17)
Impaired glucose tolerance	51 (19)
Hypercholesterolemia	109 (41)
Hypertriglyceridemia	177 (67)
Smoking	60 (23)
Previous myocardial infarction	73 (28)
Previous myocardial revascularization	77 (29)
Angina	104 (39)
Atypical chest pain	102 (38)
Medications	
β-blockers	145 (58)
Angiotensin-converting enzyme inhibitors	88 (33)
Diuretics	67 (25)
Calcium channel blockers	102 (38)
Resting heart rate (beats/min)	73 ± 15
Peak heart rate (beats/min)	139 ± 17
Resting systolic blood pressure (mm Hg)	144 ± 21
Peak systolic blood pressure (mm Hg)	169 ± 34
Exercise-induced angina	89 (34)
Exercise-induced ST segment depression	49 (18)
Achievement of target heart rate	239 (90)
Workload (W)	136 ± 45
Maximal dobutamine dose (μg/kg/min)	33 ± 10

Data are either mean ± SD or number of patients, with percentage in parentheses.

patients (8%). Nonfatal myocardial infarction occurred in 20 patients (7.5%), and 75 patients (28%) underwent coronary revascularization. This was performed early (within 90 d) in 20 patients and late in 55 patients. The annual cardiac death rate was 0.6% in patients with normal perfusion and 3.3% in patients with abnormal perfusion. Patients with a multiple-vessel distribution of abnormalities had a higher cardiac death rate than did patients with a single-vessel distribution (4.1% vs. 2.5%,  $P < 0.05$ ) (Fig. 1). The annual hard cardiac event rate was 1% in patients with normal perfusion and 4.8% in patients with abnormal perfusion. The annual mortality rate was 1.3% in patients with normal perfusion and 4.2% in patients with abnormal perfusion. The annual death rate was 5.5% in patients with a multiple-vessel distribution of perfusion abnormalities and 3.1% in patients with a single-vessel distribution ( $P < 0.05$ ). Survival curves based on extent of perfusion abnormalities are presented in Figure 2. Univariate and multivariate predictors of events are presented in Table 2. Perfusion abnormalities were independently predictive of all endpoints of interest. Analysis was additionally performed after censoring patients who underwent late revascularization. Perfusion abnormalities remained predictive of cardiac death (relative risk, 3.5; 95% confidence interval, 1.4–7.1), all causes of mortality (relative risk, 2.8; 95% confidence interval, 1.3–4.7), and hard events

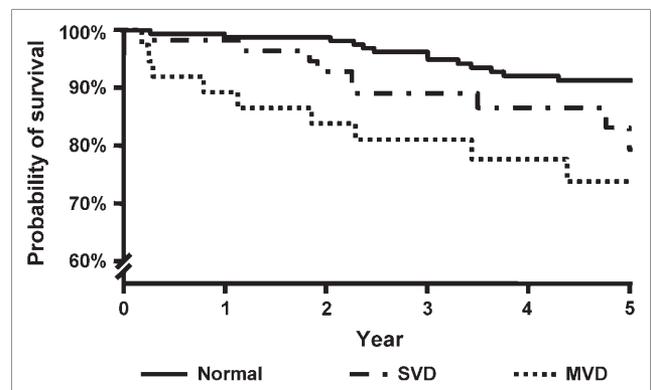


**FIGURE 1.** Kaplan–Meier survival curves (cardiac mortality) according to presence and extent of perfusion anomalies. SVD = abnormal in single-vessel distribution; MVD = abnormal in multiple-vessel distribution.

(relative risk, 2.5; 95% confidence interval, 1.4–4.9). Diabetes mellitus was associated with a 4-fold increased risk of cardiac death. Survival curves (cardiac death) in diabetic and nondiabetic patients are presented in Figure 3.

## DISCUSSION

Obesity is becoming a global epidemic in both children and adults. Studies have shown that obesity is associated with an increased risk of morbidity and mortality and a reduced life expectancy. Obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, sleep apnea, and the prothrombotic state (2). The noninvasive assessment of CAD in obese patients is a clinical challenge. Baseline electrocardiography may be influenced by the presence of obesity, creating a false-positive diagnosis of inferior myocardial infarction, low voltage, and nonspecific ST-T changes. Obese patients often have impaired exercise tolerance and are candidates for pharmacologic stress in conjunction with an imaging technique. Body habitus may have an adverse impact on image quality (2).



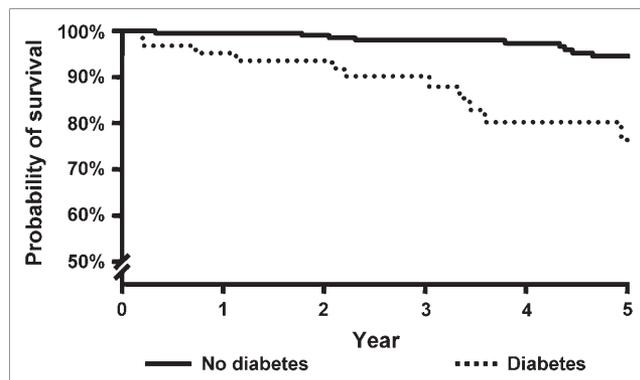
**FIGURE 2.** Kaplan–Meier survival curves (all causes of mortality) according to presence and extent of perfusion anomalies. SVD = abnormal in single-vessel distribution; MVD = abnormal in multiple-vessel distribution.

**TABLE 2**  
Predictors of Events by Cox Models

Parameter	Univariate risk ratio	Multivariate risk ratio
All causes of mortality		
Age	1.06 (1.01–1.09)	1.07 (1.04–1.11)
History of heart failure	3.4 (1.5–8)	2.6 (1.3–5.0)
Diabetes mellitus	2.2 (1.1–4.4)	2.4 (1.3–4.7)
Abnormal perfusion	3.1 (1.6–4.6)	2.7 (1.4–4.3)
Cardiac mortality		
History of heart failure	4.3 (1.6–12)	3.1 (1.2–8.6)
Diabetes mellitus	4.5 (1.8–11)	4.7 (1.9–11.4)
Abnormal perfusion	2.9 (1.4–5.8)	3.2 (1.5–6.7)
Hard cardiac events		
Age	1.04 (1.01–1.07)	Not significant
History of heart failure	2.6 (1.3–7.4)	2.4 (1.1–5.5)
ST-segment depression	2.3 (1.1–5.2)	2.1 (1.1–4.4)
Abnormal perfusion	2.6 (1.4–3.5)	2.6 (1.4–4.8)

Data in parentheses are 95% confidence intervals.

In this study, stress  $^{99m}\text{Tc}$ -tetrofosmin MPI provided independent prognostic information on mortality and cardiac events in obese patients. Patients with normal perfusion had a lower risk of death and hard cardiac events than did patients with abnormal perfusion. Perfusion abnormalities were associated with an increased risk of events after adjustment for clinical data and body mass index. The extent of perfusion abnormalities was an important determinant of prognosis. Patients with a multiple-vessel distribution of perfusion abnormalities were at greatest risk, with an annual death rate of 5.5% and an annual cardiac death rate of 4.1%. These data indicate that the results of MPI can provide the physician with valuable information regarding the risk status of obese patients and, therefore, assist in the decision on the next management strategy. It should be emphasized that the conclusions of this study apply to obese patients in whom stress testing is clinically indicated because of, for example, cardiac symptoms, multiple risk factors, previous revascularization, or myocardial infarction.



**FIGURE 3.** Kaplan–Meier survival curves (cardiac mortality) in patients with and without diabetes mellitus.

Therefore, the results should not be extrapolated to the general obese population that does not have an additional clinical indication to undergo stress testing. We used dobutamine and not vasodilator stress in patients unable to exercise. Preferring vasodilator stress to dobutamine for MPI was based on earlier studies demonstrating a better flow heterogeneity with dipyridamole than with dobutamine (13). These studies used a small dose of dobutamine without the addition of atropine and did not represent the state of the art in dobutamine stress testing. Recent studies have shown that the flow heterogeneity obtained by high-dose dobutamine–atropine stress is equal to that obtained by dipyridamole (14). It has been shown that in coronary artery beds with a noncritical stenosis, the increases in myocardial blood flow and velocity and in capillary derecruitment are similar for both dobutamine and adenosine (15). Therefore, no literature supports the suggestion that the use of a vasodilator is superior to the current protocol of dobutamine stress (16). The findings of this study are likely to be reproducible with vasodilator stress, which is the preferred method in the United States for testing patients unable to exercise.

Previous studies have shown that annual event rates (cardiac death or nonfatal myocardial infarction) in patients with normal perfusion findings ranged from 0% to 1.3%, compared with 2%–14.3% in patients with abnormal findings. The mean follow-up in these studies was 27.6 mo (5). The hard event rate of 1% in obese patients with normal perfusion during this 5.5-y study is comparable to the mean event rate in pooled data, indicating that stress MPI can reliably identify low- and high-risk patients among the obese population. It is possible that risk-factor modification during follow-up contributed to the improved outcome of patients with normal perfusion in this study and resulted in the event rate comparable to what was reported for unselected patients in previous studies.

One limitation of this study was that gated SPECT data were not available and, therefore, that the prognostic impact of left ventricular function could not be assessed. No attenuation correction was implemented. Although it is possible that the use of gated SPECT and attenuation correction could have improved risk stratification, the study has already demonstrated effective stratification without these techniques (10). It is possible that the high energy and better quality with tetrofosmin imaging enabled the distinction of true-positive defects from artifacts in most cases (11). Because coronary angiography was not routinely performed, the diagnostic accuracy of MPI in obese patients has to be determined by further studies. Finally, this study did not assess body fat distribution or measures of abdominal obesity. It is not known whether these parameters could have had an independent impact on outcome.

## CONCLUSION

Stress  $^{99m}\text{Tc}$ -tetrofosmin myocardial perfusion imaging is a useful tool for predicting cardiac and overall mortality in obese patients.

## ACKNOWLEDGMENT

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