

# The prognostic significance of normal technetium-99m MIBI myocardial perfusion spect imaging over a four-year follow-up period

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**ABSTRACT** A normal Tc-99m MIBI myocardial perfusion study has previously been shown to indicate a benign prognosis. Our aim was to determine the longer term prognosis of a normal study in our patient population.

**Methods:** A retrospective evaluation of 209 patients with a normal Tc-99m MIBI study was performed. Follow-up data was obtained in 157 patients, with complete follow-up in 121 (mean follow-up period of 56 months). In 36 patients only partial follow-up was possible (32 months follow-up). No follow-up data, except for the possible registration of deaths, could be obtained in 52. Patients were evaluated for the occurrence of primary or secondary cardiac events.

**Results:** The study group had a moderate pre-test probability for coronary artery disease (48 + 30.7%). Two possible cardiac deaths occurred (cardiac death rate of 0.95%). No primary events occurred in the group with complete follow-up, but 6 secondary events were recorded (cardiac event rate of 4.9%). No primary or secondary events occurred in the partial follow-up group during the follow-up period. The incidence of secondary or non-fatal primary events in this group for the period after they were lost to follow-up or in the group with no follow-up could not be ascertained. There was, however, no statistically significant difference between these groups regarding age, pre-test probability and exercise parameters.

**Conclusion:** Similar to the findings with Tl-201, our study indicates a favourable longer term prognosis after a normal Tc-99m MIBI study.

**Key words:** Myocardial perfusion imaging; Prognostic significance of normal myocardial perfusion imaging; Tc-99m MIBI; SPECT myocardial perfusion imaging; Long-term follow-up

## INTRODUCTION

Thallium-201 (Tl-201) has for many years been the radiotracer of choice for the scintigraphic evaluation of myocardial perfusion, but technetium-99m (Tc-99m) methoxy-isobutylisonitrile (MIBI) was shown to be a reliable alternative radiopharmaceutical for detecting

coronary artery disease (CAD) and is preferable to Tl-201 due to the better physical characteristics of the Tc-99m label for imaging. The accuracy of the two techniques to detect CAD has also been shown to be equal.<sup>(1-14)</sup> Advantages of using the Tc-99m agent include better image quality and the ability to simultaneously assess left ventricular function.<sup>(5,6)</sup>

The prognostic significance of a normal stress-redistribution Tl-201 myocardial perfusion study in patients with known or suspected CAD is well documented, showing a benign outcome in such patients over the short- and long-term, with an overall cardiac event rate of less than 1% per year.<sup>(15-31)</sup>

Previous studies have evaluated the prognostic value of a normal Tc-99m MIBI stress study over a period of 6-16 months using planar imaging,<sup>(32)</sup> over one year using single photon emission computed tomography (SPECT) or planar imaging,<sup>(33)</sup> over 19.6 months using dual isotope Tl-201 (rest) and Tc-99m MIBI (exercise) SPECT,<sup>(34)</sup> after dipyridamole Tc-99m sestamibi imaging<sup>(35)</sup> and over 22 ± 13 months after dobutamine-atropine stress.<sup>(36)</sup> All these studies confirmed a benign short-term outcome in these patients with an overall cardiac event rate of less than 1% per year.

Longer follow-up studies were also reported with Tc-99m MIBI and Tc-99m tetrofosmin.<sup>(37-40)</sup> Most of these studies reported their experience with all patients referred for myocardial perfusion imaging. However, Yang et al. specifically reported on 90 patients with normal exercise myocardial perfusion imaging studies, but with angiographic coronary artery disease.<sup>(41)</sup> All these reports confirmed an overall cardiac event rate in patients with normal myocardial perfusion imaging studies of less than 1% per year.

The aim of our study was to determine whether the benign prognostic significance of a normal Tc-99m MIBI stress-rest myocardial perfusion SPECT study over a longer term could also be proven in our patient population.

## METHODS

### Patients

We performed a retrospective analysis of the outcome in 209 consecutive patients with known or suspected CAD, reported to have a normal Tc-99m MIBI exercise-rest myocardial perfusion SPECT study

performed over a three-year period. No follow-up data could be obtained in 52 (24.8%) of these patients. Of the remaining 157 patients, follow-up was complete in 121. Only partial follow-up was possible in 36 patients, i.e. follow-up data could only be obtained for a certain period after the MIBI study was performed, whereafter the patients were lost to further follow-up.

The pre-test probability for CAD was determined by using Bayes' theorem of conditional probability of age, sex and presenting symptom.<sup>(42)</sup> Presenting symptoms were: no symptoms, typical angina pectoris, and atypical (non-anginal) chest pain.<sup>(43)</sup>

### Myocardial perfusion imaging

A same day exercise-rest protocol was utilised in all patients. Exercise was performed on a treadmill according to the Bruce protocol. An intravenous injection of 260 MBq (7 mCi) Tc-99m MIBI was administered when the patient reached the target heart rate or other accepted endpoint. Myocardial perfusion SPECT imaging commenced 30 min after injection. The rest injection of 740 MBq (20 mCi) was administered 3 hours later and SPECT imaging performed 1 hour after injection.

SPECT data were acquired for both the exercise and rest studies, using a single detector rotating gamma camera equipped with a low energy all purpose collimator. A 20% energy window, centred around 140 keV was used. Thirty images were acquired into 64x64 matrix frames in the step-and-shoot mode at 40s per step. A 180° elliptical orbit from 45° right anterior oblique to 45° left posterior oblique was used.

Transaxial slices of the myocardium were reconstructed for both exercise and rest studies, using a Hanning filter with cut-off at 0,73 cycles/cm. Horizontal and vertical long axis slices as well as short axis slices were subsequently generated and displayed according to the recommendations of the American College of Cardiology / American Heart Association / Society of Nuclear Medicine (ACC/AHA/SNM).<sup>(44)</sup>

Studies were reported by three experienced Nuclear Medicine physicians and were considered to be normal when the exercise study showed only homogenous distribution of the radiopharmaceutical in the left ventricular myocardium without any perfusion defects. Patients were included in the study group if the final report sent to the referring physician was reported as being normal.

### Follow-up

Follow-up data were obtained from hospital records and/or telephone interviews with the patients, patients' relatives or attending general practitioners. In the patients where no follow-up information could be obtained, or where the patients were lost to follow-up (partial follow-up), the Registrar of Deaths of the South African Department of the Interior was approached to obtain information regarding the number and cause of deaths that occurred in these patients.

Patients were evaluated for the occurrence of: 1) primary cardiac events (cardiac death or non-fatal myocardial infarction); 2) secondary cardiac events (recurrent chest pain requiring revascularisation by either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG)); 3) no cardiac events during the follow-up period. Cardiac catheterisation per se was not considered to be a cardiac event.

### Statistical analysis

Where applicable, values are presented as the mean value ± one standard deviation (SD) of the mean, with the range given in brackets.

Single factor analysis of variance (ANOVA) was used to test for significant differences between the groups with complete, partial or no follow-up. A p-value of less than 0.05 was considered a significant difference.

## RESULTS

### Presenting features

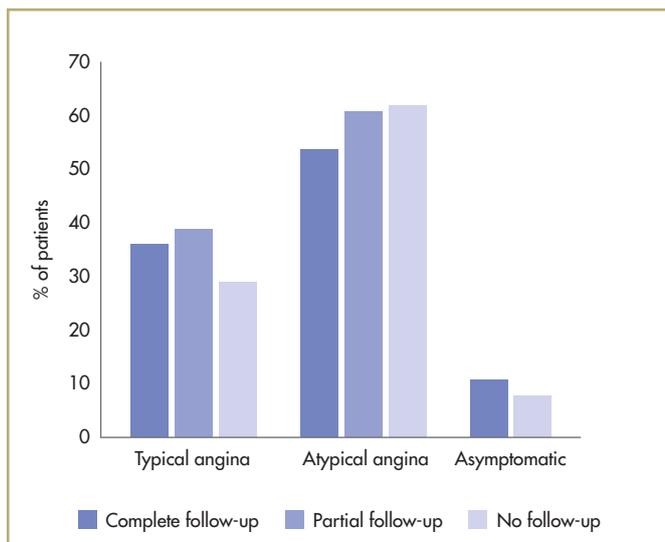
The biographical data of the patients are summarised in Table I.

	Complete follow-up	Partial follow-up	No follow-up
Number of patients	121	36	52
Male / Female	63 / 58	15 / 21	32 / 20
Age (years) *	52.5 ± 11.2 (31 – 72)	52.1 ± 10.9 (34 – 70)	48.3 ± 9.2 (30 – 67)
Pre-test probability of CAD (%)*	48.2 ± 30.4 (2.8 – 91.5)	51.3 ± 33.9 (0.8 – 91.2)	45.2 ± 29.6 (0.8 – 93.5)
Mean follow-up period (months)	55.6 ± 11.2 (9 – 78)	32.3 ± 14.6 (4 – 59)	0

Where applicable, values are presented as mean ± 1 SD followed by the range in brackets  
\*No statistically significant difference (ANOVA) between groups

ANOVA showed no statistically significant difference in mean age (p = 0.06) between the groups with complete, partial or no follow-up.

Forty-three of the 121 patients (36%) with complete follow-up presented with typical anginal chest pain, 65 (53%) had atypical chest pain, and 13 (11%) were asymptomatic. Of the 36 patients in whom only partial follow-up data were available, 14 (39%) had typical anginal chest pain at presentation, and 22 (61%) presented with atypical chest pain. In the group with no follow-up information available, 15 of the 52 patients (29%) presented with typical anginal pain, and 32 (61%) with atypical chest pain. Four patients (8%) were asymptomatic and in one (2%) the presenting symptom was unknown. The percentage of patients in each group presenting with typical angina and atypical angina, and with no symptoms is graphically represented in Figure 1.



**FIGURE 1:** Presenting symptoms of the patients in the three different follow-up categories

The mean pre-test probability for CAD in our study population was 48 ± 30.7% (0.8%-94.3%). ANOVA again showed no statistically significant difference (p = 0.65) in the mean pre-test probability between the group in whom follow-up was complete and the groups with partial follow-up or no follow-up.

Twenty-eight of the 209 patients (13.4%) (14 with complete follow-up information) underwent coronary angiography for their symptoms prior to the Tc-99m MIBI study. Of these, 11 had a normal coronary angiogram. Coronary artery disease was present in the remaining 17 patients (8.1% of the study population), of whom 11 are known to have had a revascularisation procedure (PTCA or CABG) performed prior to the MIBI study. No follow-up information was available in 1 of these 17 patients. Five of the 17 patients (2.4% of the study population) had significant (> 50%) coronary arterial narrowing in one or more coronary arteries, but had no revascularisation procedure performed during the follow-up period, although two of these patients were lost to follow-up after follow-up periods of respectively 48 and 45 months. One of these two patients subsequently died, presumably of a myocardial infarction, as will be discussed later. The data of the 5 patients with significant CAD and no revascularisation are summarised in Table 2.

**TABLE 2:** Patients with significant CAD and no revascularisation

Patient	Sex	Age	Follow-up period (months)	Pre-test probability for CAD
1*	F	70	48	90.6
2	M	47	78	87.3
3	M	54	66	92.0
4	M	52	44	92.0
5	F	65	45	90.6

\*Patient died 71 months after MIBI study (see text)

M = male; F = female CAD = coronary artery disease

### Tc-99m MIBI myocardial perfusion scintigraphy

The exercise data of the study group are summarised in Table III. ANOVA showed no statistically significant difference (p > 0.05) in any of the exercise parameters between the groups in which complete follow-up information was available and either only partial or no follow-up information was available.

**TABLE 3:** Tc-99m MIBI stress data

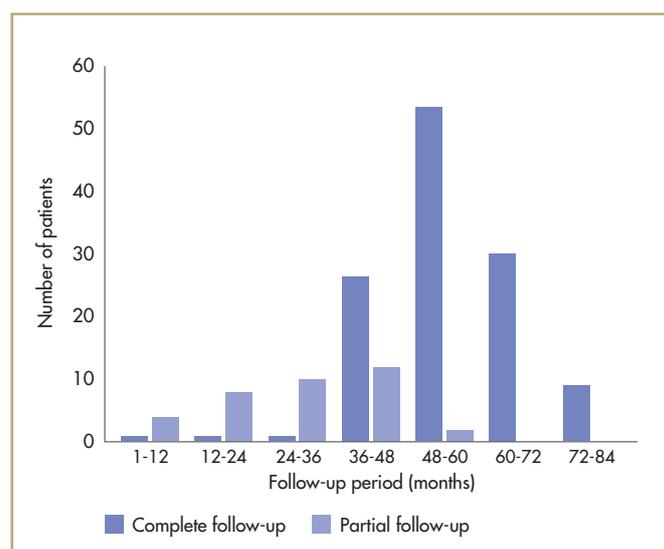
	Complete follow-up	Partial follow-up	No follow-up
Baseline heart rate / min	81 ± 16 (43 – 126)	80 ± 13 (54 – 107)	82 ± 13 (58 – 115)
Peak heart rate / min	162 ± 13 (108 – 187)	166 ± 9 (138 – 179)	164 ± 12 (122 – 178)
% of target heart rate	98 ± 5 (81 – 106)	99 ± 4 (85 – 106)	98 ± 6 (74 – 100)
Baseline systolic BP (mm Hg)	138 ± 20 (90 – 200)	128 ± 15 (100 – 160)	138 ± 24 (90 – 200)
Baseline diastolic BP (mm Hg)	89 ± 10 (60 – 110)	88 ± 8 (70 – 100)	91 ± 12 (60 – 110)
Peak systolic BP (mm Hg)	170 ± 24 (110 – 230)	165 ± 28 (120 – 210)	176 ± 32 (130 – 245)
Peak diastolic BP (mm Hg)	90 ± 12 (60 – 120)	94 ± 11 (70 – 115)	93 ± 15 (60 – 120)

BP = blood pressure

No statistically significant difference (ANOVA) was found in any of the exercise parameters between groups

### Follow-up period

The mean follow-up period for the 157 patients in whom follow-up data (complete or partial) could be obtained was 50.3 ± 15.5 months, ranging from 4 - 78 months. The mean follow-up period for the 121 patients with complete follow-up was 55.6 ± 11.2 months (range 9 - 78 months) and was 32.3 ± 14.6 months (range 4 - 59 months) for the 36 patients with partial follow-up. Figure 2 shows the number of patients involved in each 12-month follow-up period.



**FIGURE 2:** Number of patients involved in each 12-month follow-up period

The main reasons for inability to obtain follow-up data were inaccurate hospital records (wrong telephone number and/or address), the fact that patients were no longer living at the available address and the unavailability of both an address and telephone number.

### Cardiac events

#### Primary cardiac events:

None of the patients in whom complete follow-up information could be obtained, developed a cardiac death or non-fatal myocardial infarction during the follow-up period. Information obtained from the Registrar of Deaths showed that 2 patients for whom only partial or no follow-up information could be obtained, might have died from CAD. The cause of death in one patient was given as "myocardial infarction" on the death certificate. This patient died 71 months after the MIBI study. Follow-up information was available for the first 48 months after the MIBI study. This patient had coronary angiography performed prior to the MIBI study, which showed a 70% proximal left anterior descending artery lesion. No revascularisation procedure was performed. A follow-up coronary angiogram two years later failed to show any significant coronary artery lesions. In the other patient, who died 6 weeks after the MIBI study, the cause of death was given as "ischemic heart disease". Assuming that both these deaths were truly caused by CAD, the cardiac death rate in our study group was 0.95% during the whole follow-up period.

#### Secondary cardiac events:

Six of the 121 patients (4.9%) in whom follow-up was complete, had recurrent chest pain requiring coronary angiography followed by revascularisation. Of these, only 1 patient (0.8%) developed a cardiac event during the first year after the Tc-99m MIBI study. Three cardiac events (2.5%) occurred during the first two years and 4 (3.3%) during the first three years. The annual cardiac event rate in this group was 1.1%. Table 4 summarises the relevant data of these patients.

Revascularisation was performed at an average of 30 months (1 - 68 months) after the normal Tc-99m MIBI study. Only in one case (0.8%) was revascularisation performed less than one year after the MIBI study. None of the 36 patients with partial follow-up had a secondary cardiac event during the period for which follow-up information was available.

Of the 14 patients referred for the Tc-99m MIBI study after coronary angiography, and in whom follow-up was complete, none developed any coronary events during a mean follow-up period of  $55 \pm 11.5$  months (range 43 - 74 months), including 3 patients with significant stenoses in one or more coronary arteries, but who did not have a revascularisation procedure performed. These 3 patients had a high mean pre-test probability for coronary artery disease ( $90.4 \pm 2.7\%$ ) with a mean follow-up period of  $62.7 \pm 17.2$  months.

Fourteen patients in whom follow-up information was either incomplete (8) or absent (6) had coronary angiography before the MIBI study. Two of these had significant coronary artery disease but had no revascularisation procedure performed. The follow-up periods were 48 and 45 months respectively. Both had a high pre-test probability for CAD (90.6% each). As mentioned before, one died 71 months after the MIBI study.

Eleven of the 28 patients who had coronary angiography performed before the Tc-99m MIBI study, also had a revascularisation procedure (8 PTCA and 3 CABG) performed prior to the study. In 7 of these patients complete follow-up information could be obtained. No cardiac events were recorded in any of these. In 4 of the 11 patients, follow-up was incomplete. None of them developed any cardiac events during the period for which follow-up information could be obtained (mean =  $27 \pm 17.1$  months). No deaths were registered for any of these 4 patients.

### Deaths

Twelve patients (5.7%) died during the follow-up period. In seven of these complete follow-up information was available. Two of these patients died of unknown causes. The cause of death was proved to be of a non-cardiac origin in the remaining 5 patients. One of the patients in whom the cause of death could not be ascertained suffered from chronic bronchitis and emphysema. This patient was referred for the Tc-99m MIBI study because of a mildly positive effort electrocardiogram (ECG). This patient died 36 months after the MIBI study. The other patient died 61 months after the MIBI study. This patient suffered from chronic rheumatic heart disease with involvement of all four valves.

No follow-up information, except for the fact that the death was registered as well as the cause of death as given on the death certificate, was available in 5 of the 12 patients. Two of these patients presumably

TABLE 4: Patients with recurrent chest pain requiring revascularisation

Patient	Presenting symptom	Procedure	Time after MIBI (months)
1	Atypical chest pain	Mitral valve replacement and CABG	68
2	Typical chest pain	PTCA	1
3	Typical chest pain	CABG	49
4	Atypical chest pain	CABG	15
5	Atypical chest pain	PTCA	26
6	Typical chest pain	CABG	23

PTCA = percutaneous transluminal coronary angioplasty  
CABG = coronary artery bypass grafting

died of cardiac causes (as discussed previously). The causes of death in the remaining 3 patients were given as carcinoma of the pancreas, bronchial carcinoma and intracerebral haemorrhage.

## DISCUSSION

Myocardial perfusion scintigraphy with Tl-201 is well established as an excellent modality not only to diagnose CAD, but also for risk stratification. Tc-99m-MIBI imaging is also being used for risk stratification. Numerous studies have reported on the prognostic significance of a normal exercise MIBI study, over a follow-up period of less than 3 years.<sup>(32-36)</sup> These reports all confirmed the benign outcome in patients with a normal MIBI study over this follow-up period. Recently published reports have also demonstrated a good prognosis over even longer follow-up periods.<sup>(37-40)</sup>

The present study was performed to investigate the outcome in 209 patients with normal Tc-99m MIBI studies over a mean follow-up period of 4.2 years. In 157 patients either complete or partial follow-up information could be obtained. No primary cardiac events were recorded in 121 patients with complete follow-up, while 4.9% developed secondary events during the follow-up period. The annual cardiac event rate in this group was 1.1%. These results are comparable to those reported for normal Tl-201 stress imaging and the same as those reported for normal Tc-99m MIBI studies.

A major limitation of our study was the fact that only partial follow-up information was available in 36 of the 209 patients and no follow-up information in 52. None of the group that was partially followed for a mean follow-up period of 2.7 years, developed any primary or secondary events during the period for which follow-up information was available. One of these patients subsequently died of a putative myocardial infarction, 71 months after the MIBI study. One patient from the group of 52 with no follow-up information died of ischemic heart disease, according to the death certificate. From this information it is likely that 2 of the 209 patients might have died from a fatal primary cardiac event, signifying a cardiac death rate of 0.96%, confirming the low cardiac death rate reported in the literature in patients with normal MIBI or Tl-201 studies.

It is impossible to report on the incidence of secondary cardiac events or non-fatal primary cardiac events in the group with no follow-up information or in the patients with only partial follow-up for the period after they were lost to follow-up. Our data, however, show that there was no statistically significant difference between these groups and the group in which follow-up could be completed regarding mean age, treadmill exercise parameters and the pre-test probability for coronary

artery disease. Based on these findings, it could be argued that it would be highly unlikely that the incidence of cardiac events in these two groups would be significantly different from that found in the group in which follow-up could be completed. It has been reported that patients with a normal exercise thallium-201 study have a benign prognosis over a mean 2-year follow-up period even when angiographically significant coronary artery disease is present.<sup>(28)</sup> This was confirmed for Tc-99m MIBI over a short- to medium-term follow-up period<sup>(32-34)</sup> and over a longer follow-up period.<sup>(37-40)</sup>

Of the 28 patients in our study group who had coronary angiography before the MIBI study, only 5 had significant coronary artery disease, but no revascularisation procedures were performed. We are of the opinion that the small number of patients in this subset, as well as the subset of patients who had revascularisation performed prior to the MIBI study, is too small to allow any definitive conclusion to be drawn from the data.

The mean pre-test probability of coronary artery disease was moderate for this study group (48 + 31%), indicating the lack of a selection bias towards a low-risk study population and increasing the significance of the finding of a low event rate amongst this group of patients with normal Tc-99m MIBI studies. Calculation of the pre-test probability was based on the prevalence of CAD in the United States.<sup>(42)</sup> The average age-standardised mortality rate from CAD amongst Whites, Asians and Coloureds in South Africa in 1989 was 291 per 100 000, compared to 235 in the USA in 1985.<sup>(45)</sup> The mortality rate for South African Blacks was only 17 per 100 000. Our study population consisted mainly of Whites, Coloureds and Asians, with only one Black subject. It could be argued that the prevalence of CAD in our study group might be higher than in the USA, leading to the possibility that the pre-test probability might even be higher than that calculated using the American data.

The purpose of this study was to evaluate the longer term prognostic value of a normal Tc-99m MIBI SPECT myocardial perfusion study. We did not evaluate patients with abnormal studies and therefore cannot comment on the sensitivity of the test in our laboratory.

## CONCLUSION

In our study, with a mean follow-up period of 4 years, a benign outcome was found in 209 patients with a normal Tc-99m MIBI exercise-rest SPECT study, including those with angiographically proven significant coronary artery disease or prior coronary revascularisation. Our data indicates that Tc-99m MIBI is comparable to Tl-201 in this respect.

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