Prognostic significance of transient myocardial ischaemia after first acute myocardial infarction: five year follow up study

Hans Mickley, Jens R Nielsen, Jens Berning, Anders Junker, Mogens Møller

Abstract

Objective—To assess the five year prognostic significance of transient myocardial ischaemia on ambulatory monitoring after a first acute myocardial infarction, and to compare the diagnostic and long term prognostic value of ambulatory ST segment monitoring, maximal exercise testing, and echocardiography in patients with documented ischaemic heart disease.

Design—Prospective study.

Setting—Cardiology department of a teaching hospital.

Patients—123 consecutive men aged under 70 who were able to perform predischARGE maximal exercise testing.

Interventions—Echocardiography two days before discharge (left ventricular ejection fraction), maximal bicycle ergometric testing one day before discharge (ST segment depression, angina, blood pressure, heart rate), and ambulatory ST segment monitoring (transient myocardial ischaemia) started at hospital discharge a mean of 11 (SD 5) days after infarction.

Main outcome measures—Relation of ambulatory ST segment depression, exercise test variables, and left ventricular ejection fraction to subsequent objective (cardiac death or myocardial infarction) or subjective (need for coronary revascularisation) events.

Results—23 of the 123 patients had episodes of transient ST segment depression, of which 98% were silent. Over a mean of 5 (range 4 to 6) years of follow up, patients with ambulatory ischaemia were no more likely to have objective end points than patients without ischaemic episodes. If, however, subjective events were included an association between transient ST segment depression and an adverse long term outcome was found (Kaplan-Meier analysis; $P = 0.004$). The presence of exercise induced angina identified a similar proportion of patients with a poor prognosis (Kaplan-Meier analysis; $P < 0.004$). Both exertional angina and ambulatory ST segment depression had high specificity but poor sensitivity. The presence of exercise induced ST segment depression was of no value in predicting combined cardiac events. Indeed, patients without exertional ST segment depression were at increased risk of future objective end points (Kaplan-Meier analysis; $P < 0.0045$). These findings may be explained in part

by a higher prevalence of left ventricular dysfunction in patients without ischaemic changes in the exercise electrocardiogram ($P < 0.05$).

Conclusion—There seem to be limited reasons to perform ambulatory ST segment monitoring in survivors of a first myocardial infarction who can perform exercise tests before discharge. Patients at high risk of future myocardial infarction or death from cardiac causes are not identified. Ambulatory monitoring and exertional angina distinguish a small subset of patients who will develop severe angina pectoris demanding coronary revascularisation during follow up. Patients without exercise induced ST segment depression comprise a high risk subgroup in terms of subsequent objective end points. The role of ambulatory ST segment monitoring performed in unselected patients immediately after infarction when risk is maximal remains to be clarified.

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Keywords: transient myocardial ischaemia; acute myocardial infarction; prognosis

ST segment depression on ambulatory monitoring after acute myocardial infarction is associated with an adverse short and medium term prognosis.¹⁻⁸ There is, however, considerable disagreement about how the prognostic information is expressed in terms of cardiac events. The reasons for the inconsistent findings are likely to be multifactorial, reflecting differences in selection criteria, sample size, timing of ambulatory monitoring, and, probably most important, choice of end points.⁹⁻¹⁰ Some authors have included subjective (soft) end points such as unstable angina or the need for revascularisation, whereas others have assessed objective (hard) end points such as cardiac death and non-fatal myocardial infarction together or separately.

To our knowledge, this is the first study to assess the long term (five year) prognostic significance of ambulatory ST segment depression in survivors of a first acute myocardial infarction who can perform exercise testing. The association between ambulatory ischaemia, exercise test results, left ventricular ejection fraction, and subsequent cardiac events were also assessed. We have reported the data at one year follow up.¹¹

Department of
Cardiology, Odense
University Hospital,
Odense, Denmark
H Mickley
J R Nielsen
J Berning
A Junker
M Møller

Correspondence to:
Dr H Mickley, Department
of Cardiology, Odense
University Hospital, 5000
Odense C, Denmark.

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Patients and methods

Patients were enrolled in the study between October 1987 and October 1989 while admitted to this coronary care unit. Only men under 70 who had had a first myocardial infarction were included. Reasons for exclusion were previous (before enrolment) myocardial infarction, chest pain lasting more than 24 hours before admission, former coronary bypass surgery or angioplasty, QRS duration >0.12 s, second or third degree atrioventricular block, persistent ST segment depression >1 mm in a resting electrocardiogram, atrial fibrillation, severe valvar heart disease, insulin dependent diabetes mellitus, severe life threatening disease, and orthopaedic disorders likely to preclude the performance of an adequate exercise test. In patients with severe heart failure or life threatening arrhythmias exercise testing was postponed until optimal medical treatment had been instituted. If patients had angina after the infarction during their stay in hospital they were treated with antianginal drugs to eliminate symptoms. If the symptoms were not relieved the patients were referred for coronary angiography before discharge. Such patients were considered to be not eligible for inclusion in the study. The study was approved by the ethics committee at the hospital. Figure 1 shows the selection of patients. Of the 123 patients in the study, 60 had an anterior infarct and 80 a Q wave infarct. The patients had a mean age of 55 (8), and 35 received thrombolytic treatment. Thirteen patients were discharged taking calcium antagonists, 11 β blockers, and 11 long acting nitrates. Twenty five patients took at least one anti-ischaemic drug. Patients' characteristics have been described in detail.¹¹

Figure 1 Flow chart showing selection of male patients with a first acute myocardial infarction.

AMBULATORY MONITORING

Thirty six hours of Holter ST segment monitoring was started at hospital discharge. We used a calibrated amplitude modulated, two channel tape recorder (Tracker Reynolds, UK) with a frequency response from 0.05 Hz to 100 Hz. The bipolar leads were placed with the electrodes in the positions of maximal ST segment depression on predischARGE exercise testing. If no significant ST segment depression was detected on exercise, leads like V3 (B2) and V5 (C3) were used.¹² Special care was taken to avoid leads with pathological Q waves if possible. At the beginning of each monitoring an electrocardiogram (50 mm/s) was recorded while the patient was standing, sitting, and lying on the left and right sides to see whether significant ST segment depression developed in these positions. All tapes were analysed visually at 60 times real time (Pathfinder II analyser, Reynolds), and separate trend curves of changes in ST segment and heart rate (ST segment module, Reynolds), were obtained at a paper speed of 6 cm/hour. An episode of significant ST segment depression was defined as horizontal or downsloping ST segment depression of 1 mm or more measured 80 ms after the J point. One episode lasted one minute or more and two episodes were separated by two or more minutes of the ST segment at baseline values. During Holter monitoring patients were encouraged to engage in normal daily activities, to keep a detailed diary outlining any episode of chest pain, and to activate the event button on the tape recorder when they experienced angina pectoris.

ECHOCARDIOGRAPHY

Patients were studied by cross sectional echocardiography two days before hospital discharge. All examinations were performed by the same investigator (JRN), who recorded the examinations on videotapes. Global left ventricular function was measured by a cardiologist from another hospital (JB Rigshospitalet, Copenhagen), who was unaware of other patient data. His calculation of left ventricular ejection fraction was based on the wall motion index using a nine segment model.¹¹ Left ventricular dysfunction was defined as an ejection fraction less than 40%. Results of echocardiography were not known to the investigators, who instigated exercise testing, Holter monitoring, and patient follow up.

EXERCISE TESTING

The day before discharge all patients performed a maximal symptom limited bicycle exercise test with six standard limb and 12 precordial leads. The initial workload was adjusted according to age, with stepwise increments of the initial workload every third minute until exhaustion or the development of severe chest pain, severe ventricular arrhythmia, or a sustained significant decrease in systolic blood pressure (>20 mm Hg). The size of the ST segment depression was not used as an end point. The test was considered

to be positive for myocardial ischaemia if horizontal or downsloping ST segment depression of 1 mm or more was measured 80 ms after the J point when compared with the baseline electrocardiogram. Blood pressures and electrocardiograms were recorded before exercise, at the end of each three minute exercise stage, at peak exercise, and at intervals during recovery.¹¹ The haemodynamic exercise test response was considered to be reduced if the increase in double product was $<1.5 \text{ mm Hg} \times \text{beats/minute} \times 10^3$.

FOLLOW UP

Patients were seen in our clinic six weeks, three months, six months, one year, two years, and three years after myocardial infarction. Patients were not followed up regularly after three years. Patients were encouraged to contact us if their cardiac symptoms became worse. Antianginal drugs were given in response to symptoms, and the presence of ST segment depression on the exercise test or ambulatory monitoring was not an indication for anti-ischaemic treatment. During follow up coronary angiography was reserved for patients with angina refractory to medical treatment. The cardiologist who had to decide if coronary angiography was indicated did not know whether significant ST segment depression was present during predischARGE exercise testing or Holter monitoring.

At follow up in October 1993 information about hospital admissions and mortality beyond three years were obtained from our central register. If a patient had died outside hospital the cause of death was sought from his general practitioner. Objective events recorded were recurrent non-fatal acute myocardial infarction and cardiac death, including aborted sudden cardiac death. Subjective events were defined as the need for coronary bypass surgery or angioplasty. Deaths of non-cardiac origin were also noted. In patients who underwent revascularisation procedures the results of coronary angiography was recorded.

STATISTICAL ANALYSIS

Kaplan-Meier cumulative survival curves

were constructed with objective end points and a combination of objective and subjective end points. Potential differences between survival curves were analysed with the log rank test. Patients who underwent revascularisation as a first cardiac event were considered at risk of objective end points until revascularisation had been performed. All averaged data are expressed as means (SD). Two groups were compared by *t* test or Mann-Whitney U test. Rates were compared by the χ^2 test with Yates's correction. When low expected values were found, we used Fisher's exact test. Significance was taken as $P < 0.05$.

Results

AMBULATORY MONITORING

Holter ST segment monitoring was started 11 (5) days after myocardial infarction. Twenty three patients had a total of 123 ischaemic episodes, 121 (98%) of which were silent.¹¹

ECHOCARDIOGRAPHY

No difference was found in left ventricular ejection fraction between patients with (49% (13%)) and without (48% (12%)) transient ST segment depression.¹¹ Twenty two patients had an ejection fraction of less than 40%.

EXERCISE TESTING

Sixty six patients had exercise induced ST segment depression, and 19 were shown to have exertional angina. A double product of $<1.5 \text{ mm Hg} \times \text{beats/minute} \times 10^3$ was found in 14 patients.

In table 1 patients are categorised according to whether they had exertional ST segment depression. Patients with ST segment depression had a higher prevalence of other ischaemic variables and a reduced systolic blood pressure response. Left ventricular dysfunction, however, was more prevalent in patients without exertional ST segment depression.

EVENTS RECORDED DURING FIVE YEAR FOLLOW UP

No patient was lost to follow up. At five years (range 4–6) 14 patients had died; 12 deaths were cardiac in origin. Two patients died from cancer four years and five weeks and four years and 10 months after their first infarction. Two of the 12 cardiac deaths were aborted sudden cardiac death. The patients were admitted with cardiac arrest (ventricular fibrillation) 3 weeks and two months after myocardial infarction, but in both resuscitation was successful. Twelve patients had recurrent non-fatal infarction. In 14 patients coronary revascularisation was performed as a first event. Preoperative angiographic findings are shown in table 2. None of the patients had left main lesions and the proportion of patients with three vessel disease was similar in those with and without ambulatory ischaemia. Average left ventricular ejection fraction was close to normal. Another nine patients underwent revascularisation after having suffered an objective end point. These

Table 1 Relation of exercise induced ST segment depression to other stress test variables, ambulatory ischaemia, and left ventricular ejection fraction. Values are means (SD) unless stated otherwise

	<i>ST depression present on exertion</i>		
	<i>Yes (n = 66)</i>	<i>No (n = 57)</i>	<i>P value</i>
<i>Exercise testing</i>			
No (%) of patients with angina pectoris (n = 19)	17 (26)	2 (4)	<0.001
Increase in:			
Systolic pressure (mm Hg)	48 (23)	59 (22)	<0.01
Heart rate (beats/min)	74 (18)	72 (20)	NS
Double product (mm Hg × beats/min × 10 ³)	3.7 (2.2)	4.5 (2.4)	NS
Maximal work capacity (W)	147 (36)	153 (41)	NS
<i>Ambulatory monitoring</i>			
No (%) of patients with transient ST depression (n = 23)	19 (29)	4 (7)	<0.004
<i>Echocardiography</i>			
LVEF (%)*	50 (9)	46 (14)	0.10
No (%) of patients with LVEF <40% (n = 22)	7 (11)	15 (26)	<0.05

*LVEF, left ventricular ejection fraction.

Table 2 Results of coronary angiography in 14 patients who underwent coronary revascularisation as first cardiac event

	Transient ST depression present on ambulatory monitoring	
	Yes (n = 10)	No (n = 4)
Mean (SD) ventricular ejection fraction (%)	56 (11)	58 (2)
No of patients with vessel disease affecting:		
3 vessels (> 50% diameter stenosis)	4	2
1–2 vessels (> 50% stenosis)	6	2

Table 3 Relation between ambulatory ST segment depression, exercise test variables, left ventricular ejection fraction, and cardiac end points. Values are numbers (percentages) of patients unless stated otherwise

	Objective end points (n = 24)	Subjective end points (n = 14)	No end points (n = 85)
<i>Ambulatory monitoring</i>			
Transient ST depression (n = 23)	3 (12)	10 (71)	10 (12)
<i>Exercise testing</i>			
Angina pectoris (n = 19)	2 (8)	9 (64)	8 (9)
ST depression on exertion (n = 66)	7 (29)	13 (93)	46 (54)
Mean (SD) increase in:			
Systolic pressure (mm Hg)	55 (22)	40 (29)	55 (22)
Heart rate (beats/min)	73 (20)	76 (11)	73 (20)
Double product (mm Hg × beats/min × 10 ³)	4.2 (2.4)	3.2 (2.5)	4.2 (2.3)
Reduced double product (n = 14)	3 (12)	3 (21)	8 (9)
Mean (SD) maximal workload (W)	150 (40)	147 (25)	150 (40)
<i>Echocardiography</i>			
Mean (SD) LVEF (%)	44 (15)	47 (9)	49 (11)
LVEF <40% (n = 22)	8 (33)	2 (14)	12 (14)

*LVEF, left ventricular ejection fraction.

nine revascularisation procedures were excluded from all statistical analysis.

RELATION BETWEEN NON-INVASIVE TEST RESULTS AND END POINTS
Table 3 shows the association between cardiac end points, ambulatory ischaemia, exercise test variables, and left ventricular function. The prevalence of exercise induced ST segment depression in patients without future cardiac end points was about twice as high as the prevalence found in patients having objective end points. The characteristics of other exercise test variables in these two subgroups were similar. Generally, patients with objective events had low left ventricular ejection fractions. The highest prevalence of ambulatory and exercise induced ischaemia was observed in the subset of patients who subsequently had revascularisation performed. These patients also were characterised by having the poorest increase in

systolic blood pressure. Test results considering exertional angina and ambulatory ST segment depression were concordant in 95 patients.

SURVIVAL ANALYSIS
Figure 2 shows cumulative event free survival for the study group in terms of cardiac death or non-fatal reinfarction (objective end points) and cardiac death, non-fatal reinfarction, and revascularisation (objective and subjective end points).

Ambulatory monitoring
The presence of transient ischaemia did not help to identify a subgroup more likely to have an objective end point during follow up. When, however, combined events were considered, episodes of transient ST segment depression identified a small group of patients at increased risk. None of the four patients with ambulatory ischaemia but without exertional ST segment depression had an objective end point. One of them, however, underwent coronary revascularisation four years after the index infarction.

Exercise testing
The prognostic importance of exertional angina was similar to that of ambulatory ST segment depression. Exercise induced ST segment depression was of no use in identifying patients who were more likely to have a combined end point. Indeed, the lack of significant exertional ST segment changes was associated with an increased risk of objective events during follow up. The prognostic information from the double product was limited.

Echocardiography
Patients with a left ventricular ejection fraction less than 40% were at increased risk of subsequent objective events. We could not identify a subgroup that was more likely to have combined end points.

SENSITIVITY AND SPECIFICITY OF NON-INVASIVE MEASUREMENTS IN RELATION TO END POINTS
Table 4 shows the prognostic sensitivity and specificity of non-invasive test results. ST segment depression on exercise testing was more sensitive but less specific than exertional angina or ambulatory ST segment depression.

Table 4 Sensitivity and specificity of ambulatory ST segment monitoring, exercise testing, and echocardiography in predicting (a) subjective and objective end points and (b) objective end points during five year follow up

	Subjective and objective end points (n = 38)		Objective end points (n = 24)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
<i>Ambulatory monitoring</i>				
Transient ST depression (n = 23)	34	88	13	80
<i>Exercise testing</i>				
Angina pectoris (n = 19)	29	91	8	83
ST depression on exertion (n = 66)	53	46	29	40
Reduced double product (n = 14)	16	91	12	89
<i>Echocardiography</i>				
LVEF <40% (n = 22)	26	86	33	86

LVEF, left ventricular ejection fraction.

Figure 2 Cumulative objective (acute myocardial infarction and cardiac death) and combined (acute myocardial infarction, cardiac death, need for revascularisation) event free survival over a mean of five years of follow up in 23 patients with and 100 patients without transient ST segment depression on ambulatory monitoring after a first acute myocardial infarction. ECG, electrocardiography; LVEF, left ventricular ejection fraction.

Discussion

To our knowledge, this is the first study to assess the long term prognostic significance of transient ST segment depression detected on ambulatory monitoring early after a first acute myocardial infarction. The strength of the

study is the close timing of echocardiography, maximal exercise testing, and ambulatory monitoring. By use of this design the relative diagnostic and prognostic value of the three non-invasive methods can be reliably compared.

Our results clearly indicate that the presence of ambulatory ST segment depression does not help to identify a subgroup more likely to have objective events during a five year follow up period. If, however, subjective end points were included, a significant association between ambulatory ischaemia and an adverse prognosis could be shown. The development of exercise induced angina identified a comparable proportion of patients with a similar outcome. Both ambulatory ST segment depression and exertional angina have high specificity but are limited by poor sensitivity. The presence of exercise induced ST segment depression was of no value in predicting combined events. In fact, patients without ST segment depression on exertion were at increased risk of future objective end points. In accordance with previous studies, left ventricular dysfunction was predictive of objective end points.

The main message of our study is controversial: ST segment depression on Holter monitoring or exercise testing is of no use in predicting reinfarction or cardiac mortality during five years of follow up after a first infarction. Ambulatory ST segment monitoring in survivors of myocardial infarction who can perform exercise testing, however, typically identifies a subgroup of patients who present with ST segment depression on exertion.¹¹⁻¹³ Over the past 15 years several studies have assessed the value of exercise testing in postinfarction risk stratification. Despite the numerous reports available, only a few authors have found exertional ST segment depression to be predictive of future cardiac death, non-fatal reinfarction, or both.¹⁴⁻¹⁶ Indeed, most studies have shown an inability of ST segment depression to predict coronary events after myocardial infarction.¹⁷⁻²³ Furthermore, the results of a recent multicentre study of more than 900 patients have questioned the utility of both ambulatory and exertional ST segment depression in risk stratification after an acute coronary event.²⁴ Also the latest European guidelines for cardiac exercise testing emphasise the dubious prognostic value of ST segment depression after infarction.²⁵

With our current understanding of the processes leading to acute coronary catastrophes, why should patients with inducible ST segment depression after myocardial infarction be at increased risk of future cardiac death or reinfarction? We used to believe that clinically significant stenoses (>50–70%) were the sites of fast progression to severe obstruction with resulting acute infarction or death. Now we know that acute clinical events commonly arise from lesions that are initially of mild or moderate severity (<50%) but then suddenly undergo a disruptive transformation into severely obstructive culprit lesions.²⁶⁻²⁹ Although a given severe stenosis is more likely to progress or become totally occluded than a given mild or moderate lesion, objective cardiac events are more frequently precipitated by lesions of the mild or moderate type simply because these are much more numerous.³⁰

Conversely, total obstruction of a high degree coronary artery lesion often occurs without symptoms or evidence of infarction.³¹ Fixed significant coronary stenoses do not develop overnight, but are—unlike mild to moderate lesions—likely to result in ST segment depression during Holter monitoring or exercise stress testing. Given these facts, the prognostic implications of ST segment depression found in our study may simply confirm what from a theoretical point of view is to be expected.

Patients who had revascularisation procedures performed during follow up might have been at high risk of subsequent reinfarction or cardiac death, or both, if they had been treated conservatively. In our study, however, the presence of ST segment depression did not influence the decision to perform coronary angiography. The data in table 2 are based on a small number of patients. There is, however, little evidence to suggest that patients receiving revascularisation comprise a special high risk group according to future objective end points. We and others have found that the prognosis after myocardial infarction is closely related to left ventricular function. Furthermore, we found no association between the presence of ambulatory or exertional ST segment depression and left ventricular dysfunction. Indeed, patients without electrocardiographic evidence of exercise induced ischaemia were characterised by having a significantly higher prevalence of left ventricular dysfunction than patients who had ischaemic changes (table 1). These findings may help to explain why patients without exercise induced ST segment depression were found to be a subgroup at higher risk of future objective end points. Patients who have had a myocardial infarction with or without left ventricular dysfunction seem to have a relative low prevalence of ambulatory ischaemia.³²⁻³⁴ The reduced sensitivity of ST segment depression in detecting myocardial ischaemia in these patients may be due in part to the development of Q waves and a diminished R wave voltage after infarction.³⁵⁻³⁷

In patients who have been selected because they have poor left ventricular function or ventricular arrhythmias after infarction, the presence of transient ST segment changes may be associated with death at one year.¹ Also, in survivors of a first infarction who have been deemed unable to perform predischARGE exercise testing, ambulatory ST segment monitoring has been useful in identifying patients at increased risk of reinfarction or cardiac death during a two year follow up period.⁵

LIMITATIONS OF STUDY

We studied a small number of patients, who were a low risk group (youngish men with a first infarction who could perform predischARGE exercise tests). As a result our study is limited by relatively few end points. This problem, however, is to some extent overcome by the prolonged follow up period. We may also be criticised for not calculating

statistical power when we decided on the size of the sample population when designing the study.

SUMMARY AND CONCLUSIONS

Our results do not indicate that ambulatory ST segment monitoring should be routinely performed in male patients who can perform pre-discharge maximal exercise testing after a first acute myocardial infarction. The presence of transient ischaemia does not predict cardiac death or reinfarction during a five year follow up period. A subgroup of patients who are more likely to need coronary revascularization can be identified, but this information is already available from the development of angina during exercise testing before discharge. The precise role of ambulatory ST segment monitoring performed in unselected patients immediately after infarction at the time of maximum risk remains to be clarified.

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