Diagnostic procedures for myocardial ischaemia

S. O. Gottlieb

From the Midatlantic Cardiovascular Associates, Baltimore, Maryland, U.S.A.

It is important to detect the problem of ischaemic heart disease at a manageable stage at which treatments could have beneficial effects. A positive exercise test in patients with known ischaemic heart disease is a risk factor for cardiac mortality and there is a need to devise treatment strategies that take into account different approaches to higher- and lower-risk patients with ischaemic heart disease. In patients with stable angina pectoris, ST-segment depression on continuous ambulatory ECG monitoring is a reliable method of assessing ischaemic events in patients going about their normal daily activities. However, at the present time both of these assessment methods should only be considered for screening individuals already suspected of being at high risk of cardiovascular morbidity and mortality.

Key Words: Ischaemic heart disease, exercise testing, continuous ambulatory ECG monitoring.

Introduction

The aim of this paper is to focus specifically on discussion of the methods used to detect myocardial ischaemia in the context of the total ischaemic burden, rather than to provide an exhaustive overview of all the possible methods that can be used to detect ischaemia. One of the main problems in this field faced by physicians is that when angina pectoris, the clinical manifestation of ischaemic heart disease, is detected, the extent of the problem is already quite advanced. It is important to find methods to detect the problem at a more manageable level where treatments, either behavioural, surgical or pharmacological, could have beneficial effects.

Abnormal exercise tests as a guide to risk

Exercise testing remains the principal method for screening and for detection of patients with active ischaemic heart disease and is an established procedure for assessing cardiac performance in patients with known or suspected heart disease. An abnormal exercise test (an abnormal ST-segment response on the exercise ECG) has indicated a significant increase in risk for cardiac events in several different studies from around the world, including U.S. Air Force recruits, Italian factory workers, study cohorts from the Multiple Risk Factor Intervention Trial (MRFIT) and the Lipid Research Clinics (LRC) study (Table 1). These latter two studies were larger in number, used cardiac mortality as their endpoint, recruited individuals with a significantly positive ST-segment response to exercise and a reasonable pre-test probability of disease and resulted in approximately a 3-5- to 6-times increased risk for cardiac mortality.

In relation to these diagnostic methods it is important to consider not just the presence or absence of a positive exercise test, but also the degree of positivity of the results. For instance, in the LRC cohort placebo group, a strongly positive, or early positive, treadmill test resulted in a significantly increased risk of coronary events. An intermediate level of risk was associated with a weakly positive result and a low level of risk with a negative exercise test (Fig. 1). A positive test remained a statistically significant predictor for death due to ischaemic heart disease in this study, even after adjustment for other risk factors, of which low-density lipoprotein cholesterol and smoking history were the most important. The estimated relative risk associated with a positive exercise ECG changed very little compared with the unadjusted estimates. A positive test was associated with 5-7- and 4-9-fold increases in death from ischaemic heart disease in the placebo and active lipid-lowering treatment (cholestyramine) groups, respectively. If a man had a strongly positive test, the relative risk for death from ischaemic heart disease was markedly increased, by a factor of 10-3 in the placebo group and 6-3 in the active treatment group. In addition, it was found that cardiac death occurred very early during the follow-up period in men with a strongly positive exercise test. However, in contrast to death due to ischaemic heart disease, neither a weakly nor strongly positive exercise test was predictive of non-fatal myocardial infarction (MI). This was in agreement with the MRFIT study, which reported a...
Table 1  Abnormal exercise tests and relative risk of coronary events in asymptomatic subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Air Force recruits (1976)</td>
<td>1390</td>
<td>6.3 years</td>
<td>14.3</td>
</tr>
<tr>
<td>Italian factory workers (1983)</td>
<td>514</td>
<td>6.0 years</td>
<td>5.5</td>
</tr>
<tr>
<td>MRFIT cohort (1986)</td>
<td>12,422</td>
<td>7.0 years</td>
<td>3.4*</td>
</tr>
<tr>
<td>LRC cohort (1986)</td>
<td>3,600</td>
<td>8.1 years</td>
<td>4.3-5.8†</td>
</tr>
</tbody>
</table>

*CAD mortality; †CAD mortality, normo-, hyperlipidaemics.

CAD = coronary artery disease; LRC = Lipid Research Clinics; MRFIT = Multiple Risk Factor Intervention Trial.

The concept of weakly or strongly positive exercise tests in relation to differences in treatment and prognosis has also been demonstrated to be very important in the European Coronary Surgery Study (ECSS). This study investigated survival rates among 767 men with mild or moderate angina pectoris, ≥50% stenosis in at least two major coronary arteries and good left ventricular function 10-12 years after they were randomly assigned to either early coronary bypass surgery or medical therapy. The benefit of surgical treatment was greatest for patients with markedly positive exercise tests as compared with those who had normal or less markedly positive tests (Fig. 2).

Improvements on the exercise test

In patients with angina or previous MI, the positive but painless exercise test can often stand alone as a true marker of silent ischaemia but this is not necessarily true in asymptomatic populations. In such patients, exercise tests are usually combined with other procedures in order to increase the sensitivity and specificity of the test for the detection of occult CAD. This is necessary because of the frequency of false-positive test responses, a function of Bayes' theorem which states that test results cannot be adequately interpreted without knowing the prevalence of the disease in the population under study.

It is not always possible to perform exercise testing as peripheral vascular disease, or other problems, may prevent some individuals from performing treadmill or bicycle tests. The thallium-201 scintigram provides a non-invasive method for evaluating myocardial perfusion. It can be used in conjunction with pharmacological stress tests to detect ischaemic heart disease through perfusion defects and to obtain prognostic information in such patients. For instance, the presence of dipyridamole-induced thallium scan defect is highly correlated with cardiac events. It is interesting to note that in a patient with a significant coronary stenosis, the coronary flow at rest can be relatively normal in the area that is supplied by the occluded vessel (Fig. 3a). However, when dipyridamole causes vasodilatation of the vascular bed, a type of coronary steal is produced, a significant shift of blood away from the zone supplied by
the occluded vessel occurs and the area shows up as a perfusion defect on the thallium scan (Fig. 3b).

The relationship between exercise tests and continuous ambulatory ECG monitoring

Along with the exercise test the continuous ambulatory ECG (or Holter) monitor has become closely identified with the quantification of total and silent myocardial ischaemia. Indeed, continuous monitoring is the best way of detecting transient myocardial ischaemia in daily life and the validity of this approach has been widely confirmed\(^\text{[10]}\). A consensus has now emerged on what constitutes an ischaemic episode on continuous monitoring, i.e. ST-segment depression of at least 1.0 mm (0.1 mV) lasting for 1 min and separated from other episodes by at least 1 min, otherwise known as the ‘\(1 \times 1 \times 1\)’ rule\(^\text{[11]}\). It is also now apparent that 48-h periods of continuous monitoring are more appropriate than 24-h periods\(^\text{[10]}\). One of the most important studies that correlated ECG and physiological markers of myocardial ischaemia during exercise, cold pressor tests and during continuous monitoring was carried out by Deanfield and coworkers in 1984\(^\text{[12]}\). Positron emission tomography was used to look at the relatively normal perfusion of the left ventricle in the control setting and indicated that there was a significant perfusion defect during exercise, which was reproduced during cold pressor tests. In addition, spontaneous or unprovoked episodes of ST-segment depression were monitored. This study provided important validation that in patients with typical chronic stable angina pectoris, CAD and a positive exercise test, the easily recorded sign of ST-segment depression is a reliable marker of important ischaemic events in the myocardium that may be used to assess the activity of myocardial ischaemia when such patients are going about their normal daily activities.

Mulcahy and coworkers\(^\text{[13]}\) examined the relationship between exercise test results and continuous monitoring with the aim of finding out how the frequency of silent ischaemic episodes is related to the level of symptoms in a group of 114 patients with confirmed CAD and varying degrees of angina who were receiving anti-ischaemic therapy. A majority of the patients (66-5\%) did not have any ischaemic episodes on 48-h continuous monitoring, 24% had up to two episodes per day, only 6% had between two and five episodes per day and only 3.5\% had five or more episodes per day. The presence of silent ischaemia during continuous monitoring was significantly related to a positive exercise test \((P<0.01)\) but the study also suggested that, in patients with a negative exercise test, it is not worthwhile performing continuous monitoring in order to detect active ischaemia in daily life (Fig. 4). In addition, the amount of measured ST-segment change in the patients with poorly controlled angina was about the same as in those who were well controlled, indicating that angina may be a rather insensitive marker of ischaemic heart disease (Fig. 4).

An interesting correlation between continuous monitoring and the exercise treadmill test has been

\[\text{Figure 2 Ten-year cumulative survival rates and 95\% confidence intervals for the surgically treated (Sur) and medically treated (Med) groups, stratified according to cardiovascular response to exercise graded by ST-segment depression, maximal heart rate and maximal workload. 'A' denotes a normal or slightly positive test result, 'B' a positive test result and 'C' a markedly positive test result. 'n' denotes number of patients and '%S' percentage surviving. (Reproduced with permission from Varnauskas et al.\(^\text{[17]}\).)\]
shown by Campbell et al.\textsuperscript{[14]} in patients with a positive stress test and established CAD. The patients, stratified according to their time to ST-segment depression during exercise, underwent continuous monitoring and were then followed up. Relatively few of the patients developed active ischaemia after 6 min on the treadmill and if they only became positive at a high workload then their continuous monitoring was also less likely to be positive. The converse was true for patients who were positive early on in the treadmill test. However, there were prognostic differences between patients with positive treadmill tests. For instance, some patients who were positive within 2 and 3 min on the treadmill had no ischaemic episodes on continuous monitoring but there were also patients with the same positive treadmill test responses who had multiple long duration ischaemic episodes on continuous monitoring. This suggests that patients with CAD who have an early positive exercise treadmill test are a diverse group. Within the group there may be differences in behaviour, stability of the coronary disease, likelihood of plaque rupture or having vasoconstriction and additional spontaneous ischaemic events. This means that it is important to refine the notion of what a positive exercise test is and which patients within that population are at risk of developing cardiac events.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Coronary flow in a patient at rest (a) and coronary steal in a patient with coronary artery disease after i.v. dipyridamole infusion (b).}
\end{figure}
The relationship between the mean frequency of silent ischaemic episodes and a positive or negative exercise test in patients with confirmed coronary artery disease and varying degrees of angina. Group 1 consisted of patients with poorly controlled angina, despite adequate anti-anginal therapy, who were referred for coronary artery bypass grafting and group 2 consisted of patients whose angina was well controlled on standard anti-anginal treatment. ETT = exercise treadmill test. (Reproduced with permission from Mulcahy et al. 

The use of continuous ambulatory ECG monitoring for screening of high-risk patients

Two-year follow-up of 70 patients with unstable angina revealed that silent ischaemia on continuous monitoring is significantly associated with an increased risk of death or recurrent infarction\(^1\)\(^5\) (Table 2). There was a five-fold relative risk for outcomes associated with silent ischaemia and a three-fold relative risk associated with chest pain during the initial 2 days. When both variables were present, the relative risk for experiencing an adverse outcome was increased by a factor of 15 (Fig. 5). The study suggested that the prognostic information provided by continuous monitoring for ischaemic ST-segment changes should be incorporated into clinical management of patients with unstable angina.

The possible use of continuous monitoring as a screening method is controversial but the 'Men born in 1914' study from Malmö in Sweden\(^6\)\(^1\)\(^6\)\(^1\) has indicated that it may be a reasonable, relatively low-cost option for detecting high-risk elderly patients. ST-segment analysis was carried out on 24-h continuous monitoring recordings from 394 men in a randomized sample of all men resident in Malmö in 1982 who were born in 1914. The incidence of ischaemic heart disease deaths and non-fatal MI, during 3 years of follow-up, in men without ST-segment depression and without a history of coronary disease, was 2.3%. In contrast, men with ST-segment depression had a 4.4-times higher relative risk \((P=0.005)\) and, in men with both ST-segment depression

### Table 2  Two-year adverse clinical outcomes for unstable angina patients with and without silent ST-segment changes on initial 48-h continuous ambulatory ECG monitoring. (Reproduced with permission from Gottlieb et al.\(^1\)^\(^5\)\(^1\)

<table>
<thead>
<tr>
<th>Adverse clinical outcome</th>
<th>Group I Silent ischaemia ((n=37)) (%)</th>
<th>Group II No silent ischaemia ((n=33)) (%)</th>
<th>(P) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>2 (27)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>8 (30)</td>
<td>1 (3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CABG or PTCA for symptoms</td>
<td>11 (30)</td>
<td>5 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>21 (57)</td>
<td>6 (18)</td>
<td></td>
</tr>
</tbody>
</table>

*Derived from Kaplan–Meier analysis. Breslow test.
CABG = coronary bypass surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

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Figure 4  The relationship between the mean frequency of silent ischaemic episodes and a positive or negative exercise test in patients with confirmed coronary artery disease and varying degrees of angina. Group 1 consisted of patients with poorly controlled angina, despite adequate anti-anginal therapy, who were referred for coronary artery bypass grafting and group 2 consisted of patients whose angina was well controlled on standard anti-anginal treatment. ETT = exercise treadmill test. (Reproduced with permission from Mulcahy et al.)

Figure 5  Relative risk curves derived from Cox's hazard function analysis demonstrating the risk for death, myocardial infarction or revascularization for recurrent symptoms and illustrating the effects of the silent ischaemia (SI) and recurrent chest pain (CP) variables on adverse outcome. (Reproduced with permission from Gottlieb et al.\(^1\)^\(^5\))

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and a history of coronary disease, the incidence of ischaemic heart disease deaths and non-fatal MI was 160-times greater ($P=0.001$). Thus, this study showed that asymptomatic ST-segment depression is a frequent finding in elderly men and that its occurrence on ambulatory monitoring was an independent risk factor for cardiovascular mortality.

**Conclusions**

In summary, abnormal exercise test responses appear to be reliable predictors of future cardiac events and are also valuable as indicators of occult CAD. In view of the possibility of false-positive responses in an asymptomatic population, stress tests and continuous monitoring should be considered as screening procedures for CAD only in those individuals with multiple risk factors and/or family history of premature CAD.[17]

**References**


