Reliability of Holter registration in ischemic heart disease

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Abstract

Introduction   We studied the reliability of a new ST-segment analysis on a 24-hour 12-lead holter recording comparing ST-depression during exercise testing with active molsidomine and placebo drugs in a randomized, double-blind, crossover, clinical trial.

Methods and results   35 patients with proven coronary heart disease received either 4 mg regular molsidomine, 8 mg molsidomine SR (Sustained Release) or placebo tablets. Exercise tests were performed at 3 and 12 hours after drug intake. Myocardial ischemia was measured using conventional cyclo-ergometry (onset of ST-depression during exercise test on cyclo-ergometer E.C.G.) and 24 h holter monitoring (Mortara H12) also during the exercise tests.
Holter analysis was performed with locally developed software, the commercial analysis being unsatisfactory.

**Conclusion** The holter parameters (onset of ischemia, heart rate at onset of ischemia and total ischemic burden) better discriminated the active drugs from the placebo drug than conventional cyclo-ergometry. The time-to-onset of ischemia during exercise on holter was the best predictor and was better than the time-to-onset of ischemia on cyclo-ergometer E.C.G. (p<0.05). Holter recording can improve the power of clinical trials in cardiac ischemia. Ischemia at rest may prove to be an interesting endpoint to evaluate in end-stage cardiac patients, but validation of the usefulness of holter recording should be verified in further clinical trials.

**Keywords:** holter, exercise test, anti-anginal drugs, myocardial ischemia

**Introduction**

Placebo-controlled clinical trials with anti-anginal drugs are difficult to conduct in the Western world because of the proven efficacy of currently available anti-ischemic drugs and the ethical problem of exposing patients to a nonactive treatment in a life-threatening health condition. The common use of more invasive therapy, such as percutaneous transluminal coronary angioplasty (PCTA) and coronary artery bypass, restricts patient recruitment for these trials to patients with minor anginal symptoms. In these patients the golden study inclusion criterium: ‘exercise test discontinuation for typical anginal symptoms with an ST-depression of 1 mm or an ST-depression of 2 mm’ is exceptional.

ST-depression on E.C.G. is considered to be the most reliable parameter for detection of cardiac ischemia. The time to significant ST-depression during an exercise test and the total ischemic burden (ST-depression x duration) are often used as endpoints for the evaluation of the efficacy of anti-anginal drugs. However, it is not always easy to interpret the ST-segment and the results can easily be influenced by subjective factors.

More objective (investigator independent) measurements of the ST-segment are needed to demonstrate the efficacy of new drugs in a population with proven coronary artery disease.
Several studies such as the ‘CAPE Trial’ used holter recording to measure ‘silent ischemia’, e.g. transient ST-depressions with or without symptoms. However, the sensitivity/specificity of holter readings, even by trained analysts, did not contribute significantly to a higher study power and thus a reduction of study population\[5\].

In order to improve the power of a clinical trial comparing a new galenical formula of molsidomine SR to regular molsidomine, we developed a new method for the analysis of the ST-segment on holter, as the commercial analysis was unsatisfactory.

**Methods**

**Objective**

We studied the reliability of a new ST-segment analysis on a 24-hour 12-lead holter recording comparing ST-depression during exercise and at rest with active molsidomine and placebo drugs. A valid measurement of cardiac ischemia is expected to show more ST-depression during exercise than at rest and more with placebo than with active drugs.

**Holter**

In this study a 12-lead holter (Mortara H12) recording over 24 hours was used. During this 24 hour period 2 exercise tests were performed. The cyclo-ergometer E.C.G. electrodes were placed beside the holter electrodes.

The holter recording on a magnetic card was converted using Mortara's Misha.exe to an ASCII file giving for every beat the RR interval, the type of beat (supraventricular extrasystoles, ventricular extrasystoles, noise, normal) and ST-depression in the 12 leads.

With the Mortara's H-Scribe II analyser, a summary report was printed. The principle investigator chose the lead where the ST-depression was maximal, and it was designated as the 'primary lead'.

The ST-segment of the primary lead was then processed by locally developed software, eliminating beats which were considered as noise and calculating the average ST-segment value for 'valid' beats per 30 seconds. The ST-segment values per 30 seconds were related to the average ST-segment value for the total recording which was referred to as the baseline (0-value).

When the ST-segment value for a 30 seconds period was more than 4 standard deviations below
baseline, then that period was labeled as a 'significant depression'. The threshold value was chosen in function of the best ratio of 'significant depression' during exercise vs. at rest. This ratio was 100 to 1 at a threshold of 4 Standard deviations.

**Ethical**

Written informed consent was obtained from each patient and the study protocol was approved by the Ethical Committee of the AZ VUB prior to the study.

**Study Design**

In a multicentre, randomized, double blind, cross-over study we compared the effect of a molsidomine 8 mg SR tablet B.I.D. (a sustained release formulation containing 8 mg of molsidomine for twice daily intake) of Laboratoires S.M.B. Belgium to a regular molsidomine 4 mg tablet T.I.D. (Corvaton® of Therabel Pharma, Belgium) and to a placebo tablet in patients with proven coronary heart disease with discontinuation of all nitrate derivatives and molsidomine. The molsidomine 8 mg SR tablet is a new galenical formulation with extended release properties. The mean half-life of elimination for regular molsidomine was $t_{1/2} = 2.4$ hours compared to 3.5 hours for molsidomine SR.

Patients were included on basis of a positive exercise test at entry: ST-depression of more than 1 mm at 60 msec beyond the J point combined with either typical anginal symptoms or proven coronaropathy during coronarography or electrocardiographically documented previous myocardial infarction.

At randomization eligible patients discontinued all oral and topical nitrate derivatives and molsidomine and began their intake of the first study drug for two weeks (Figure 1).

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**Figure 1: Study flow chart**
At the end of this period, the patient then took the second drug for two weeks and finally the third drug for another 2 weeks. Randomization was blocked per 6 treatment packages to counteract the training effects on exercise tests. At the end of each treatment period of 2 weeks holter and exercise tests were performed simultaneously (Figure 2).

Two exercise tests were performed:
the first at 3 hours, the second at 12 hours after study drug intake.

Exercise tests at study visits with intake of study medication were performed on cyclo-ergometers, starting at 50 W with an increase of 25 W every 2 minutes. The test was stopped when signs or symptoms of coronary insufficiency occurred (anginal pain or ST-depression > 2 mm) or at the point of the patient’s exhaustion.

![Figure 2: Study visit schedule](image)

The reliability of the following test methods was evaluated: time-to-onset of significant ST-depression on cyclo-ergometer E.C.G. (cardiologist) and on holter: time-to-onset of significant ST-depression, heart rate at the start of ST-depression and total ischemic burden (duration x amplitude of significant ST-depressions).

**Analysis**

Regular molsidomine 4 mg and molsidomine 8 mg SR were expected to reduce cardiac ischemia during the first exercise test (3 hours after drug intake) contrary to the placebo. The test method which best discriminates the active drugs from the placebo was considered to be the most reliable test. The higher the difference and the lower the variance of the difference the higher the
discrimination will be. The calculated z-value for the mean difference between the active drugs and the placebo in this study can be considered as the best index for the discrimination power of the test methods. For this evaluation the results were only compared (paired cases) when both measurements had a value which was different from zero because negative exercise tests could not be interpreted for the validation of the test variables.

For the second exercise test (12 hours after drug intake) an anti-ischemic effect of regular molsidomine 4 mg was not expected. The effect of molsidomine 8 mg SR was unknown. Therefore the results of the second exercise test could not be used for the evaluation of the discrimination power of the test methods.

**Results**

**Holter analysis**

V5 was used as the primary lead for 32 patients and DII for 3 patients (holter analysis Figure 3). The standard deviation of the ST-segment for the total holter recordings of all patients ranged from 9 mV to 53 mV (average 23 mV). V1, V5 and DII each had a smaller standard deviation than the other leads.
Baseline characteristics

Twenty investigators enrolled a total of 37 patients. All patients had proven coronary heart disease. 38 % of patients previously had a myocardial infarction. In 56 % of patients clinical angina pectoris was mentioned as an active medical problem. More than half of the patients already had a coronary intervention prior to the study, i.e. either a PTCA and/or a coronary bypass operation.

Approximately half of the patients had been taking molsidomine or another nitrate therapy prior to their entry into the study.
Time to onset of significant ST-depression on cyclo-ergometer E.C.G.

A total of 107 first exercise tests could be evaluated for the onset of significant ST-depression on cyclo-ergometer E.C.G. 45 tests were negative (45 %). 32 pairs of tests (placebo-molsidomine 4 mg and placebo-molsidomine 8 mg) could be used (both results were positive) for the evaluation of the predictability of the test method.

The average duration with active drug was 342 seconds before the onset of a significant ST-depression. This was 8 seconds more than in exercise tests with placebo drug for the same patients. The standard deviation of the differences between the values with placebo and the values with active drugs was 66 seconds. The calculated z-value was 0.65. This result was not statistically significant due to the small sample size. Approximately 300 patients would have been needed to obtain a statistically significant result.

Time to onset of ST-depression on Holter

13 out of 107 (12%) holter recordings performed during the first exercise test failed due to various logistical reasons (battery failure, holter delivery, disconnection of electrodes), 16 exercise tests were negative (16 %). 78 holters were evaluable resulting in 42 pairs.

The mean duration before the onset of ischemia on holter for the first exercise test was 253 seconds with active drugs. This was 46 seconds more than with placebo drug. The standard deviation of the differences between the value with placebo and the value with active drugs was 112 seconds. The calculated z-value was 2.64 . With the actual sample size the result showed a statistically significant difference between the active drugs and placebo (p < 0.01).

Compared to the 'onset of ST-depression on cyclo-ergometer E.C.G.', the same variable on holter was statistically superior (z-value = 1.99, p < 0.05).

Heart rate on holter at the onset of ST-depression

The average heart rate on holter at the onset of ischemia was 106.7 under active medication and 103.9 under placebo. The standard deviation of the differences was 10.6 beats per minute. With 42 evaluable pairs the z-value was 1.71. To arrive at a statistically significant difference 60 pairs would have been needed.
Total ischemic burden on holter during exercise testing

The mean difference of the total ischemic burden in 42 pairs was 210 mm.sec, with a standard deviation of 933 mm.sec and a z-value of 1.46. To arrive at a statistically significant difference 80 pairs would have been needed.

**Discussion**

ST-segment analysis on holter is a valuable tool in clinical trials evaluating anti-anginal drugs. Among the different variables ‘onset to ischemia on cyclo-ergometer E.C.G.’, ‘onset to ischemia on holter’, ‘heart rate on holter at the onset of significant ST-depression ’ and ‘total ischemic burden on holter’, ‘onset to ischemia on holter’ appears to be the best test method to discriminate between the active and placebo drugs during exercise tests (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>average under placebo</th>
<th>average under active drugs</th>
<th>number of pairs</th>
<th>standard deviation of differences</th>
<th>z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>onset ST depression on cyclo-ergometer</td>
<td>334</td>
<td>342</td>
<td>32</td>
<td>66.37</td>
<td>0.65</td>
</tr>
<tr>
<td>onset ST depression on holter</td>
<td>207</td>
<td>253</td>
<td>42</td>
<td>112.10</td>
<td>2.64</td>
</tr>
<tr>
<td>HR on Holter at onset of ischemia</td>
<td>103.9</td>
<td>106.7</td>
<td>42</td>
<td>10.58</td>
<td>1.71</td>
</tr>
<tr>
<td>total ischemic burden on holter</td>
<td>-1303</td>
<td>-1093</td>
<td>42</td>
<td>933.1</td>
<td>1.46</td>
</tr>
</tbody>
</table>

**Table 1**: discrimination between active product and placebo during exercise test

This variable was significantly better (p<0.05) than the conventional test variable ‘onset to ischemia on cyclo-ergometer E.C.G.’.

There are other aspects that make the use of holter in clinical trials attractive. For instance, it is a test method which is entirely independent of subjective interpretation which is not the case for cyclo-ergometer testing.

In this study the percentage of positive cyclo-ergometer tests was 100 % at screening, where it was only 55 % with the study drugs (including placebo). This reduction was probably due to the willingness of the investigator to include patients. On holter the percentage of positive exercise tests was equal at screening (77 %) and with the study drugs (85 %).
The reliability of the ST-measurement by holter depends heavily on the cleaning of the signal and the definition of the threshold for ischemia. This study showed that the regular (commercial) ST-segment analysis was not precise enough whereas the locally developed signal analysis was much more reliable.

Holter has the potential to evaluate ischemia at rest during daily living activity. In this study ischemia on holter during exercise test was 100 times more frequent than at rest. Ischemia at rest was five times more frequent during the early morning hours contrary to the middle of the night. This is consistent with the circadian variation of ischemia described in other studies with holter recording \[5\]. Ischemia at rest may prove to be an interesting endpoint in clinical trials with end-stage cardiac patients who are treated conservatively and who are reluctant to undergo exercise testing.

An analysis of ischemic burden in function of the drug interval may give an indication of the duration of pharmacodynamic action of the tested drugs. In this type of trial the holter registration could be combined with an electronic Drug Exposure Monitor (e.g. eDEM®, Aardex).

The statistical definition of a positive ST-depression on holter took into account interindividual ST-variability due to factors such as obesity (variance of ST-segment correlated \( r = -0.42 \) with Body Mass Index), conduction velocity and placement of electrodes. This finding emphasizes that the reading of absolute ST-deviations in mm is probably biased by such factors while a statistically based holter analysis isn’t. From a logistical standpoint the holter analysis is fully automated and does not require reading by experts.

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