Heart rate variability in time and frequency domains: effects of gallopamil, nifedipine, and metoprolol compared with placebo

M W F Schweizer, J Brachmann, U Kirchner, I Walter-Sack, H Dickhaus, C Metze, W Kübler

Abstract

Objective—To assess the effects of three different antianginal drugs on heart rate, blood pressure, and heart rate variability. Design—Randomised, single blind, placebo controlled, cross over study. Setting—University hospital. Participants—Nine healthy male volunteers. Interventions—Oral administration of either 50 mg gallopamil, 20 mg nifedipine, 100 mg metoprolol, or placebo according to a random crossover plan. Main outcome measures—Time intervals between consecutive R waves in electrocardiograms measured with an accuracy of 5 ms from digital Holter recordings. Blood pressure monitored continuously by finger plethysmography. Results—Metoprolol lowered heart rate from 62(6) to 51(5) beats/min (p = 0.003) after 78(23) minutes. Nifedipine provoked reflex tachycardia from 56(5) to 94(18) beats/min (p < 0.001) at 10(3) minutes after treatment followed by an exponential decline in heart rate to baseline values with a time constant of 34(7) min in seven subjects but 83 minutes in one volunteer. One subject showed no exponential decline in heart rate. Nifedipine significantly lowered the supine mean arterial pressure from 86(6) to 67(6) mm Hg (p = 0.004) after 11(2) minutes, indicating an acute reduction in arterial resistance. Gallopamil did not significantly change mean heart rate or blood pressure. In the sitting position three hours after administration gallopamil and metoprolol significantly lowered power spectral density in the low frequency band (0-03 Hz to 0-15 Hz) compared with placebo (p < 0.05). Nifedipine did not produce such an effect. Conclusions—Gallopamil and metoprolol both inhibit cardiac sympathetic activation compared with placebo, whereas nifedipine causes reflex sympathetic activation.

Subjects and methods

The study was a randomised, placebo controlled, cross over trial and single blind for data evaluation. The experiments were carried out between July and October 1991. The study protocol was approved by the ethics committee of the Medical Faculty of the University of Heidelberg.
Table 1  Individual characteristics of nine healthy male volunteers

<table>
<thead>
<tr>
<th>Case no</th>
<th>Age (years)</th>
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<th>Weight (kg)</th>
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<td>74</td>
</tr>
<tr>
<td>9</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>29.8 (4.15)</td>
<td>179.7 (10.74)</td>
<td>75.0 (14.26)</td>
</tr>
</tbody>
</table>

with increments of 25 W every two minutes. The exercise test was discontinued when the volunteer was exhausted. During exercise every minute an electrocardiogram of 15 seconds’ duration was recorded from the chest leads V1 to V6. Every two minutes blood pressure was measured in the right arm by the Riva-Rocci method. During the next three hours the volunteer was allowed to walk around in the hospital under the surveillance of a physician. Thereafter he was discharged.

DATA ACQUISITION AND PROCESSING
The beat to beat values of heart rate were calculated from the corresponding RR intervals on the Holter electrocardiogram. The time resolution of the RR interval measurements was 5 ms. The beat to beat values of integrated mean arterial blood pressure were directly obtained from the plethysmograph and stored on an IBM compatible personal computer. Data processing was performed on this computer and the software was written in the laboratory in the programming languages Basic and C.

In the time domain the beat to beat values of heart rate and blood pressure were averaged every minute and plotted against the cumulative time. From these data the time between the baseline values before the administration of the test drug and the first peak or trough in heart rate and blood pressure after drug administration were calculated. The changes in heart rate and blood pressure were obtained by subtracting the peak values from the baseline values. Heart rate variability in the time domain was assessed by counting the number of absolute changes greater than 50 ms between consecutive RR intervals in sinus rhythm during evaluation periods of 15 minutes’ duration at baseline and one hour and three hours after drug administration.

In the frequency domain spectral analysis of 512 RR intervals was carried out from recordings during sinus rhythm according to the method of Rompelman et al. The RR intervals were first normalised by subtracting the mean RR interval and dividing each RR interval by the mean RR interval. Then the Hanning function was applied to the data. The periodogram was calculated using the discrete fast Fourier transformation. The sampling frequency was calculated from the mean RR interval. Finally, to reduce the variance of the spectral estimates the power spectra were smoothed using an averaging technique. Every discrete spectral estimate was expressed as the mean of itself and its two neighbours. The power at the frequency zero and at the next two discrete frequencies was cut off (direct current removal) and total power spectral density was obtained by integration over the remaining values. As an index of cardiac sympathetic tone the low frequency power spectral density was obtained by integration of the power spectrum between 0-03 Hz and 0-15 Hz. The high frequency power spectral density was calculated between 0-15 Hz and 0-30 Hz. Low and high frequency power spectral densities were

SUBJECTS
Nine male volunteers participated in the study after they had given written informed consent. Table 1 shows their individual characteristics. The volunteers were healthy as judged by medical history, physical examination, electrocardiographic findings, and results of routine laboratory tests of blood and urine. All volunteers had normal sinus rhythm without extra beats, and they had no history of palpitations. None of the volunteers was a smoker, a heavily active sportsman, or taking drugs short term or long term.

INTERVENTIONS
The volunteers received orally either a tablet of placebo or 50 mg gallopamil (Procourum, Minden Pharma), 100 mg metoprolol (Lopresor, Ciba Geigy), or 20 mg nifedipine (Adalat, Bayer). All drugs were given in immediate release formulations and administered according to a random cross over plan. There was a wash out phase of at least one week between the study days.

EXPERIMENTAL PROCEDURES
On the morning of each study day the volunteers were admitted to the research unit. A plastic cannula was inserted into a forearm vein as an emergency line. The digital Holter-recorder (Cardiolight, software revision 3-0; Medset, Hamburg) and a finger plethysmograph to measure blood pressure31 (2300 Finapres; Ohmeda, Madison, Wisconsin) were connected to the volunteer. The measurements started in all instances between 8 am and 9-15 am. For baseline data evaluation the volunteer rested supine for at least 15 minutes and then sat for another 15 minutes. Then the test drug was administered with 100 ml of mineral water at room temperature, and the volunteer returned to supine position. Periods of 15 minutes’ duration in the supine and sitting positions were repeated one hour and three hours after drug administration. Continuous Holter recordings and blood pressure measurements were maintained over the first four hours after drug administration. Two hours after receiving the drug the volunteer had a standardised breakfast.

Four hours after drug application a bicycle ergometry stress test was performed (Dynavit Conditronic S; Keiper, Rockenhausen, Germany). Initial performance was set to 50 W
expressed as percentages of total power spectral density.

**STATISTICAL TESTS**

Peak and trough values of heart rate and blood pressure in each volunteer were compared with baseline values with the Kruskal-Wallis test. Power spectral densities of heart rate between different time phases within one study day were compared with the Kruskal-Wallis test. Drug values were compared with placebo values with the paired t test. The term significant means an error probability p < 0.05 and the term highly significant means p < 0.001. Data are expressed as means (SD).

**PHARMACODYNAMIC CALCULATIONS**

The exponential decline in heart rate after the rise of heart rate to peak values caused by nifedipine was examined by the following method. After the baseline heart rate before drug administration was subtracted from all values the data were transformed to the natural logarithm and a regression line was drawn through the values during the decline of heart rate. From the slope of this regression line the time constant of the exponential decline in heart rate (t<sub>1/e</sub>) was calculated. During t<sub>4</sub> heart rate (expressed as the average value every minute) declines to 1/e (with e as the basis of the natural logarithms, e = 2.71828) of its initial value.

**Results**

**HEART RATE AND TIME DOMAIN HEART RATE VARIABILITY**

Table 2 shows the numerical results for heart rate in the nine volunteers.

**Gallopalom**

When baseline values in each subject were compared gallopalom had no effect on heart rate. In case 2, however, an atrioventricular block II type Mobitz occurred 45 minutes after drug application. It caused asymptomatic pauses with a duration of less than two seconds and lasted over 35 minutes. Heart rate while subjects were supine and sitting did not differ at baseline from values with placebo. After one hour supine heart rate was significantly higher (61 (5) beats/min v 58 (5) beats/min) and after three hours heart rate while sitting was significantly lower (72 (9) beats/min v 76 (10) beats/min). Heart rate variability did not significantly differ from values with placebo.

**Nifedipine**

All subjects showed a significant increase in heart rate while taking nifedipine. Two subjects (cases 1 and 5) had excessive reflex tachycardia with flushing and headache. The increase in heart rate was followed by an exponential decline to baseline values in almost all subjects. In one subject (case 2), however, the rapid increase in heart rate was followed by a rapid non-exponential decline to baseline value within four minutes. Heart rate was not significantly different at baseline from placebo values. After one hour heart rate had significantly increased in the supine position (68 (8) beats/min v 58 (5) beats/min) as well as in the sitting position (75 (7) beats/min v 66 (5) beats/min).

**Metoprolol**

It caused (supine: 137 (130) v 295 (116); sitting: 87 (80) v 162 (80)). After three hours the increase in heart rate was significant only in the supine position (69 (7) beats/min v 66 (7) beats/min) and heart rate variability did not differ from placebo values.

**Table 2 Heart rate variables after gallopalom, nifedipine, metoprolol, and placebo in nine healthy volunteers**

<table>
<thead>
<tr>
<th>Gallopalom</th>
<th>Nifedipine</th>
<th>Metoprolol</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>Baseline (beats/min)</strong></td>
<td><strong>Peak or trough (beats/min)</strong></td>
<td><strong>Time to peak RPP (mm Hg/min)</strong></td>
<td><strong>Baseline (beats/min)</strong></td>
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<tr>
<td><strong>Case</strong></td>
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*<i>p < 0.001 compared with baseline. </i><i>tp = 0.003 compared with baseline. </i><i>p = 0.05 compared with placebo. RPP = rate-pressure product at maximal heart rate during exercise. t<sub>4</sub> = Time constant of exponential decline in heart rate. ND = not determinable.</i>
Table 3  Blood pressure variables after gallopamil, nifedipine, metoprolol, and placebo in nine healthy volunteers

<table>
<thead>
<tr>
<th>Case no</th>
<th>Gallopamil Baseline (mm Hg) Peak or trough Time to peak (min)</th>
<th>Nifedipine Baseline (mm Hg) Peak or trough Time to peak (min)</th>
<th>Metoprolol Baseline (mm Hg) Peak or trough Time to peak (min)</th>
<th>Placebo Baseline (mm Hg) Peak or trough Time to peak (min)</th>
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<tr>
<td>Mean (SD) 81 (7)</td>
<td>90 (7)</td>
<td>49 (6)</td>
<td>86 (6)</td>
<td>84 (11)</td>
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</table>

ND = not determinable.

**Placebo**

There were no effects on heart rate or heart rate variability.

**BLOOD PRESSURE**

Owing to a systematic effect of posture the integrated mean arterial blood pressure in the sitting position exceeded the pressure in the supine position by a mean of 25 mm Hg. Table 3 shows the numerical results for supine blood pressure only.

**Gallopamil**

Gallopamil showed no effect on blood pressure.

**Nifedipine**

Blood pressure decreased in six subjects from 86 (6) mm Hg to 67 (6) mm Hg within 11 (2) minutes after nifedipine administration. Two subjects (cases 2 and 6), however, showed an increase. Thirteen minutes after drug administration blood pressure measurement was discontinued in one subject (case 9) because of a technical problem until 30 minutes after drug administration. At this time the volunteer had the same blood pressure as at baseline.

**Metoprolol**

Compared with placebo metoprolol caused a slight but significant decrease in blood pressure three hours after administration in the supine position (placebo: 85 (10) mm Hg; metoprolol: 79 (11) mm Hg).

**Placebo**

Placebo had no effect on blood pressure.

**SPECTRAL ANALYSIS OF HEART RATE VARIABILITY**

Table 4 shows the low frequency power spectral density at different times after drug administration as an index of cardiac sympathv tone. If there were high values of low frequency power spectral density (>80) a single peak near 0-10 Hz was usually found. If there were low values of low frequency power spectral density (<2) the main spectral power was usually found at frequencies lower than 0-03 Hz. In 89% of all measurements the high power spectral density was below 10% of total power spectral density. Because of these irrelevant values and because there were no changes between the different phases or drugs the data are not presented in detail.

**Gallopamil**

Compared with placebo gallopamil significantly reduced the low frequency power spectral density after three hours in the sitting position. When compared with the preceding period in the supine position low frequency power spectral density did not increase in the sitting position at baseline and after one hour and three hours.

**Nifedipine**

Compared with placebo nifedipine significantly decreased low frequency power spectral density after three hours in the supine position. When compared with the preceding period in the supine position low frequency power spectral density significantly increased in the sitting position at baseline and after three hours. One hour after drug administration, however, it did not significantly change.

**Metoprolol**

Compared with placebo metoprolol significantly decreased the low frequency power spectral density after three hours in the sitting position. When compared with the preceding period in the supine position low frequency power spectral density significantly increased in the sitting position at baseline but not after one hour or three hours.

**Placebo**

When compared with the preceding period in the supine position, low frequency power spectral density significantly increased in sit-

**RATE-PRESSURE PRODUCT WITH EXERCISE**

Table 2 shows the numerical results. Although maximal workload did not differ between the drugs (in all subjects and under each drug it was 185 (23) Watts), nifedipine and metoprolol both significantly lowered maximal systolic blood pressure compared with placebo (nifedipine: 157 (24) mm Hg; metoprolol: 151 (17) mm Hg; placebo: 171 (24) mm Hg). In addition, metoprolol significantly lowered maximal heart rate under exercise (122 (15) beats/min) compared with placebo (160 (20) beats/min). With gallopamil maximal heart rate and systolic blood pressure during exercise did not differ from placebo values.
ting body position at baseline but not after one hour or three hours.

Discussion

Compared with placebo gallopamil caused a mild but significant increase in heart rate after one hour in the supine position. The lack of an increase after the change to sitting and the fact that one subject developed an atrioventricular block II type Mobitz indicate that gallopamil inhibits sympathetic activation and prolongs atrioventricular conduction. Compared with placebo, heart rate after three hours was lower only in the sitting position but not in the supine position. This may be explained by the fact that under enhanced sympathetic tone the differences to placebo may become more obvious and finally reach significance.

Nifedipine caused reflex sympathetic activation with tachycardia, followed by an exponential decline in heart rate in all but one volunteer. The time constant of the decline had a remarkably low variance and was 34 (7) min in seven of the nine volunteers. One volunteer, however, showed a prolonged time constant of 83 minutes and may have had a prolonged reaction in his cardiovascular reflexes. Differences in drug disposition also could explain this phenomenon. Time domain heart rate variability with nifedipine significantly decreased after one hour indicating that parasympathetic activity was strongly overdriven by reflex sympathetic activity. With metoprolol time domain heart rate variability significantly increased showing a high parasympathetic activity after β adrenergic blockade. In addition, there was a persistent negative chronotropic effect. The lowering effect of nifedipine on the rate-pressure product on exercise was caused by its lowering effect on maximal systolic blood pressure, though reflex tachycardia was no longer present after four hours. This is in good agreement with the finding, that reflex tachycardia declines exponentially with a time constant of \( t_d = 34 \) minutes, which means that after 3 \( t_d = 102 \) min there would be no further effect on heart rate.

Spectral analysis of RR intervals and calculation of low frequency power spectral density as an index of sympathetic cardiac activity gave some interesting results. With gallopamil there were no differences between the supine and sitting positions. This probably means that the normal increase in low frequency power spectral density after the change in posture did not appear, because gallopamil inhibits cardiac sympathetic activation. In addition, compared with placebo, gallopamil significantly lowered low frequency power spectral density three hours after administration in the sitting position. Both findings sup-
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