## HYPERTENSION

# The Effects of Rilmenidine on Cardiac Autonomic Function in Healthy Volunteers

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**Introduction and objectives.** Rilmenidine is an antihypertensive drug whose antihypertensive effect occurs via a sympatholytic action on the central nervous system. However, the effects of rilmenidine on autonomic cardiovascular function are not clear. The aim of this study was to evaluate the acute effect of rilmenidine on autonomic cardiac function by measuring heart rate variability.

**Subjects and method.** A total of 20 healthy men (mean age, 26±3 years) were included in the study; 1 mg of rilmenidine or placebo was given to participants on different days in a double-blind crossover randomized study protocol. After drug administration, time domain and frequency domain parameters of heart rate variability were determined before and after 2 h with the patient in supine decubitus and during the handgrip exercise with 5-min electrocardiographic recordings.

**Results.** Rilmenidine caused an increase in mean RR values after administration when compared to pre-drug administration recordings with the patient in supine decubitus (929 ms vs 860 ms, $P<.05$), but this effect was not found in the placebo group. However, there were no differences in other time domain parameters or in any of the frequency domain parameters (normalized low frequency unit, normalized high frequency unit and low frequency/high frequency ratio) with the participant in supine position in either group. In addition, neither rilmenidine nor placebo modified heart rate variability parameters during the handgrip exercise.

**Conclusion.** Administration of a single dose of rilmenidine increased vagal tone without affecting vagal modulation in the supine position. The absence of vagal tone increase during the handgrip exercise suggests that this effect of rilmenidine is minimal.

**Key words:** Rilmenidine. Heart rate variability. Sympathovagal balance.

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## Efectos de la rilmenidina en la función del sistema nervioso autónomo cardíaco de voluntarios sanos

**Introducción y objetivos.** La rilmenidina es un medicamento antihipertensivo cuyo mecanismo de acción es su efecto simpaticolítico en el sistema nervioso central. No obstante, los efectos de la rilmenidina en las funciones del sistema nervioso autónomo cardiovascular todavía no han sido definidos. El objetivo de este estudio es evaluar el efecto agudo de la rilmenidina en las funciones del sistema nervioso autónomo cardíaco mediante el uso de la variabilidad en la frecuencia cardíaca (VFC).

**Sujetos y método.** Se incluyó en el estudio a un total de 20 varones sanos (edad media, 26 ± 3 años). El estudio tuvo un diseño de grupos cruzados con asignación aleatoria y control doble ciego, y durante su curso se administró 1 mg de rilmenidina o placebo a los participantes en días diferentes. Se determinaron los parámetros de tiempo y frecuencia de la VFC antes y 2 h después de la administración del fármaco o placebo, mientras los sujetos permanecían en decúbito supino o realizaban ejercicio con *handgrip*, con registros electrocardiográficos de 5 min.

**Resultados.** La rilmenidina produjo un incremento de los intervalos R-R medios durante la fase posterior a la administración del fármaco (en comparación con la fase previa a su administración), mientras los participantes permanecían en decúbito supino (929 frente a 860 ms; p < 0,05), pero este efecto no fue observado en el grupo placebo. Sin embargo, no hubo diferencias en otros parámetros de tiempo y en ninguno de los parámetros de frecuencia (unidad de frecuencia baja [FB] normalizada, unidad de frecuencia alta [FA] normalizada y cociente FB/FA) entre ambos grupos. Además, ni la rilmenidina ni el placebo modificaron los parámetros de la VFC durante el ejercicio tipo *handgrip*.

**Conclusión.** La administración de una dosis única de rilmenidina incrementó el tono vagal sin modificar la modulación vagal en decúbito supino. La ausencia de incremento del tono vagal durante el ejercicio de *handgrip* indica que este efecto de la rilmenidina es mínimo.

**Palabras clave:** Rilmenidina. Variabilidad de la frecuencia cardíaca. Equilibrio simpático vagal.

## ABBREVIATIONS

HRV: heart rate variability.
SDNN: the standard deviation of R-R interval.
RMSSD: the root mean square of successive
  R-R interval differences.
LF: low frequency.
HF: high frequency.
VLF: very low frequency.

## INTRODUCTION

Rilmenidine is a new antihypertensive agent whose mechanism of action via a sympatholytic effect at the medullary vasomotor centre.[1,2] In experimental studies, it was shown that administration of oral or intravenous rilmenidine to hypertensive mice decreased sympathetic tonus, heart rate and blood pressure.[3,4] The sympatholytic effect of rilmenidine was induced by activation of imidazolin receptors.[5]

Heart rate variability (HRV), which is a noninvasive diagnostic method, has been used to provide risk stratification in cardiological and noncardiological diseases. Cardiac autonomic functions were identified with HRV in left ventricular dysfunction, diabetes mellitus and after myocardial infarction.[6-9] The risk was estimated with frequency and time domain analyses of HRV in short term recordings (5 minutes). Different conditions such as upright position, exercise, and mental stress induce sympathetic stimulation and consequently heart rate and HRV parameters were changed. Previously the chronic effects of rilmenidine on HRV has been studied in patients with hypertension,[10] but the acute effect of rilmenidine on HRV is not known. Therefore, the aim of this study is to investigate the effects of rilmenidine on cardiac autonomic functions during rest and mild exercise in healthy volunteers.

## MATERIAL AND METHOD

### Study Population

A total of 20 healthy volunteers (mean age, 26±3 years) were included in the study. The participants having known coronary artery disease, respiratory, neurological, or systemic diseases as well as any other disorder that might influence the autonomic nervous function. Study participants had normal physical examination, resting 12-lead electrocardiograms and exercise tests. Routine biochemical and hematological values including fasting blood glucose, blood urea nitrogen, serum electrolytes, and hemoglobin levels were in normal ranges as well. Written informed consents were obtained from all participants, and the protocol of the study was approved by ethical committee of our faculty (Medicine Faculty, Afyon Kocatepe University, Afyon Turkey).

### Study Design

The participants were involved in a randomized, double-blinded, placebo controlled, cross-sectional study with 2 identical experimental sessions at least 5 days apart. The half-life elimination of rilmenidine is approximately 8 hours in healthy individual,[11] and 5 half life period of this drug is about 40 hours. Our participants took the drugs in 2 sections 5 days apart which was equal to 15 half-life metabolism periods of rilmenidine. Patients were evaluated in the morning following at least 8 hours of sleep and after having breakfast free of caffeine-containing beverages. All HRV parameters were recorded in a dimly lighted room with a comfortable temperature (22°C-24°C). Frequency and time domain analysis of HRV were calculated from short term recordings (5 minutes). After an adjustment period of at least 15 minutes rest in supine position, their electrocardiograms were recorded in supine and during handgrip exercise in sitting position for 5-minutes. Participants performed an isometric handgrip exercise at 25% of their predetermined maximum volunteer capacity in a manner of 45-second contraction and 15-second resting per minute using a Jamar hydraulic hand dynamometer (Sammons Preston, Canada). Basal data were obtained before administration of drugs (pre-drug phase), and participants received either a single oral dose of 1 mg rilmenidine or placebo with 200 ml water. The administration of test drugs were randomized and subjects were blinded to them. Two hours after drugs administration (post-drug phase), the participants once again underwent the same procedures as mentioned above. Blood pressure measurements were obtained from the left arm, at the level of the heart, by a physician well experienced in using sphygmomanometer.

### HRV Analysis

ECG data were transferred to a personal computer and digitized via an analog-to-digital conversion board (PC-ECG 1200, Norav Medical Ltd, Israel). All

recordings were visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artifact were automatically and manually identified and excluded. Both time and frequency domain of HRV analysis were performed using by Heart Rate Variability Software (version 4.2.0, Norav Medical Ltd, Israel). Mean R-R interval (mean-RR), the standard deviation of R-R interval (SDNN) and the root mean square of successive R-R interval differences (RMSSD) were measured assesing time domain parameters. For the frequency domain parameters, power spectral analysis based on the Fast Fourier transformation algorithm was used. Three components of power spectrum were computed following different bandwidths: high frequency (HF) (0.15 Hz-0.4 Hz), low frequency (LF) (0.04 Hz-0.15 Hz), and very low frequency (VLF) (0.003 Hz-0.04 Hz). The normalized unit LF (LFnu=LF/[LF+HF]), normalized unit HF (HFnu-=HF/[LF+HF]), and LF/HF ratio were also calculated.

## Statistical Analysis

Data are presented as mean ± standard deviation. Dependent variables at baseline and after placebo or rilmenidine administration were tested by Wilcoxon Signed Rank test and a $P$-value of <.05 was considered as statistically significant.

## RESULTS

All participants well tolerated the study and no adverse side effects such as chest discomfort, palpitation, tremor, headache, and rhythm disturbance were observed.

Rilmenidine administration caused decrease in systolic and diastolic arterial blood pressures compared with the pre-drug phase at rest (Pre-drug phase: 104±10/67±7, post-drug phase: 98±9/64±8 mm Hg; $P$<.05) and during handgrip exercise (Pre-drug phase: 120±16/ 83±13, Post-drug phase: 113±13/77±9 mm Hg, $P$<.05). Placebo administration did not change systolic and diastolic arterial blood pressures.

The pre-drug values of time and frequency domain parameters for each group were not significantly different at rest and during handgrip exercise period. Rilmenidine caused an increase in mean RR values in the supine position during the post-drug phase compared with the pre-drug phase (Post-drug phase: 929 ms vs pre-drug phase: 860 ms; $P$<.05). However there were no difference in other time or frequency domain parameters in all maneuvers in rilmenidine group ($P$>.05, Table 1). In contrast placebo administration had no change in HRV parameters in a supine position and during handgrip exercise ($P$>0.05, Table 2).

## DISCUSSION

Rilmenidine decreases blood pressure by activating $\alpha^2$ adrenergic receptors and imidazolin receptors, located in the central nervous system.[12] Rilmenidine's antihypertensive action occurs with binding to imidazolin receptors in the C1 region.[13] Besides the antihypertensive effect of imidazolin receptor agonists (rilmenidine and moxonidine), additional benefits such as antiarrhythmic effects have been reported.[14] Although antiarrhythmic effects of rilmenidine were shown in experimental studies, it was not accepted as an antiarrhythmic drug. The antiarrhythmic effects of imidazolin receptor agonists were considered to appear by a decrease of sympathetic activity or, as a result of receptor activation in the C1 region, to an increase of vagal stimulus input in this region.[15]

In experimental studies with animals it was shown

TABLE 1. **The Effect of Rilmenidine on HRV Parameters During Rest and Handgrip Exercise***

| | Rest | | | Handgrip Exercise | | |
|---|---|---|---|---|---|---|
| | **Pre-Drug** | **Post-Drug** | ***P*** | **Pre-Drug** | **Post-Drug** | ***P*** |
| Mean R-R, ms | 884 (183) | 924 (175) | <.05 | 747 (93) | 763 (109) | .14 |
| SDNN, ms | 53 (20) | 55 (17) | .54 | 73 (42) | 68 (40) | .42 |
| RMSSD, ms | 46 (20) | 45 (22) | .60 | 39 (22) | 36 (20) | .49 |
| LFnu | 0.49 (0.16) | 0.52 (0.14) | .35 | 0.76 (0.10) | .79 (0.08) | .11 |
| HFnu | 0.51 (0.17) | 0.48 (0.16) | .48 | 0.25 (0.11) | 0.21 (0.08) | .27 |
| LF/HF ratio | 1.25 (1.02) | 1.04 (0.59) | .23 | 3.17 (2.07) | 3.46 (2.31) | .18 |

*SDNNindicates standard deviation of R-R interval; RMSSD, root mean square of successive R-R interval differences; LFnu: low frequency normalized unit; HFnu: high frequency normalized unit.

TABLE 2. **The Effect of Placebo on HRV Parameters During Rest and Handgrip Exercise***

| | Rest | | | Handgrip Exercis | | |
|---|---|---|---|---|---|---|
| | Pre-Drug | Post-Drug | *P* | Pre-Drug | Post-Drug | *P* |
| Mean R-R, ms | 889 (135) | 895 (146) | .25 | 762 (104) | 759 (110) | .31 |
| SDNN, ms | 57 (19) | 58 (18) | .48 | 75 (32) | 71 (31) | .33 |
| RMSSD, ms | 46 (20) | 49 (21) | .65 | 47 (33) | 41 (24) | .71 |
| LFnu | 0.52 (0.13) | 0.51 (0.15) | .54 | 0.70 (0.13) | 0.74 (0.10) | .41 |
| HFnu | 0.47 (0.14) | 0.49 (0.14) | .48 | 0.29 (0.12) | 0.26 (0.10) | .35 |
| LF/HF ratio | 1.10 (0.63) | 1.23 (1.14) | .35 | 3.05 (2.55) | 3.50 (2,48) | .14 |

*SDNNindicates standard deviation of R-R interval; RMSSD, root mean square of successive R-R interval differences; LFnu: low frequency normalized unit; HFnu: high frequency normalized unit.

that rilmenidine reduced blood pressure, heart rate, and noradrenalin levels by sympatholytic effect. But still there was no evidence on its autonomic effects. Rilmenidine has accepted to have central sympatholytic effects. But some other studies with decerebrated rats showed that rilmenidine also had peripheral sympatholytic effect.[16,17] Furthermore some authors claim that the sympatholytic effect of rilmenidine was occurs by activating α receptors,[16,18] while others support that this effect is obtained by activating imidazolin receptors.[19-21] Some studies support that the sympatholytic effect of rilmenidine is due to activation of both types of receptors.[22,23] Another controversial issue is the localization of the receptors binding to rilmenidine. It is known that in humans imidazolin receptors are located on the antero and ventrolateral medulla, while in spontaneously hypertensive rats, rilmenidine carries out its effects affected by binding imidazolin receptors in the thoracolombar spinal cord.[21] Although there are various studies about rilmenidine's autonomic effects on experimental animals, its autonomic effects in humans still remain unknown.

The main finding of the present study was that administration of 1 mg oral rilmenidine did not change HRV parameters except mean RR during rest and autonomic maneuvers (handgrip exercise) in healthy individuals. Rilmenidine administration only increased mean RR during supine position. This effect suggests that rilmenidine only increases vagal tonus without changing vagal modulation and the sympathovagal balance during rest. However rilmenidine has no effect on vagal tonus during handgrip exercise. The reason of drawing this conclusion was as Hedman[24] et al stated, heart rate decrease (increase in mean RR) occurring without changing parasympathetic modulation indicators of HRV (HF and RMSSD) could be attributed to an increase in parasympathetic tonus. Although

Goldenberger et al stated[25] that this effect was seen in high saturated parasympathetic input levels, our results suggest that 1 mg of oral rilmenidine administration could produce this effect in low saturated parasympathetic input levels.

The absence of effects on time and frequency domain parameters of HRV by single dose rilmenidine administration during light exercise shows that the drug does not affect neither sympathetic tonus and modulation nor sympathovagal balance in healthy individuals during increased sympathetic activity. Despite the sympatholytic effects of rilmenidine which has been previously reported,[3-5] we could not find any change in sympathovagal balance during exercise in healthy volunteers. These effects can be explained in a way that all individuals were healthy and had no sympathetic hyperactivity or hypertension. Also rilmenidine's sympatholytic activity is dose dependent,[4] and 1 mg rilmenidine was not enough in affecting sympathovagal balance. So it could be speculated that administration of higher doses of rilmenidine may change sympathovagal balance in patients with increased symphathetic activity in diseases such as hyperthyroidism, myocardial infarction, and hypertension.

Eryonucu et al[10] showed that the chronic effects of rilmenidine administration had no effect on HRV parameters in hypertensive patients. Although our participants had different characteristics, the effects of a single dose of rilmenidine on HRV parameters is similar to that demonstrated by Eryonucu et al. Therefore our findings confirm these results.

Various experimental studies reported rilmenidine's sympatholytic effects. We could not determine this effect in our study. There should be several potential reasons for discordancy between experimental and clinical findings. It is well known that using

anesthetic materials in experimental studies cause an increase in basal sympathetic activity.[26] In the state of increased sympathetic activity, rilmenidine's sympatholytic effects become more appearent. Due to lack of using anesthetic material in clinical studies, sympathetic activity remains normal and rilmenidine may not form clear sympatholytic effects in humans. While in experimental studies sympatholytic effects were determined by reduction in noradrenalin levels,[16,19] in our study this was evaluated using HRV parameters. Consequently there was a methodology difference between experimental and clinical studies. Another reason may be related to the routes of administrating the drug. In experimental studies it was observed that intracisternal is more effective than intravenous drug administration. In experimental studies, rilmenidine was administrated parenterally, while it was administrated orally in human studies.[27] Also, experimental studies used higher dose of rilmenidine than in clinical studies.

## CONCLUSIONS

Administration of a single 1 mg dose of rilmenidine does not affect sympathovagal balance nor vagal and sympathetic modulation during exercise in healthy volunteers. At rest it increases vagal tonus without changing vagal modulation. Further research is warranted to investigate the effects of different doses of rilmenidine on cardiac autonomic functions in diseases with increased sympathetic activity.

### ACKNOWLEDGEMENT

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