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RAPID COMMUNICATION

Low-dose resveratrol supplementation on heart rate variability in hypertensive volunteers: a controlled double-blind trial

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OBJECTIVE: Hypertension decreases the heart rate variability (HRV). Resveratrol, a phenolic compound found in grapes and their products, has been explored for its potential to treat hypertension. We evaluated the effects of low-dose resveratrol on HRV in hypertensive volunteers.
METHOD: Twenty-one hypertensive volunteers of both sexes were supplemented with resveratrol (n = 11) or placebo (n = 10) for 30 days. HRV parameters were measured before and during a standardized treadmill exercise. One resveratrol- and 3 placebo-treated patients were lost to follow-up.
RESULTS: There were no anthropometric differences between resveratrol (n = 10) and placebo (n = 7) other than a difference in body mass index. The measured HRV parameters did not differ between resveratrol and placebo, or between control and treadmill exercise.
CONCLUSION: Low-dose resveratrol did not alter HRV in hypertensive patients.

KEYWORDS: Grape seed extract , Hypertension , Autonomic nervous system.

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INTRODUCTION

High blood pressure is often elusive to diagnose and difficult to control, constituting one of the main risk factors for cardiovascular diseases; it impairs the cardiac autonomic modulation, increasing sympathetic and decreasing parasympathetic activity.

Heart rate variability (HRV) is a simple and noninvasive measurement related to the performance of the autonomic nervous system on the heart. Reductions in HRV have been associated with increased risks of adverse cardiac events, organ damage, and mortality.[1]

Resveratrol, a phenolic compound found in grapes and their products, has been considered a hypotensive agent.[2] This action is a result of its antioxidant[3], anti-inflammatory[4] and anti-obesity[5] properties.

The isolated effect of resveratrol on HRV in humans has not been tested. Spaak et al.[6] investigated the influence of one or two glasses of water, wine or alcohol on HRV. Compared to water, one glass of wine or ethanol lowered the time- and frequency-domain markers of vagal modulation. Compared to their respective baseline values, two drinks of wine or ethanol raised the heart rate by decreasing the vagal and increasing the sympathetic heart rate modulation. In animal models, resveratrol was shown to modulate the autonomic function and promote cardiac redox benefits.[7]

To the best of our knowledge, there are no reports on the effects of low doses of resveratrol (≤150 mg) on the linear and nonlinear indexes of HRV. Therefore, the aim of this study was to evaluate the effects of resveratrol at low doses on the HRV in healthy volunteers.

MATERIAL AND METHODS

This study, conducted according to the Declaration of Helsinki guidelines, was approved by the Institutional Ethics Committee and registered in the database of the Brazilian Clinical Trials Registry (ReBEc - RBR-2xj368). Written informed consent was obtained from all

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participants before the study, by adopting the CONSORT statement.[8]

Participants

Twenty-one hypertensive volunteers of both sexes, aged 35 years or older, were included. The exclusion criteria were: (a) physical limitations preventing the individuals from executing the treadmill test; (b) uncontrolled hypertension (systolic blood pressure higher than 180 mmHg and/or diastolic blood pressure higher than 100 mmHg) and/or diagnosis of diabetes; (c) frequent ingestion of wine and/or full grape juice, peanuts and/or blackberry; (d) initial practice of physical exercise after being selected to this study; (e) intolerance to resveratrol; (f) incomplete stages of the tests.

Allocation and intervention

Allocation of participants to the groups was based on www.randomization.com. The intervention group was supplemented for 30 days with a daily dosage of 100 mg of resveratrol, while the placebo group was supplemented for the same period with an equivalent 100mg-capsule of maltodextrin. The capsules had the same size and color and were separated in individual, matte packages by a researcher of the team who did not participate in the data collection. Both groups were instructed to ingest the capsule on an empty stomach in the morning.

Data collection

Data were collected by means of a structured interview about tobacco dependence, physical activity frequency, and alcohol consumption frequency. Physical examination was then conducted, including blood pressure and anthropometric measurements.

Participants went to the collection site on four non-consecutive days, in the morning, to comply with the following tasks: a) participation in a meeting in which the project was presented; b) determination of maximum heart rate by means of the Cooper test; c) assessment of pre-supplementation HRV, and d) assessment of post-supplementation HRV.

Assessment of heart rate variability (HRV)

Measurements of HRV were obtained by using Polar S810i (Polar Electro, Finland). Records were extracted and converted into text by employing the Polar ProTrainer software, and the data on RR interval were analyzed by using Kubios HRV software.

Pre-and post-supplementation HRV was assessed at rest and during a treadmill test for 15 minutes each. During the treadmill test, the target HR was set at 70 to 75% of the individual's maximum HR.

HRV was analyzed based on linear and nonlinear rates (time and frequency domain). The measurements in the time domain included: mean of RR intervals (msec); standard deviation of all intervals recorded in a period expressed as msec (SDNN); square root of the average of the square of differences between adjacent normal RR intervals in a time interval expressed as msec (RMSSD); percentage of adjacent RR intervals with duration difference greater than 50 msec (pNN50), and the triangular index. The frequency domain covers the component of very low frequency (VLF), expressed as ms^2 and %, component of low frequency (LF), ms^2 and %, component of high-frequency (HF), ms^2 and%, and LF / HF ratio. For the quantitative analysis of nonlinear indexes, the following parameters were calculated: short-term variability (SD1), long-term variability (SD2), approximate entropy (ApEn), and sample entropy (SampEn).

Statistical Analysis

Continuous variables with normal distribution were described based on the mean and standard deviation and compared per Student's t test. Categorical variables expressed as absolute and relative frequencies were compared between groups according to Fisher's exact or G-test. Analysis of variance (ANOVA) with repeated measures was adopted to compare the interaction of the factors group and time (pre and post-supplementation) for HRV. The software SPSS 21.0 was used for data analysis. The critical significance level adopted in all tests was the maximum error probability of 5%.

RESULTS

Twenty-one participants were randomized to the groups (resveratrol – RG, n=11; placebo – PG, n=10). One individual in the resveratrol group and three individuals in the placebo group were lost to follow-up (Table 1).

There were no significant differences between groups for age, gender, systolic and diastolic arterial pressure and years from hypertension diagnosis. Significant differences were found for body mass index between groups. None of the participants smoked and almost no participant consumed alcoholic drinks; they practiced less than 30 minutes of exercise per day.

The results of HRV are shown in Tables 2 (linear indexes) and 3 (nonlinear indexes). There were no significant differences in any of the factors (interaction, time and group) for the time- and frequency-domain HRV and nonlinear HRV analyses.

DISCUSSION

This is the first study that investigated the effects of low-dose resveratrol supplementation on HRV in humans. A previous study employed red wine, which induced a

Table 1 - General anthropological data of participants

	Resveratrol group (n=10)	Placebo group (n=7)	p
Age (years)	54.4±9.0	55.7±9.0	0.77
Male/Female	6/4	0/7	0.64
Systolic Blood pressure (mm Hg)	136.0±11.7	140.0 ± 22.4	0.64
Diastolic Blood pressure (mm Hg)	90.0±12.7	95.7±12.7	0.37
Years from diagnosis of hypertension	10.4±10.1	10.6±7.6	0.97
Body Mass Index	35.2±5.2	29.3±3.5	0.01
Smokers	none	none	-
Alcoholic drink consumers	70.4%	70.0	0.55
Exercising activity (less than 30 min/day)	85.7%	90.0%	>0.99

Continuous variables are displayed as mean ± standard deviation

considerable increase in blood resveratrol, and alcohol.[6] In an animal model, results were described for a diet based on resveratrol or grape juice supplementation.[7]

Our study analyzed linear and nonlinear indexes in hypertensive volunteers at rest and under stress conditions, while Spaak et al.[6] evaluated only linear rates in healthy subjects at rest. Despite the flavoring of water and ethanol in the study by Spaak et al,[6] the comparison between the flavors of beverages was different. In this study, participants were offered capsules (placebo and resveratrol) of identical external appearance for double-blind characterization. Another difference was the administration time: in the present study, participants took 100 mg capsules on a daily basis for 30 days, while in the study by Spaak et al.[6] the administration time was 3 days. It must be noted that the concentration of resveratrol in Brazilian wines ranged from 0.82 to 5.75 mg / L, average of 2.57 mg / L, as previously reported.[9]

HRV evaluation time was set to 15 minutes, considering the operating safety margin of the frequency meter. For short-term recordings of HRV, a standardized minimum time of 5 minutes is suggested.[10] The stress condition was increased due to the change in the neural modulation, compared to the rest condition, showing increased sympathetic activation and decreased parasympathetic activation in healthy adults.[11]

There were no significant differences in HRV parameters considering time domain, frequency domain and nonlinear indexes. In the study by Spaak et al,[6] one or two glasses of red wine per day significantly decreased RMSSD, pNN50 and total HF, but increased the LF spectral power when compared to the control group (water) and the average pre-ingestion value. This decrease in the vagal modulation and the sympathetic modulation activation can be justified by the dose-dependent effect of alcohol. The absence of difference between ethanol and red wine seems to exclude resveratrol as a causative agent of HRV alterations.

Nonlinear indexes of HRV can be analyzed based on short-term ECG recordings and provide additional information about each RR interval that cannot be obtained by using conventional linear methods of analysis.[12] Patients after acute myocardial infarction have significantly lower SamEn, SD1 and SD2 than patients with preserved cardiac output.[13] ApEn has been shown as a predictor of mortality and sudden death in patients with heart failure.[14]

Previous clinical studies indicated that resveratrol in humans varies in dosage from 5 to 5000 mg. The doses of this substance are categorized as low (≤150 mg / day) and high and the duration of its administration can be divided into short (<3 months) and long term.[2] The nutraceutical administration of low-dose resveratrol (100 mg) was chosen because there are no studies assessing its effects on HRV. There was no occurrence of gastrointestinal side effects in the present study.

Although resveratrol has gained notoriety and attracted attention in the early 1990's, it is still trying to establish itself as a promising adjuvant treatment for cardiovascular diseases. Similarly to most issues in this research field, there is no unanimity about it. Some researchers support the potential benefits of resveratrol; some are against it; and some are in favor of a new "chance". Future studies should include larger samples, cross-over design, longer administration periods, and different doses. HRV measurements should be considered mandatory.

CONCLUSION

This study showed that there was no effect of low-dose resveratrol on the HRV in hypertensive patients.

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AUTHOR PARTICIPATION

Silva-e-Oliveira, Ferrão Damasceno and Furtado delineated the study design and protocol and coordinated

Table 2 - Linear variables of HRV between the placebo and the resveratrol group in the time and frequency domains, at rest and under stress, in the pre and post-supplementation periods.

		Placebo group	Resveratrol group	Interaction*	Time*	Group*
At rest	TIME DOMAIN					
	Mean RR (msec)					
	Pre	832.01 ±101.98	774.430 ±186.73	0.31	0.14	0.84
	Post	854.18 ±142.06	888.19 ±136.45			
	SDNN					
	Pre	36.7 ±20.12	40.97 ±10.03	0.88	0.54	0.45
	Post	39.62 ±23.02	45.73 ±21.12			
	RMSSD					
	Pre	20.28 ±16.71	28.04 ±16.55	0.98	0.90	0.15
	Post	20.87 ±7.49	28.77 ±15.64			
	PNN50					
	Pre	6.74 ±13.05	4.22 ±6.94	0.16	0.83	0.65
	Post	2.92 ±2.64	9.38 ±15.01			
	Triangular Index					
	Pre	6.97 ±3.71	8.42 ±3.08	0.66	0.30	0.52
	Post	8.80 ±3.42	8.80 ±3.42			
	FREQUENCY DOMAIN					
	VLS (ms^2)					
	Pre	530.48 ±520.07	781.9 ±404.19	0.69	0.47	0.27
	Post	655 ±636.34	1210 ±1750.04			
	HF (ms^2)					
	Pre	248.42 ±357.29	218.89 ±272.71	0.34	0.85	0.53
	Post	152.42 ±98.24	360.20 ±555.85			
	LF (ms^2)					
	Pre	347.57 ±341.11	346.3 ±403.96	0.98	0.91	0.97
	Post	336.85 ±264.38	329.4 ±383.49			
	LF/HF					
	Pre	3.42 ±3.48	1.82 ±1.68	0.59	0.37	0.08
	Post	2.48 ±1.1	1.58 ±0.8			
Stress (on the treadmill)	TIME DOMAIN					
	Mean RR (msec)					
	Pre	586.58 ±156.90	552.88 ±77.45	0.29	0.30	0.81
	Post	540.95 ±64.95	553.51 ±93.99			
	SDNN					
	Pre	24.01 ±20.49	30.73 ±12.08	0.45	0.63	0.51
	Post	25.37 ±11.13	24.86 ±9.37			
	RMSSD					
	Pre	11.10 ±13.53	17.59 ±16.65	0.47	0.29	0.52
	Post	9.44 ±10.01	8.90 ±11.80			
	PNN50					
	Pre	0.87 ±2.09	1.84 ±3.71	0.59	0.63	0.65
	Post	0.92 ±1.82	0.82 ±2.5			
	Triangular Index					
	Pre	4.12 ±1.79	4.93 ±2.03	0.95	0.54	0.21
	Post	4.42 ±0.77	5.29 ±1.63			
	FREQUENCY DOMAIN					
	VLS (ms^2)					
	Pre	591.71 ±1165.02	302.80 ±193.56	0.52	0.40	0.39
	Post	292.14 ±237.23	259.70 ±127.7			
	HF (ms^2)					
	Pre	80.71 ±199.61	78.14 ±162.79	0.91	0.41	0.95
	Post	32 ±69.81	40.1 ±116.28			
	LF (ms^2)					
	Pre	114 ±277.54	107 ±132.49	0.85	0.41	0.76
	Post	74.42 ±161.78	45.6 ±102.57			
	LF/HF					
	Pre	2.46 ±1.37	3.37 ±2.50	0.94	0.24	0.44
	Post	3.07 ±1.98	4.06 ±3.65			

Table 3 - Nonlinear variables of HRV between the placebo and the resveratrol group at rest and under stress, in the pre and post-supplementation periods.

		Placebo group	Resveratrol group	Interaction*	Time*	Group*
At rest	SD1					
	Pre	15.15 ± 10.84	19.75 ± 11.73	0.89	0.97	0.16
	Post	14.75 ± 5.29	20.36 ± 11.07			
	SD2					
	Pre	49.2 ± 27.1	53.8 ± 11.91	0.89	0.50	0.53
	Post	53.85 ± 32.47	60.82 ± 28.42			
	ApEn					
	Pre	1.15 ± 0.43	1.03 ± 0.37	0.82	0.32	0.13
	Post	1.32 ± 0.18	1.13 ± 0.3			
	SamEn					
	Pre	1.19 ± 0.56	1.02 ± 0.5	0.86	0.27	0.19
	Post	1.41 ± 0.22	1.19 ± 0.45			
Stress (on the treadmill)	SD1					
	Pre	7.85 ± 9.58	12.44 ± 11.78	0.47	0.29	0.52
	Post	6.67 ± 7.05	6.3 ± 8.34			
	SD2					
	Pre	32.74 ± 27.55	40.65 ± 15.41	0.49	0.73	0.56
	Post	34.94 ± 14.79	34.08 ± 11.87			
	ApEn					
	Pre	0.72 ± 0.35	0.67 ± 0.28	0.44	0.77	0.77
	Post	0.66 ± 0.28	0.78 ± 0.33			
	SamEn					
	Pre	0.66 ± 0.40	0.59 ± 0.31	0.33	0.74	0.69
	Post	0.58 ± 0.33	0.75 ± 0.34			

* ANOVA repeated measurements; data described as mean ± standard deviation; ApEn: approximate entropy; SamEn: sample entropy.

the literature searches. Silva-e-Oliveira and Ferrão wrote the first draft of the manuscript. All authors contributed to and have approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest relating to this project.

SUPLEMENTAÇÃO DE BAIXA DOSE DE RESVERATROL NA VARIABILIDADE DA FREQUÊNCIA CARDÍACA EM HIPERTENSOS: ENSAIO CLINICO CONTROLADO E DUPLO CEGO

OBJETIVO: A hipertensão arterial diminui a variabilidade da frequência cardíaca (VFC). Resveratrol têm sido estudado como tendo potencial para o tratamento da hipertensão. Foram avaliados os efeitos de baixas doses de resveratrol na variabilidade da frequência cardíaca em voluntários hipertensos.

MÉTODO: Vinte e um voluntários hipertensos, de ambos os sexos foram suplementados com resveratrol (n = 11) ou placebo (n = 10) durante 30 dias. Parâmetros da VFC foram medidos antes e durante o exercício em esteira padronizado. Um paciente tratado com resveratrol e três tratados com placebo foram perdidos.

RESULTADOS: Não houve diferenças antropométricas entre os integrantes dos grupos resveratrol (n = 10) vs. placebo (n = 7), exceto uma diferença de índice de massa corporal. Não foram observadas diferenças para nenhum dos parâmetros da VFC entre resveratrol vs. placebo, ou entre controle vs. exercício em esteira.

CONCLUSÃO: A baixa dose de resveratrol não afetou a VFC em hipertensos.

PALAVRAS-CHAVE: extrato de semente de uva, hipertensão, sistema nervoso autônomo

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