COMPARISON of the EFFECTS of CAPTOPRIL and VALSARTAN on HEART RATE VARIABILITY in HEALTHY MEN

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Summary

Objective: *Angiotensin II is well known to have several effects on cardiovascular autonomic functions. However, there is no data regarding the head to head comparison of the effect of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, the major drugs to inhibit angiotensin II, on heart rate variability (HRV). The aim of this study is to compare the effects of a single dose ACE inhibitor (captopril: 25 mg) and an angiotensin receptor blocker (valsartan: 80 mg) on HRV parameters.*

Material and Methods: *The effects of a single oral dose of captopril, valsartan and placebo on 9 healthy male individuals (mean age 28±2 years) were studied in a double blind crossover placebo controlled study on three occasions. Frequency and time domain parameters of HRV were measured during supine position and during handgrip exercise before and after taking each agent.*

Results: *Baseline blood pressure values, heart rates and HRV parameters were not found statistically different on each occasion. With captopril but not valsartan administration, heart rate at supine position decreased significantly in comparison with the baseline values without a change in HRV parameters (865±33 vs. 917±39, p=0.038). When compared to placebo during handgrip exercise, captopril caused a significant increase in the standard deviation of R-R interval (SDNN), which is a global HRV marker (50±5 ms vs. 58±5 ms, p=0.035, respectively).*

Conclusion: *Captopril not only increases vagal tone at rest without altering vagal modulation but also increases SDNN during handgrip exercise. However these effects are not observed with valsartan.* ***(Arch Turk Soc Cardiol 2003;31:338-46)***

Key words: *Captopril, heart rate variability, valsartan*

Özet

Kaptopril ve Valsartan'ın Kalp Hızı Değişkenliği Üzerine Olan Etkilerinin Sağlıklı Erkeklerde Karşılaştırılması

Giriş: *Anjiyotensin-II'nin kardiyovasküler otonomik fonksiyonlar üzerine olan farklı etkileri iyi bilinmektedir. Bununla beraber, anjiyotensin-II'nin başlıca inhibitörü olan anjiyotensin dönüştürücü enzim (ACE) inhibitörleri ve anjiyotensin reseptör blokerlerinin kalp hızı değişkenliği (KHD) üzerine olan etkilerinin bire bir karşılaştırılmasına ait veri yoktur.*

Amaç: *Çalışmamızın amacı, tek doz ACE inhibitörü (Kaptopril: 25 mg) ve anjiyotensin reseptör blokeri'nin*

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METHODS

Study Subjects

Nine healthy volunteer men, mean age 28±2 years (range 19 to 40 years), were studied in a randomized, double blind, placebo-controlled, crossover study design. Male volunteers were chosen in order to avoid the well-known effects of hormonal changes on cardiovascular autonomic functions[13]. The subjects with coronary artery disease, respiratory, neurological or any other systemic disorder that might influence autonomic function, allergy to the drugs used, history of smoking and diabetes mellitus were excluded from the study. Written informed consent was obtained from all participants before attending the study and the ethical committee of our institution approved the study protocol. All participants were asked to refrain from alcohol and caffeine-containing beverage and strenuous exercise for 24 hours prior to each study session.

Study design

In order to avoid any interaction at the absorption phase of the drugs, all participants were taken into the study after at least 8 hours of fasting. All subjects were taken to a quite, dimly lit and at a 22-24°C-temperature room. Each volunteer attended three testing sessions separated by at least 72 h to eliminate the possibility of carryover effects from the previous test. The studies were performed between 08.00 pm and 11:00 pm to avoid circadian variation of HRV parameters. All participants were taken to the test room and rested in supine position at least 15 minutes on a comfortable bed. Electrocardiographic recordings were taken at supine position and during handgrip exercise in sitting position with 5-minute intervals. 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 Jamar hydraulic hand dynamometer (Sammons Preston, Canada). After baseline data were obtained, captopril (25 mg), valsartan (80 mg) or placebo was administered.

The reason behind choosing captopril and valsartan as study drugs was the fact that they are not prodrugs and the maximum duration of action is short (approximately 2 hours) and similar to each other[14,15]. The short-acting agents were chosen in an attempt to complete the study before circadian changes took place. The order of administration of test drugs was randomized and subjects were blinded to the test drug received. One hundred and twenty minutes later, the participants once again underwent the same procedures as mentioned above. Blood pressure measurements were obtained from the left arm supported at the heart level by a trained physician using a sphyngomanometer prior to and after each period, and mean arterial blood pressures were calculated according to the classical formula [systolic blood pressure+(2 diastolic blood pressure) / 3].

HRV analysis

Electrocardiographic data were fed to a personal computer and digitized via an analog-to-digital conversion board (PC-ECG 1200, Norav Medical Ltd, Israel). All records were visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artifact were automatically and manually identified and excluded. HRV analysis was performed using Heart Rate Variability Software (version 4.2.0, Norav Medical Ltd, Israel). Both time and frequency domain analyses were performed. For the time domain, 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. For the frequency domain analysis power spectral analysis based on the Fast Fourier transformation algorithm was used. Three components of power spectrum were computed following bandwidths: high frequency (HF) (0.15-0.4 Hz), low frequency (LF) (0.04-0.15 Hz) and very low frequency (VLF) (0.003-0.04 Hz). The LF/HF ratio, LF/Total power and HF/Total power were also calculated.

Statistical analysis

Data are presented as mean±SEM. The time- and frequency-domain parameters were analyzed with Wilcoxon Signed-Rank Test. A p value <0.05 was considered as statistically significant.

RESULTS

The study drugs were well tolerated by all of the participants. There were no adverse effects that might be attributed to the study drugs. On each of the three days that the study took place, there were no differences in the baseline blood pressure values. The mean blood pressure values at supine position after administration of captopril and valsartan tended to be lower, however, this decline was not statistically significant. This tendency of decrease in the mean blood pressure values persisted during handgrip exercise with captopril but not with valsartan. Placebo administration did not result in any tendency to fall in the mean blood pressure values both at supine position and during handgrip exercise. The mean blood pressure values of the participants before and after taking each agent are shown in Table 1.

The heart rate values and HRV parameters of the subjects at baseline were found to be similar on each study day. The significant changes in heart rate values, HRV parameters and the mean blood pressure values produced by handgrip exercise, showed that the handgrip exercise yielded sufficient modification of the cardiovascular autonomic functions resulting in sympathetic stimulation. Captopril but neither valsartan nor placebo administration caused a significant decrease in heart rate values at supine position in comparison to the baseline values (865±33 vs; 917±39, p=0.038) (Figure 1). In contrast, during handgrip exercise after administration each of the three agents, there were no statistically significant changes in heart rate values in comparison to the baseline values. The SDNN values, the global marker of HRV, did not differ significantly at supine position after each agent whereas the SDNN values increased significantly after captopril administration during handgrip exercise compared to placebo (50±5 ms vs. 58±5 ms, p=0.035, respectively). Such an effect was not observed with valsartan administration. Handgrip exercise caused a significant decrease in the RMSSD values that show parasympathetic modulation, however, neither captopril nor the valsartan administration caused significant changes in RMSSD values both at supine position and during handgrip exercise. When the frequency domain parameters are evaluated, it was observed that captopril and valsartan administration did not have any significant effect on absolute powers of LF and HF, LF/Total Power, HF/Total Power and LF/HF ratio parameters both at supine position and during handgrip exercise. Table 2 shows all HRV parameters during handgrip exercise after each drug administration.

Table 1: *Mean blood pressure measurements during both supine position and handgrip exercise on each stage of the study*

	Supine MBP (mmHg)			Handgrip MBP (mmHg)		
	Baseline	Post-Drug	p value	Baseline	Post-Drug	p value
Captopril	82±3	77±2	0.0075	105±3	102±3	0.342
Valsartan	82±1	77±2	0.080	102±2	104±3	0.624
Placebo	86±2	89±3	0.343	107±3	111±4	0.326
MBP: Mean blood pressure						

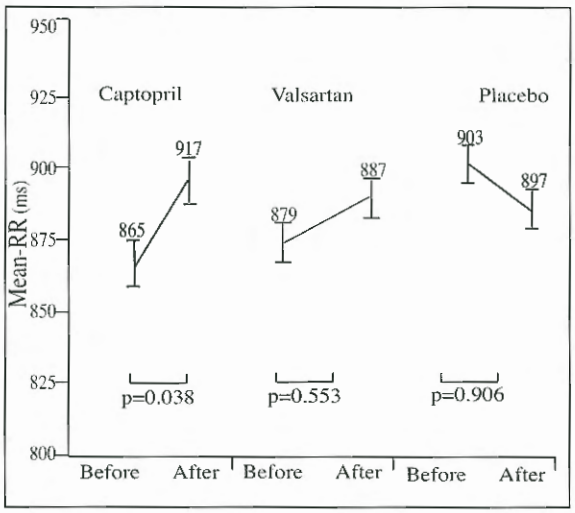

Figure 1: *Mean-RR values of each study session. Captopril administration but not valsartan or placebo causes a decline in heart rate during supine position*

Table 2: *HRV parameters during handgrip exercise after each drug administration*

	Captopril	Valsartan	Placebo
Mean RR (ms)	746±24	731±34	731±27
SDNN (ms)	58±5*	56±5	50±5
RMSSD (ms)	31±3	30±4	26±3
LF (ms^2)	278±26	290±37	300±30
HF (ms^2)	69±7	73±8	60±5
LF/Total Power	0.45±0.04	0.44±0.04	0.47±0.04
HF/Total Power	0.11±0.01	0.12±0.01	0.10±0.01
LF/HF Ratio	4.15±0.32	3.77±0.66	5.37±0.80

ms: millisecond, *p<0.05 compared to placebo

DISCUSSION

Angiotensin II plays a crucial role in the pathophysiology of the cardiovascular diseases. It is known to have negative effects on the prognosis of patients with heart failure or myocardial infarction. These effects cannot be solely explained by hemodynamic actions[16,17]. It has been established that angiotensin II increases sympathetic activity and decreases parasympathetic modulation acting through central and peripheral pathways[18,19]. Numerous studies showed that alterations of cardiac autonomic functions are related to the ultimate prognosis [20,21]. The vagal reactivity is shown to be increased in patients under long-term ACE inhibitor therapy who have shown hemodynamic improvement[22]. Also it is widely accepted that these positive actions of ACE inhibitors on the parasympathetic functions contribute significantly to the improved prognosis[23]. With the advent of angiotensin receptor blockers, it was thought that the specific receptor blockade independent of the angiotensin II level could prevent the unfavorable effects of angiotensin II more strongly, at least the idea was that the angiotensin receptor blockers would have similar beneficial actions as the ACE inhibitors had. However, the studies evaluating the actions of angiotensin receptor blockers on patients with hypertension and congestive heart failure have shown that despite their positive hemodynamic effects this group of drugs did not cause any significant change in heart rate and HRV parameters[24,12]. The fact that although all the cardiac autonomic actions of angiotensin II were mediated by AT1 receptors, their selective blockade did not yield the expected autonomic improvement gained our attention as an area of new investigation. In the human and animal studies evaluating the autonomic effects of these two groups of drugs, angiotensin receptor blockers and ACE inhibitors were compared with respect to their actions on baroreceptor sensitivity and it was concluded that there was no difference between two groups of drugs[25,26]. However to our knowledge, there has been no study yet comparing these two groups of drugs with respect to their actions on HRV parameters. Our study designed in an attempt to address these unanswered questions yielded basically the following results: 1- captopril caused a decrease in the resting heart rate values differently from valsartan, 2- captopril but not

valsartan administration caused an increase in SDNN values during handgrip exercise in comparison to placebo, 3- the resultant increase in SDNN despite the observed increment in sympathovagal balance during mild sympathetic stimulation, led us to consider that this increase might have occurred independent of autonomic modulation, 4- neither captopril nor valsartan did show any effect on the frequency domain parameters.

The finding that captopril caused a decrease in the resting heart rates without changing parasympathetic modulation parameters gave way to the thought that this drug increased vagal tone without influencing vagal modulation. The decrease observed in heart rate values without an accompanying increase in HF power, which is the only vagal modulation marker in the frequency domain parameters, is interpreted in the same way [27]. Similarly, HRV parameters are markers of autonomic modulation rather than mean autonomic tone[9]. These findings led to the consideration that captopril caused an increase in vagal tone but did not cause any change in vagal autonomic modulation at rest. Ajayi and colleagues obtained similar results where they investigated autonomic functions with various maneuvers[28]. In their study, captopril administration to healthy volunteers did not cause any significant change in the parasympathetic response to facial immersion, valsalva maneuver and the baroreflex functions but the absence of reflex tachycardia to the decrease in blood pressure was interpreted as an increase in vagal tone.

The fact that captopril but not valsartan caused a significant increase in SDNN during handgrip exercise in comparison to placebo shows that with captopril administration there is an increase in overall HRV. This action that was manifest during handgrip exercise but not at rest, was interpreted as a result of captopril inhibiting the decrease in HRV caused by sympathetic stimulation and even increasing HRV. To relate the increase observed in HRV to the change in autonomic functions does not seem reasonable when the other parameters are taken into consideration. The reason behind this is that all the parameters except SDNN recorded during exercise point to a decrease in parasympathetic modulation and an increase in sympathetic modulation (decreased RMSSD and HF, increased Mean RR, LF, LF/HF ratio). These findings lead to the consideration that captopril might cause an increase in HRV by not only its actions on the autonomic functions but also by other less well known mechanisms; since HRV is an end-organ response determined by nerve firing, electrochemical coupling, adrenergic receptor sensitivity, postsynaptic signal transduction, and multiple neural reflexes[29]. However there is no evidence showing that captopril and other ACE inhibitors act through the explained mechanisms. Nevertheless, when the results are evaluated from this standpoint, the result that HRV could be influenced by mechanisms other than autonomic functions is reached and indeed the physiological relationship of the low frequency oscillations of HRV are not exactly known[9] and probably the actions of RAS is prominent on these physiological pathways.

Our study demonstrated two different effects on HRV as a result of the renin angiotensin system blockade produced by the two different drug groups. The increase in vagal tone at rest and HRV during handgrip exercise caused by captopril was not observed with valsartan. The different autonomic actions displayed by captopril and valsartan can be explained by the following mechanisms: 1- It has been thought that the central actions of angiotensin II on autonomic functions are mediated through the different angiotensin II receptors in the area postrema and the subfornicular organs, so circulating angiotensin II may have effects on these regions where blood-brain barrier is absent[30]. ACE inhibitors, independently of their ability to cross the blood-brain barrier, decrease the serum concentrations of angiotensin II and thus decrease

the amount of angiotensin II that reaches the centers of interest. On the contrary, angiotensin receptor blockers do not decrease circulating angiotensin II concentrations and may even increase its levels. In order for the angiotensin receptor blockers to inhibit the central actions of angiotensin II they need to cross the blood-brain barrier and reach the angiotensin receptors. The angiotensin receptor blockers are found to cross blood-brain barrier only in high doses in rats and such a finding for humans has not been established yet[31]. Consequently, the thought that central nervous system is exposed to higher angiotensin II levels during angiotensin receptor blocker administration than that with ACE inhibitor is reasonable, 2- Other possible mechanism may be that the autonomic alterations caused by ACE inhibitors are partly independent of their effects on angiotensin II functions. Different from angiotensin receptor blockers it was shown that ACE inhibitors increased serum and tissue concentrations of bradykinin and angiotensin[1-7] [32]. In studies with rats it was shown that both of these peptides act through the central baroreflex mechanisms[33,34]. It is also considered that at the tissue level these molecules directly themselves and indirectly by inducing the synthesis of nitric oxide, prostaglandins and protein kinase-C might influence heart rate control. Nitric oxide was demonstrated to decrease sympathetic efficiency both central and peripheral ways[35,36,37]. As a result we showed that captopril but not valsartan reduces vagal tone at rest and increase HRV during mild exercise. Therefore we conclude that captopril has more favorable effects than valsartan on HRV. However, clinical utility of our findings remain to be determined with further studies.

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