Original Article

Analysis of Heart Rate Variability in Hypertensive Patients Before and After Treatment with Angiotensin II-Converting Enzyme Inhibitors

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Objective

To compare heart rate variability in normotensive and hypertensive individuals and to observe the behavior of the autonomic nervous system after treatment with angiotensin II-converting enzyme inhibitors.

Method

The study comprised 286 patients diagnosed with arterial hypertension (AH) for the first time and divided into 4 groups according to diastolic blood pressure (DBP) levels: group A - DBP<90 mmHg; group B - DBP 90-99 mmHg; group C - DBP 100-109 mmHg; group D - DBP>110 mmHg. Group A (110 healthy individuals) and group C (79 patients with moderate AH) underwent 24-hour Holter-ECG with analysis of heart rate variability in time domain (TD) and frequency domain (FD). The group C patients were treated with ACE inhibitors for 3 months, and, after this period, they underwent a new 24-hour Holter-ECG study for assessing heart rate variability, the values being compared with those of normotensive individuals.

Results

The SDNN and PNN50 parameters (TD), and the LF spectrum (FD) were significantly different in the 2 groups, with clearly reduced values in hypertensive individuals (P<0.05). Group C patients, after treatment with ACE inhibitors, showed a recovery in all variables of heart rate variability, achieving values close to those of normotensive individuals.

Conclusion

Heart rate variability was reduced in hypertensive patients when compared with that in normotensive individuals, indicating a decrease in the baroreceptor reflex. A functional autonomic adjustment after the antihypertensive treatment with ACEI was observed, indicating recovery of parasympathetic tonus.

Key words

arterial hypertension, ACE inhibitors, autonomic nervous system, heart rate variability

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The autonomic nervous system (ANS) plays a fundamental role in the control of arterial blood pressure and heart rate, and, therefore, may be considered an important pathophysiologic factor in the development of arterial hypertension[1]. Currently, the status of autonomic action of the heart may be known through the study of heart rate variability. Heart rate varies per beat as a consequence of the constant adaptations promoted by the ANS to maintain cardiovascular system balance. These alterations may be assessed through the variations in R-R intervals, therefore, constituting the heart rate variability[2]. The integration between the sympathetic and parasympathetic modulations determines heart rate variability[3]. As a research tool, assessment of heart rate variability has provided a better understanding of the participation of the ANS in different physiological and pathological situations of the cardiovascular system. The assessment of heart rate variability has stimulated a large number of observations, indicating the potential value of that approach in the diffusion of knowledge about the alterations in the mechanisms of blood pressure control involved in hypertension[4-6].

The existence of sympathetic hyperactivity has been frequently associated with arterial hypertension[7,8]. Evidence exists indicating that the sensitivity of baroreceptor control, impaired in some hypertensive individuals[9-11], involves mainly parasympathetic mechanisms[12-14].

Although several studies indicate that sympathetic and parasympathetic alterations are simultaneously involved in the pathogenesis and development of arterial hypertension, the results obtained using heart rate variability are controversial. Population-based studies have reported reduced heart rate variability in patients with long-term arterial hypertension, despite treatment with antihypertensive drugs[15]. However, one does not know whether abnormal autonomic cardiovascular regulation is a primary characteristic preceding the onset of hypertension, or whether it may be reversed with antihypertensive therapy. In addition, it is not known whether the improvement in autonomic regulation is related to a reduction in blood pressure or whether it is an immediate effect of the drug[16].

The present study aimed at analyzing and comparing heart rate variability in normotensive and hypertensive individuals and at observing the behavior of the ANS after administration of ACE inhibitors to these hypertensive patients.

Method

This study comprised 286 patients of both sexes, older than 18 years, with the primary diagnosis of essential hypertension, and, therefore, not using antihypertensive medications. The patients selected were informed about the study and signed a written informed consent. A clinical history was obtained and clinical and complementary examinations were performed for assessing arterial hypertension and possible lesions in target organs.

The following patients were excluded from the study: patients with a previous diagnosis of arterial hypertension, whether users or nonusers of antihypertensive medication; patients suspected of having secondary arterial hypertension, or renal, heart or hepatic failure; those who had experienced any recent cardiovascular event; those with neuropathies, diabetes mellitus, autoimmune disease, Parkinson's disease, cardiac arrhythmias, and other conditions affecting neuroautonomic function; and those using antidepressants, neuroleptics, antiarrhythmic drugs, and lithium.

Patients had their blood pressure measured on an outpatient basis, at least 3 distinct times with aneroid sphygmomanometers properly calibrated according to the instructions of the IV Brazilian Guidelines on High Blood Pressure (IV Diretrizes Brasileiras de Hipertensão Arterial)[17] and the Joint National Committee[18]. The mean of the last 2 measurements was used for classification of blood pressure values.

Based on the measurement of diastolic blood pressure, the patients were divided into the following 4 groups according to the classification recommended by the IV Brazilian Guidelines on High Blood Pressure[17]: group A – DBP < 90 mmHg; group B - DBP 90-99 mmHg; group C - DBP 100-109 mmHg; group D – DBP > 110 mmHg.

The patients in groups A and C, with normal blood pressure values and moderate arterial hypertension, respectively, were chosen for follow-up of the analysis of heart rate variability. They underwent 24-hour Holter-ECG monitoring with Hill-Med™ devices, model 3.0, and Hill-10™ tape recorders with magnetic tapes, according to international regulations[2]. Three electrocardiographic leads (V1, V5, and aVF) were recorded during the examination. The recordings were divided into 5-minute segments. All ectopic beats were classified, and only the segments with ectopia smaller than 2% were used. Each abnormal R-R interval was replaced by the next R-R interval. The sequence of normal R-R intervals was analyzed in the time and frequency domains, using the indices described in chart I. The data obtained in the analysis of heart rate variability in groups A and C were then compared.

After analyzing heart rate variability, group C patients were treated with angiotensin II-converting enzyme inhibitors for 3 month, without adding a second drug. Enalapril and ramipril were preferably used due to their greater availability and greater number of studies reported in the medical literature related to their use. The dosage administered varied and depended on the characteristics of each patient. If 1 patient had an adverse effect due to the use of the angiotensin II-converting enzyme inhibitors, the medication was changed and the patient was excluded from the study. After 3 months, these patients underwent a new 24-hour Holter-ECG study and analysis of heart rate variability and were compared again with the normotensive group, independent of their blood pressure levels, to assess possible autonomic alterations resulting from the treatment.

Chart I - Description of the indices of heart rate variability (HRV) used for analysis

Index	Definition	Unit
Time domain		
SDNN	Standard deviation of all R-R intervals	ms
RMSSD	Square root of the mean of the successive differences between adjacent R-R intervals	ms
PNN50	Percentage of successive differences between R-R intervals greater than 50 ms	%
Frequency domain		
LF	Low frequency spectrum (between 0.04 and 0.15 Hz)	ms^2
HF	High frequency spectrum (between 0.15 and 0.40 Hz)	ms^2
LF/HF	LF/HF ratio	-

The data were analyzed using Epi Info 6.2 statistical software. For comparison between the 2 groups and statistical validation, the Pearson correlation (r) and the 2-tailed Student *t* test (p) were used with an alpha of 5% and 95% confidence interval.

Results

Group A comprised 110 (38.4%) patients; group B 69 (24.1%) patients; group C 79 (27.6%) patients; and group D 28 (9.7%) patients. Groups A and C were followed up for analyzing heart rate variability.

The base characteristics of the patients in both groups are shown in table I. Although the hypertensive patients in group C were slightly younger and more obese, and had a greater prevalence of smoking, no significant difference was observed as compared with the findings in the normotensive group. Only the blood pressure levels were significantly different between the 2 groups, but this was already expected.

The 24-hour Holter-ECG was regularly recorded in all patients, and no episode of recording error, which could jeopardize the results of the examination, occurred. All patients had at least 21 hours of recording available for the analysis of heart rate variability. The SDNN (standard deviation of all R-R intervals) ($P = 0.03$), PNN50 (percentage of successive differences between the R-R intervals > 50 ms) ($P < 0.001$), and LF (low frequency spectrum between 0.04 and 0.15 Hz) ($P < 0.001$) were significantly smaller in the hypertensive group when compared with those in the normotensive group (fig. 1 and 2). A nonsignificant tendency towards an increase in the LF (low frequency spectrum)/HF (high frequency spectrum) ratio ($P = 0.06$) could also be observed (fig. 2). No significant difference was observed in the other indices evaluated.

All group C patients received angiotensin II-converting enzyme inhibitors for 3 months, during which time none of them had persistent dry cough or any other adverse effect that could be attributed to the medication. After 3 months, those patients were reassessed. Not all patients achieved satisfactory control of blood pressure with monotherapy with angiotensin II-converting enzyme inhibitors. The mean systolic blood pressure measured after that period was 135 ± 12 mmHg, and the mean diastolic blood pressure was 88 ± 4 mmHg. Those patients underwent a new 24-hour Holter-ECG, and the results were compared with those in the normotensive group.

Table I - Basic characteristics of group A and group C patients

Characteristics	Group A	Group C	P
Age	52.2 ± 10	47.5 ± 12	0.23
Male sex (%)	42%	49%	0.31
BMI (kg/m²)	25 ± 4	27 ± 5	0.21
Smoking (%)	19%	25%	0.09
SBP (mmHg)	118 ± 13	154 ± 21	<0.001
DBP (mmHg)	77 ± 9	103 ± 2	<0.001
HR (bpm)	60 ± 3	65 ± 4	0.08

BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood pressure; HR - heart rate. The values are shown as mean ± standard deviation.

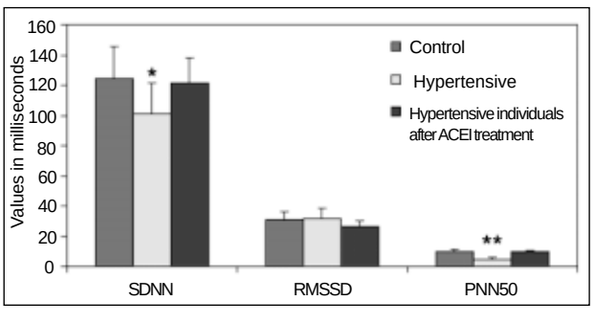

Fig. 1 - Compared analysis of heart rate variability in time domain between group A, group C, and group C after treatment with angiotensin II-converting enzyme inhibitors. *P<0.05; **P<0.001.

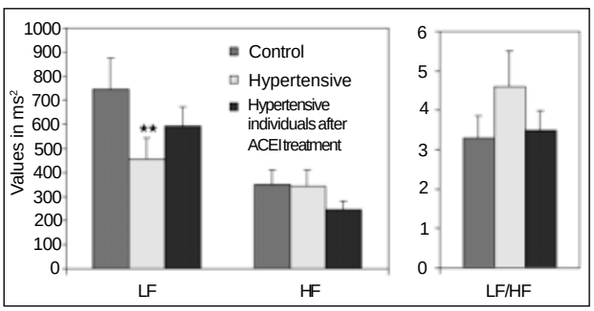

Fig. II - Compared analysis of heart rate variability in frequency domain between group A, group C, and group C after treatment with angiotensin II-converting enzyme inhibitors. **P<0.001.

After administration of the angiotensin II-converting enzyme inhibitors, correction was observed in all parameters of heart rate variability in the hypertensive group, no significant difference being observed between both groups (fig. 1 and 2).

Discussion

Our study found significant distortions in heart rate variability in patients with moderate hypertension when compared with that in a control group of normotensive patients, showing substantial changes in the autonomic function of hypertensive patients, reflected mainly by an accentuated reduction in SDNN, PNN50, and LF.

The differences in heart rate variability between hypertensive and normotensive individuals found in the present study are in accordance with previous reports in regard to changes in SDNN[19], PNN50[20], and LF[15,20,21]. A nonsignificant increase in the LF/HF ratio was also found in hypertensive individuals, similarly to the findings reported by Pikkujamsa et al[9] and Sevre et al[22].

Previous studies reported controversial results in heart rate variability in hypertensive individuals. Usually, the LF spectrum is said to be modulated by sympathetic and parasympathetic activities. Our findings regarding LF may be consequent to the reduction observed in the parasympathetic activity in hypertensive individuals. Some studies reported that when heart rate varied under strictly controlled circumstances, the LF spectrum was mainly influenced by sympathetic activity. However, other data suggest that when heart rate variability is calculated using 24-hour Holter-ECG recordings under unrestricted conditions, the LF spectrum reflects mainly the parasympathetic activity[21], in accordance with our findings.

The decrease in the parasympathetic activity is also implicated in the low PNN50 values in patients with moderate hypertension, because the value of this index of time domain mainly reflects the vagal tonus.

After 3 months of antihypertensive treatment with angiotensin II-converting enzyme inhibitors, a notable recovery was observed in the variables of heart rate variability initially assessed.

The recovery of the parasympathetic tonus, previously reduced in group C patients due to the use of angiotensin II-converting enzyme inhibitors, was consistent with previous investigations showing that angiotensin II is a potent inhibitor of arterial baroreflex activity[16,23]. In addition, Wollert and Drexler[24] reported that the lower sensitivity of the baroreceptor reflex caused by angiotensin II significantly contributes to the pathophysiology of arterial hypertension and also of heart failure.

Several other studies[25-31] reported that the infusion of angiotensin II resulted in an increase in central sympathetic activity. Therefore, it was expected from our results, that a reduction in the concentration of angiotensin II, due to an angiotensin II-converting enzyme inhibitor, would be accompanied by an increase in the parasympathetic tonus and an increase in the activity of the systemic arterial baroreceptor reflex.

The action of the arterial baroreceptors involves mainly a reflex reduction in sympathetic activity and an increase in vagal activity[32]. Our study did not include specific research on the sensitivity of the baroreceptor reflex, but an impaired vagal activity in hypertensive patients, who recover by using angiotensin II-converting enzyme inhibitors, which allows for the inference about the influence of these medications on baroreceptors. Some questions still need clarification, such as whether the alteration in baroreceptor sensitivity precedes or is part of the development of hypertension, or whether the deficiency in the baroreflex control of heart rate depends on the alteration in vagal activity. Because the vagal component predominates in the reflex responses of heart rate[32], and considering our results, it is more evident that is certainly impaired in hypertensive individuals, and, in addition, that the angiotensin II-converting enzyme inhibitors substantially recover the activity of that reflex.

In addition, other physiological effects resulting from the use of angiotensin II-converting enzyme inhibitors should be considered, because the inhibition of this enzyme can alter the concentration of other substances, such as bradykinin, which alone also influences the autonomic balance. Bradykinin has a complex autonomic function, because it can sensitize both vagal stimuli and sympathetic afferent fibers, mediating mechanoreceptors and chemosensitive reflex arches[33-37]. Such mechanisms may also contribute to the course of the autonomic changes observed in this study through the administration of angiotensin II-converting enzyme inhibitors.

Therefore, our findings support those of other studies in the medical literature by demonstrating that heart rate variability,

both in time and frequency domains, is diffusely decreased in patients with moderate arterial hypertension as compared with that in normotensive individuals. This reduction reflects the degree of cardiac autonomic activity determined by the baroreceptor reflexes, which are impaired in arterial hypertension. Our data also allow for the statement that antihypertensive therapy with angiotensin II-converting enzyme inhibitors allows for a significant recovery of the variables of heart rate variability to values close to those in healthy individuals. The antihypertensive therapy with angiotensin II-converting enzyme inhibitors certainly causes an improvement in the autonomic modulation activity and a more satisfactory cardiovascular prognosis in managing hypertensive patients.

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