Heart Rate Variability and Autonomic Nervous System Response in Hypertensive Patients with and without ACE Inhibitors Treatment

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Summary

Heart rate variability evaluation is a useful non-invasive tool for the assessment of autonomic cardiovascular neural inputs. Heart rate variability analysis has been recently proposed for the evaluation of cardiovascular autonomic function in diseases such as hypertension, after several observations indicated the potential of heart rate variability evaluation to expand the knowledge on the alterations in cardiovascular control mechanisms in essential hypertension. Furthermore, the advent of spectral heart rate variability analysis may aid in the estimation of underlying parasympathetic and sympathetic influences. The present study was designed to compare cardiac autonomic control in normotensive and hypertensive patients and observe behavior of the autonomic nervous system following angiotensin-converting enzyme inhibitor therapy in hypertension. A total of 256 subjects underwent ambulatory blood pressure monitoring and the investigation of essential hypertension. Based on the determined diastolic blood pressure, patients were divided in 5 groups (A - E). Patient group A, with normal diastolic blood pressure (mean value 85 ± 7 mmHg) and the groups C with mild hypertension (107 ± 5 mmHg), comprising 110 and 80 patients, respectively, underwent ambulatory 24h Holter ECG recording and subsequent heart rate variability analysis. The SDNN, pNN50, and low-frequency band parameters were significantly different for the two study groups. Patients from group C were thereafter treated with angiotensin-converting enzyme inhibitors over a 3-month period, and a repeated heart rate variability analysis showed recovery of all heart rate variability variables to values not significantly different from the values in patient group A. Our study findings indicated the presence of a functional autonomic adjustment, which was probably due to a protective effect of antihypertensive therapy.

Key Words

Heart rate variability, autonomic nervous system, hypertension, angiotensin-converting enzyme inhibitors

Introduction

Clinical observations from laboratory studies and ambulatory monitoring have shown that systemic hypertension induces significant changes in the entire cardiovascular system. The RR interval lengthening, induced by baroreceptor stimulation, is reduced in both secondary and primary hypertension and also characterizes borderline hypertension. Heart rate variability (HRV) is a recurrent change in R-R intervals characteristic for a balanced cardiac control mechanism. The use of HRV analysis has been stimulated by a number of observations indicating a potential value of this approach to expand the knowledge on the alterations in the cardiovascular control mechanisms underlying the essential hypertension. In particular, when the evaluation of HRV is extended over a 24 hour period, a unique dynamic picture of cardiovascular regulation can be obtained. Seemingly, HRV may represent a useful noninvasive tool for an early diagnosis of the heart and peripheral circulation before problems become clinically evident [1]. The advent of spectral analysis

techniques permits an additional evaluation of the specific parasympathetic and sympathetic influences on heart function.

Hypertension is often associated with findings of sympathetic hyperactivity [2]. There is additional evidence that the sensitivity of the reflex arterial baroreceptor control of heart rate, which is impaired in human hypertension, involves primarily parasympathetic mechanisms [3,4,5]. Although several studies indicated that the sympathetic and parasympathetic changes were jointly involved in the pathogenesis and development of hypertension, the results obtained using HRV analysis were conflicting [6]. Population-based studies demonstrated a reduced HRV in patients with long-term hypertension despite antihypertension treatment [7]. It is not known, however, whether the abnormal cardiovascular autonomic regulation is a primary feature related to and preceding the onset of systemic hypertension or it is can be reversed through intensive drug therapy. Furthermore, it is unknown whether the improvement of autonomic regulation is related to blood pressure reduction or to immediate drug effect [8].

The present study was designed to compare the cardiac autonomic control in normotensive and hypertensive patients. A secondary objective was to observe behavior of the autonomic nervous system after angiotensin-converting enzyme (ACE) inhibitor therapy in selected hypertensive patients.

Material and Methods

A total of 256 subjects using no antihypertensive therapy underwent investigation of essential hypertension and initial screening that consisted of a complete anamnesis and physical examination. The study population was divided into five groups according to the diastolic blood pressure (DBP) determined based on ambulatory blood pressure monitoring (Table 1). Exclusion criteria were conditions likely to affect neuroautonomic function, such as neuropathies, diabetes, heart disease, renal failure, cardiac arrhythmias, and liver disease or any other systemic disease.

Patient groups A and C, with normal blood pressure and mild hypertension, respectively, underwent ambulatory 24h Holter ECG recording. In addition to the evaluation of standard ECG parameters, namely QRS complex duration, type of R-R interval abnormalities, etc., the sequence of all R-R intervals was stored and each interval was labeled with a code number identifying its level of abnormality (if any). The sequence of normal R-R intervals was analyzed in the time and frequency domains using the following variables:

Group	DBP (mmHg)
A - Normotensive	80 to 89
B - Mild hypertensive	90 to 99
C - Moderate hypertensive	100 to 109
D - Severe hypertensive	110 to 119
E - Very severe hypertensive	> 120

Table 1. Classification of patients according to diastolic blood pressure (DBP) level.

Time domain:

- SDNN: Standard deviation of normal-to-normal intervals
- rMSSD: Root mean square of successive differences
- pNN50: Proportion of cycles where the difference was > 50 ms

Freqency domain:

- LF: low-frequency spectral power (0.04 - 0.15 Hz)
- HF: high-frequency spectral power (0.15 - 0.34 Hz)
- LF/HF ratio

Data from patient groups A and C were then compared using Student's t-test. P value < 0.05 was considered statistically significant.

After this initial investigation, patient group C was treated with ACE inhibitors over a period of 3 months. The ambulatory 24h Holter ECG recording and HRV analysis were then repeated to make comparison with the baseline results in normotensive patients (group A).

Results

Figure 1 illustrates distribution of patients over all groups. The two largest groups, A and C, comprised 110 and 80 patients, respectively. These two groups were selected for 24h Holter ECG recording and HRV analysis as their size promised a sound statistical analysis. Mean DBP values were: 85 ± 7 mmHg (group A) and 107 ± 5 mmHg (group C). Mean DBP values in the remaining 66 patients were: 98 ± 7 mmHg (group B), 110 ± 4 mmHg (group D) and 123 ± 5 mmHg (group E).

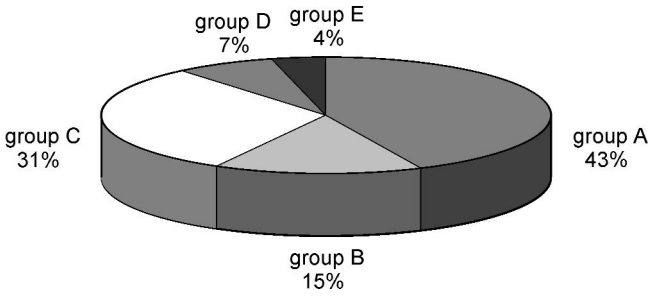

Figure 1. Distribution of patients over groups A-C, according to the criteria defined in Table 1.

The outcome of the HRV analysis is shown in Table 2. A significant difference in the SDNN, pNN50 and LF values was observed between the two study groups. Table 3 compared HRV results in patient group C after 3 months of antihypertensive therapy with the baseline results in patient group A. As seen, there was no significant difference in any parameter.

Discussion

Reports published earlier presented conflicting findings on HRV in hypertensive patients, which may be partly explained by the differences in prevailing physiology that arose during ECG recording. In our study, the LF value in patients with mild hypertension was significantly reduced as compared to the normotensive group. The LF power spectrum is jointly modulated by sympathetic and parasympathetic activity; our findings may be a consequence of the observed reduction in the parasympathetic activity in patients from group C. Several reports indicated that when the HRV analysis was performed under strictly controlled circumstances, the LF power was mainly influenced by sympathetic activity. Other data, however, suggested that when the HRV was calculated from 24h ECG recordings under unrestricted conditions, the LF power spectrum mostly reflected parasympathetic activity [6], which is in accordance with our findings.

Parasympathetic withdrawal is also implied by lower values of pNN50 in patients with moderate hypertension. The pNN50 value represented a percentage of the difference > 50 ms between adjacent normal RR-intervals, computed over the entire 24h ECG recording. The pNN50 parameter belongs to the time domain HRV analysis and strongly reflects vagal tone. Despite the evidence that blood pressure differences should not be responsible for the differences in HRV parameters in normotensive versus moderately hypertensive patients, after 3-month antihypertensive treatment with ACE inhibitors we observed a noticeable recovery of all HRV variables initially evaluated (Tables 2 and 3). Yitalo et al. postulated that reducing circulating levels of angiotensin II and aldosterone using ACE inhibitors could increase HRV [8]. Previously, Wolk suggested that ACE inhibitors could selectively augment vagal cardiac responses to carotid stimuli [9].

	Group A	Group C	P value
SDNN (ms)	124.6	101.4	< 0.05
rMSSD (ms)	30.9	32.0	ns
pNN50 (%)	9.6	4.8	< 0.05
LF (ms^2)	747.7	453.7	< 0.05
HF (ms^2)	351.1	341.7	ns
LF/HF	3.3	4.6	0.06

Table 2. Comparative analysis of heart rate variability in normotensive subjects (group A) versus moderately hypertensive patients before antihypertensive drug therapy (group C).

	Group A	Group C after treatment	P value
SDNN (ms)	124.6	121.3	0.68
rMSSD (ms)	30.9	29.5	0.71
pNN50 (%)	9.6	9.5	0.94
LF (ms^2)	747.7	591.2	0.09
HF (ms^2)	351.1	247.2	0.21
LF/HF	3.3	3.3	0.92

Table 3. Comparative analysis of heart rate variability in normotensive subjects (group A) versus moderately hypertensive patients (group C) after 3 months of antihypertensive therapy.

Conclusion

Heart rate variability analysis is increasingly important therapeutic and diagnostic method, facilitated by its noninvasive nature and ease of handling with the aid of modern data processing tools. Several standards have been already introduced in the field of statistical evaluation of HRV measurements, with spectral analysis of normal beat-to-beat intervals being used to classify HRV [10]. Even though research aimed at establishing quantitative criteria for classification of the autonomic nervous system status is still ongoing, our study evidenced that antihypertensive therapy in hypertensive patients led to a recovery of HRV variables to the values seen in healthy subjects. In this way, at least a qualitative marker that reflects autonomic dysfunction status has been found.

References

[1] Parati G, Rienzo M, Roppelli A, et al. Heart rate and blood pressure variability and their interaction in hypertension. In: Malik M, Camm AJ (eds). Heart Rate Variability. Mount Kisco, NY; Futura Publishing Company. 1995: 467-478.

[2] Piccirilo G, Munizzi MR, Fimognari FL, et al. Heart rate variability in hypertensive subjects. International J Cardiol. 1996; 53: 291-298.

[3] Mancia G, Ludbrook J, Ferrari A, et al. Baroreceptor reflex in human hypertension. Cir Res. 1978; 43: 170-177.

[4] Mancia G, Ferrari A, Gregorini L, et al. Control of blood pressure by carotid sinus baroreceptor in human beings. Am J Cardiol. 1979; 44: 895-902.

[5] Mancia G, Mark A. Arterial baroreflexes in humans. In: Shepard JT, Abbud FM (eds). Handbook of Physiology, the Cardiovascular System III. American Physiological Society, 1983: 755-793.

[6] Petretta M, Bianchi V, Marciano F, et al. Influence of left ventricular hypertrophy on heart period variability in patients with essential hypertension. J Hypertension. 1995; 13: 1299-1306.

[7] Huikuri HV, Ylitalo A, Pikkujämsä SM, et al. Heart rate variability in systemic hypertension. Am J Cardiol. 1996; 77: 1073-1077.

[8] Yitalo A, Airaksinen KEJ, Sellin L, et al. Effects of combination antihypertensive therapy on baroreflex sensitivity and heart rate variability in systemic hypertension. Am J Cardiol. 1999; 83: 885-889.

[9] Wolk R, Kulakowski P, Ceremuzynski L. Nifedipine and captopril exert divergent. Effects on heart rate variability in patients with acute episodes of hypertension. J Human Hypertension. 1996; 10: 327-332.

[10] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996; 93: 1043-1065.

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