



HEART RATE AND BLOOD PRESSURE VARIABILITY IN HYPERTENSIVE PATIENTS

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Summary. The aim of our research was to compare heart rate variability and blood pressure variability in hypertensives with (LVH) or without LVH and to prove their correlation with degree LVH and the degree of ventricular arrhythmias discovered by Holter monitoring.

Design and Methods: 28 hypertensive patients, aged 56.5 ± 7 were examined. All the patients had a echocardiogram recording, 24 h ambulatory blood pressure monitoring and 24 h electrocardiographic monitoring (DelMar system). Eighteen patients, aged 57.5 ± 8 had LVH with left ventricular mass index (ILVM) 168.7 ± 17.5 g/m² while 10 patients without LVH aged 54.7 ± 5.4 and ILVM: 110.9 ± 8.4 .

Results: ILVM correlated to standard deviation of all NN intervals (SDNN) ($R=0.57$; $p<0.002$), standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN) ($R=0.57$; $p<0.001$), standard deviation 24 hours systolic blood pressure ($R=0.44$; $p=0.025$) and to degree BP reduction at night (systolic BP: $R=-0.52$; $p=0.013$ and diastolic BP: $R=-0.439$; $p=0.041$). Patients with LVH had a considerably lower SDNN- (104.3 ± 33 vs 147.7 ± 7.9 ms; $p<0.001$) and lower SDANN- (93.1 ± 26 vs 137 ± 8.4 ms; $p<0.005$). The degree of ventricular arrhythmias correlated to SDNN ($p<0.005$) and SDANN ($p<0.005$). Standard deviation systolic BP in 24 hour time was higher in patients with LVH but that deviation was not statistically relevant (16.4 ± 6 vs 13.1 ± 2) while the decrease of systolic BP in these patients was smaller during the night (8.3 ± 8 vs 12.4 ± 4 %). 12 out of 18 patients with LVH belonged to a non dipper group (67%) while there were 2 patients (33%) in the group without LVH.

Conclusions: Increased sympathetic activity was associated with degree of LVH and degree ventricular arrhythmias.

Key words: Hypertension, left ventricular hypertrophy, heart rate variability, blood pressure variability, ventricular arrhythmias

Introduction

The role of the autonomic nervous system in essential hypertension is an important area of investigation. Does essential hypertension result from augmented sympathetic activity with altered responsiveness of neural regulatory mechanisms (1)?

Arterial hypertension is usually accompanied with many cardiovascular diseases, such as myocardial infarct, heart insufficiency, cerebrovascular insult and sudden death. A main aim of a clinical doctor who specializes in hypertension is to find out high risk patients who are liable to these complications.

Data from Framingham Heart Study also showed that the detection of left ventricular hypertrophy (LVH) by echocardiography provides persuasive prognostic information beyond that derived from traditional risk factors such as blood pressure, smoking, and lipid

levels. In that study as well as in the investigation carried out at the New York Hospital-Cornell Medical Center, left ventricular mass and age were the strongest predictors of prognosis (2).

The mechanism of LVH occurrence in arterial hypertension is very complex. Blood pressure, sympathetic nervous system, hormones, growth factors, age, sex, race, are interrelated and determine its development.

In vitro studies have shown that the addition of adrenergic agonists to the perfusing medium stimulates cardiac myocyte and vascular smooth muscle growth. This provides evidence that adrenergic influences favour the structural alterations and LVH (3).

Importantly, there is an association of LVH with complex ventricular arrhythmias, a possible precursor of sudden death in hypertensive patients.

Ventricular arrhythmias on ambulatory electrocardiographic (ECG) monitoring have been shown to have independent prognostic value for both the prediction of

sudden cardiac death and total cardiac death (4,5,6).

Heightened sympathetic activity has been shown to favour the development of cardiac arrhythmias, whereas increased vagal tone is thought to be protective. Heart rate variability has been shown to be a non-invasive marker of autonomic input into the heart (7).

Patients with greater BP variability had a significantly higher level of end-organ damage than those with the same mean BP level, but less variability. BP variability is a highly complex phenomenon and both very slow fluctuations and much more rapid changes commonly occur in response to a variety of factors (8,9).

Having all this in mind we wanted in our research to compare the heart rate variability and blood pressure variability in hypertensives with left ventricular hypertrophy (LVH) or without LVH, and to prove their correlation with degree LVH and the degree of ventricular arrhythmias discovered by Holter monitoring.

Subjects and methods

We studied 28 patients with essential hypertension, aged 56.5 ± 7 . Criteria for patient selection, have been: 1) age ranging from 40 to 65 years; 2) patients must have sitting diastolic blood pressure, mean readings of 90 to 115 mm Hg or sitting systolic blood pressure mean readings of 160 to 200 mm Hg after a 2-week period without antihypertensive drugs (previously treated patients) or a 1-week observation period (previously untreated patients). Exclusion criteria were secondary hypertension, history and/or signs of cardiovascular complications (eg, congestive heart failure, myocardial infarction, stroke, angina pectoris) or major target organ damage (eg, serum kreatinin >1.5 mg/dL).

All the patients had an echocardiogram recordings, 24 h ambulatory blood pressure monitoring and 24 h electrocardiographic monitoring (DelMar system).

Echocardiography The echocardiographic studies were performed in the morning, with the subject in a supine left lateral decubitus position, after 30 minutes of rest. Only one physician was responsible for recording the echocardiogram. The measurements of left ventricular wall thickness and chamber diameter were made in diastole in accordance with methods outlined by the American Society of Echocardiography. Left ventricular mass (LV mass) was estimated by the modified cubed formula using measurements obtained in accordance with the "Penn" convention:

$$LV_{mass} (g) = 1.04 [(LVIDd + IVSd + PWTd)^3 - (LVIDd)^3] - 136$$

where LVIDd is left ventricular internal dimension, IVSd is ventricular septal thickness, and PWTd is posterior left ventricular wall thickness in diastole.

LV mass indexed by body surface area (g/m^2). Cut-off values for LV hypertrophy by Penn convention (g/m^2) criteria were ≥ 134 g/m^2 for men and ≥ 110 g/m^2 for women. Left ventricular wall thickness was defined

as $\text{sum IVST and PWT, relative wall thickness was defined as (left ventricular wall thickness/LVID) \times 100\%$ and index LVID (LVID/ body surface area (10).

Ambulatory blood pressure monitoring was performed with Del Mar Avionics, model P-VA or P6 equipment. The monitoring equipment was applied in the morning after the medical visit. The device was set to obtain automatic blood pressure readings at 15-minute intervals during the day (from 7 AM to 11 PM) and at 30-minute intervals during the night (from 11 PM to 7 AM). The results are consisted of (1) the calculation of 24-hour average SBP, DBP, and heart rate, (2) separate calculations of daytime and nighttime average blood pressures and heart values and differences (nocturnal SBP and DBP fall - %) and (3) the standard deviation (SD) of 24h average blood pressure (11).

24-hour Holter monitoring (model 465; Del Mar Avionics, Irvine, California).

Evaluation of premature ventricular complexes followed the grading system of Lown and Wolf (12,13). Since the classification suggested by Lown and Wolf combines prevalence with morphology of ventricular ectopy, in a second analysis we compared hypertensive patients with complex ventricular ectopy with those without complex ventricular ectopy.

The program automatically detects abnormal QRS complex and filters them out, so that the HRV is calculated only on NN intervals with normal QRS complexes. The program produced the following time-domain indexes: 1) standard deviation of all 24-hour NN intervals (SDNN, ms); 2) SD of the average NN intervals in all 5-minute segments (SDANN); and 3) the root-mean square of successive differences between adjacent normal NN intervals (rMSSD, ms). The first 2 indexes reflect total HRV, whereas the rMSSD reflect vagal tone (14).

Results

The eighteen patients with and ten patients without left ventricular hypertrophy did not significantly differ in regard to age (mean age of 57.5 ± 8 years with LVH and 54.7 ± 5.4 without LVH), gender, body habitus and conventional laboratory parameters.

In contrast, the patients with left ventricular hypertrophy had higher left ventricular mass index (168.7 ± 17.5 g/m^2 vs 110.9 ± 8.4 g/m^2 , $p < 0.0001$) (Table 1).

The ventricular arrhythmias degree was higher in patients with LVH than in those without LVH, but the difference was not statistically significant ($p < 0.09$) (Table 2)

The patients with LVH had a significantly lower heart rate variability than the patients without LVH in all three parameters of time domain analysis (Table 2).

Variability BP, expressed in standard deviation average 24 SBP and DBP was higher in the patients

with LVH, but the difference was not significant. Average BP fall during night was less in the patients with LVH, but it was statistically insignificant, either (Table 2).

Table 1. Clinical and echocardiographic characteristics of patients with essential hypertension with and without left ventricular hypertrophy

Variable	LVH (n=18)	no LVH (n=10)
Age	57.5±8	54.7±5.4
SBP mmHg	177.7±27.8	160.6±16.1
DBP mmHg	109.8±11.8	101.4±7.5
HR /min	74.2±13	70.9±8.3
BSA	1.9±0.2	1.9±0.1
LV mass index g/m ²	168.7±17.5***	111±8.5
IVSd mm	12.9±1.3	11.25±1.03
PWTd mm	11.4±1	10.25±0.4
LVIDd mm	52.7±4.6	50.8±3.5
E/A	0.89±0.2	1.01±0.4

Values are unadjusted means ±SD. IVSd, interventricular septum thickness; PWTd, posterior wall thickness; LVIDd, left ventricular internal dimension in diastole; E/A, peak of early and late filling velocity. *** p<0,001

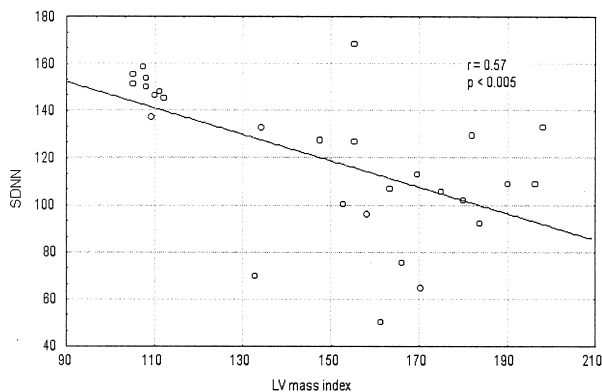


Fig. 1. Correlation between the standard deviation of all 24-hour NN intervals (SDNN, ms) and echocardiographically derived left ventricular mass index.

Table 2. Left ventricular mass index, heart rate variability and blood pressure variability in hypertensive patients with and without left ventricular hypertrophy

Variable	LVH	no LVH
LV mass index g/m ²	168.7±17.5***	111±8.5
SDNN ms	104.3±28.2***	147.7±7.9
SDANN ms	93.2±26.1**	137±8.9
rMSDD ms	24.7±15.5**	27.2±3.8
VA (Lown)	3.1±1.5	1.7±1.2
SD average 24 SBP mmHg	16.4±5.5	13.1±2.2
SD average 24 DBP mmHg	16±5.3	14.1±1.6
Nocturnal SBP fall %	8.3±7.6	12.4±4.5
Nocturnal DBP fall %	13.7±5.9	15.7±2.5

Values are unadjusted means ±SD. VA, ventricular-arrhythmias; SD, standard deviation. *** p<0,001, ** p<0,005.

LVH degree expressed in LVM index significantly correlated in negative terms ($R=-0.57$; $p<0.002$) with variability parameters of heart frequency (SDNN and SDANN) and SBP variability expressed in standard deviation ($R=0.44$; $p<0.03$) (Table 3).

A degree of correlation between SDNN and LVM index is graphically shown on the graph 1. It was also noticed a significant correlation between degree of ventricular arrhythmia registered by Holter and variability of heart frequency, as shown in Table 4 and Graph 2.

Finally, a significant correlation between heart rate variability and systolic blood pressure variability was detected. ($R=0.44$; $p = 0.03$) (Graph 3).

Table 3. Heart rate variability and blood pressure variability vs. Left ventricular mass index in hypertensive patients

Variable	Correlation of HR and BP variability vs left ventricular mass index	
	R	p
SDNN ms	-0.57	.002
SDANN ms	-0.57	.002
rMSDD ms	-0.14	N.S.
VA /Lown	0.33	N.S.
SD average 24 SBP mmHg	0.44	.03
SD average 24 DBP mmHg	0.38	N.S.
Nocturnal SBP fall %	-0.21	N.S.
Nocturnal DBP fall %	-0.43	.04

R: correlation coefficient

Table 4. Ventricular arrhythmias and blood pressure variability vs heart rate variability (SDNN)

Variable	Correlation of HR variability vs ventricular arrhythmias and BP variability	
	R	p
VA /Lown	-0.54	.003
SD average 24 SBP mmHg	-0.43	.03
SD average 24 DBP mmHg	-0.4	N.S.
Nocturnal SBP fall %	0.01	N.S.
Nocturnal DBP fall %	0.17	N.S.

R: correlation coefficient

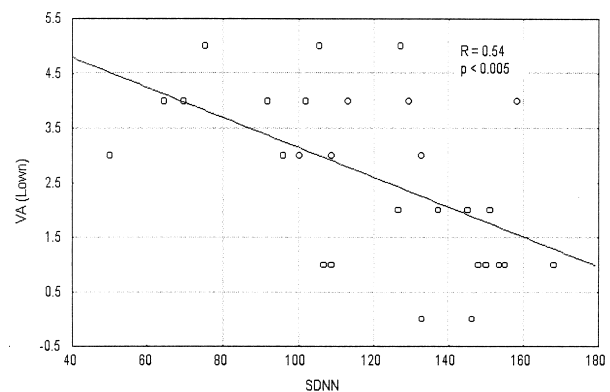


Fig. 2. Correlation between the VA (Lown) after 24-hour Holter monitoring and the standard deviation of 24h SDNN.

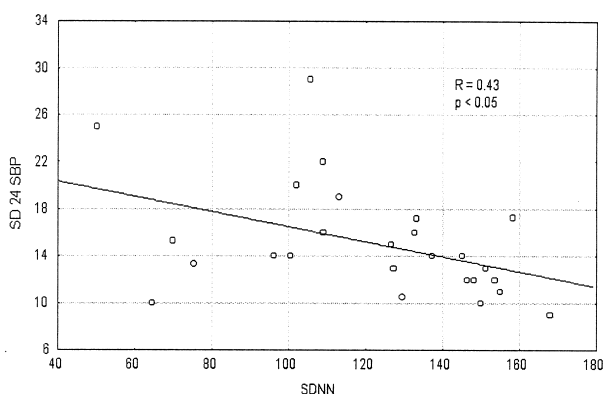


Fig. 3. Correlation between the standard deviation of all 24-hour NN intervals (SDNN, ms) and standard deviation of 24h average blood pressure.

Discussion

The findings in this study do establish an association between hypertensive target organ damage (LVH) with heart rate variability and blood pressure variability.

Analyzing correlation between left ventricular mass in hypertensive patients and other clinical parameters including blood pressure rates, measured in 24-hour ambulatory monitoring by exercise tests, age, sex, body surface etc, we found out that HRV showed the greatest correlation.

The biological mechanism explaining our present results is unknown. In a meta-analysis of a large number of studies Goldstein showed that in essential hypertensive individuals plasma norepinephrine concentration was higher than in normotensive controls (15). In vitro studies have shown that the addition of adrenergic agonists to the perfusing medium stimulates cardiac myocyte and vascular smooth muscle growth. This provides evidence that adrenergic influences favour the structural alterations of the cardiovascular system (3).

Heart rate variability is a marker of sympathetic and parasympathetic influences on the modulations of heart rate. These findings suggest that the level of end-organ damage correlates with neuronal alteration in essential hypertension.

Analyzing pathoanatomic and electrophysiologic characteristics of myocard in LVH it can be shown that hypertensive myocard has a tendency to show electric instability and arrhythmias. The hypothesis of hypertrophy per se leading to electrophysiologic changes that may trigger lethal arrhythmias may be even more attractive.

It has been suggested that the increased incidence of sudden death in hypertensive patients, particularly those with left ventricular hypertrophy, may be casually related to the increased number and complexity of ventricular arrhythmias that have been demonstrated in these patients (5,16,17).

Importantly, there is an association of LV hypertrophy with complex ventricular arrhythmias. The pathologic findings related with ectopic impulse generation in LVH are multifactorial (18) and include enlarged myocytes, the expansion of the collagen matrix, fibrosis, subendocardial ischemia and medial hypertrophy of the coronary arteries, impending homogeneous impulse propagation throughout the myocardium. The arrhythmogenic substrate of LV hypertrophy itself may explain reentry mechanisms, such as fibrillar stretching, anisotropy, and triggered activity due to late potentials, depending on activation of slow calcium channels.

Heart rate variability is a powerful predictor of arrhythmia-related complications in patients surviving the acute phase of myocardial infarction. The predictive value of depressed heart rate variability after myocardial infarction has been shown to be independent of other risk factors, such as left ventricular ejection fraction, frequency of ventricular premature complexes on the 24-h Holter recording and the presence of late potentials on signal-averaged electrocardiograms (ECGs) (19).

In patients with heart disease, increased sympathetic tone an/or decreased parasympathetic tone, which predispose to ventricular fibrillation, have been proposed as mechanisms explaining the associations of reduced heart rate variability with increased mortality (20,21).

A part from an obvious correlation between hypertension, left ventricular hypertrophy, ventricular arrhythmias and a decrease of heart rate variability, our research pointed out to a special risk group in hypertensive population.

In this study we used Time Domain Methods measurement of HRV software pacjet by Del Mar company. We analyzed three time domain HRV assessment (parameters):

- 1) standard deviation of the NN intervals (SDNN) - estimate of overall HRV - and approximate frequency domain correlate total power;
- 2) standard deviation of the average NN intervals, calculated over shorts periods - 5 minutes (SDANN) - estimate of long-term components of HRV - and approximate frequency domain correlate ULF;
- 3) the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) - estimate of short-term components of HRV - and approximate frequency domain correlate HF (14).

The results of this study showed that blood pressure variability registered as the standard deviation of 24-hour average blood pressure correlated with index left ventricular mass and ventricular arrhythmias. Our patients with higher standard deviation and small BP decrease during night had a more severe LVH degree and ventricular arrhythmias.

Furthermore, this correlation between HRV and BP variability pointed out the similar mechanisms which are the base of this problem.

This findings may have very important clinical

implications. Firstly, it is possible to detect hypertensive patients of greater risk (LVH, decrease of HRV, increase of BP variability) with greater precision and secondly it suggests, that even if we control clinic BP more or less perfectly, we cannot eliminate the cardiovascular risk. Whether regression of LVH, increased HRV and eliminating BP variability will provide the answer, remains to be determined.

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Conclusion

Decreased heart rate variability and increased BP variability were associated with degree of LVH and degree of ventricular arrhythmias in our hypertensive patients.

VARIJABILNOST SRČANE FREKVENCE I KRVNOG PRITISKA U HIPERTENZIVNIH PACIJENATA

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Kratka sadržaj: Cilj naše studije bio je da uporedi varijabilnost srčane frekvence i varijabilnost krvnog pritiska u pacijenata sa hipertrofijom leve komore (HLK) ili bez nje, i utvrdi njihovu korelaciju sa stepenom HLK i ventrikularnih aritmijama utvrđenih Holter monitoringom

Metod: 28 pacijenata, starosti 56.5±7 uključeno je u studiju. Svim pacijentima urađen je ehokardiografski pregled, 24 satni monitoring krvnog pritiska i 24 satni monitoring EKG (Holter sistem - DelMar). Osamnaest pacijenata, starosti 57.5±8 imalo HLK sa prosečnim indeksom mase leve komore (ILVM) 168.7±17.5 g/m2 dok je 10 pacijenata bilo bez

HLK starosti 54.7±5.4 i ILVM: 110.9±8.4.

Rezultati: ILVM korelisao je standardnom devijacijom svih NN intervala (SDNN) (R=0.57; p<0.002), standardnom devijacijom NN intervala u 5-minutnim segmentima registrovanja (SDANN) (R=0.57; p<0.001), standardnom devijacijom 24 satnog sistolnog krvnog pritiska (R=0.44; p=0.025) i stepenom smanjenja krvnog pritiska u toku noći (sistolni KP: R=-0.52; p=0.013 and diastolni KP: R=-0.439; p=0.041). Pacijenti sa HLK imali su značajno manju SDNN-(104.3±33 vs 147.7±7.9 ms; p<0.001) i manju SDANN-(93.1±26 vs 137±8.4 ms; p<0.005) nego pacijenti bez HLK. Stepem ventrikularnih aritmija korelisao je sa SDNN (p<0.005) i SDANN (p<0.005). Standardna devijacija sistolnog KP u toku 24 sata bila je veća u pacijenata sa HLK ali ta razlika nije statistički značajna (16.4±6 vs 13.1±2). Ova grupa pacijenata pokazala je manji pad sistolnog KP u toku noći (8.3 ± 8 vs 12.4 ± 4 %). 12 od 18 pacijenata sa HLK pripadalo je non dipper grupi (67%) dok samo 2 pacijenta (33%) iz te grupe nije imalo HLK.

Zaključak: Povećana simpatička aktivnost u hipertenzivnih bolesnika udružena je sa težim stepenom HLK i ventrikularnih aritmija.

Ključne reči: Hipertenzija, hipertrofija leve komore, varijabilnost srčane frekvence, varijabilnost krvnog pritiska, ventrikularne aritmije

Received: November 3, 1998