Differences in autonomic activity in individuals with optimal, normal, and high-normal blood pressure levels

Optimal, normal ve yüksek-normal kan basıncı düzeyleri olan kişilerde otonomik aktivite farklılıkları

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Objectives: We investigated differences in autonomic activity in normotensive individuals having optimal, normal and high-normal blood pressure (BP) levels according to the guidelines of the European Society of Hypertension and European Society of Cardiology (ESH/ESC).

Study design: The study included 294 normotensive subjects (135 males, 159 females; age range 16 to 75 years) with similar clinical, morphometric, biochemical, electrocardiographic, and echocardiographic features. The subjects were classified into the following BP groups: group 1 (n=113) with optimal BP (<120/80 mmHg); group 2 (n=104) with normal BP (120-129/80-84 mmHg), and group 3 (n=77) with high-normal BP (130-139/85-89 mmHg). All the subjects underwent 24-hour Holter monitoring to obtain heart rate variability (HRV) parameters of 24-hour, daytime, and nighttime periods. Normalized low (LF_n) and high (HF_n) frequency powers, and logarithmic (Log) values of HRV parameters were also calculated.

Results: On 24-hour Holter monitoring, heart rates were similar in three groups. Compared to group 1 and 2, group 3 exhibited significantly higher LF/HF ($p<0.001$) and LF_n ($p=0.001$) values, and significantly lower HF_n ($p=0.001$), pNN50 ($p=0.001$), and rMSSD ($p=0.005$) values. There were no significant differences between the groups with respect to daytime HRV parameters; however, nighttime LF/HF, LF_n, and HF_n values were significantly different between the groups. Log LF/HF values obtained during the 24-hour and nighttime periods showed significant differences between group 1 and group 3 (for 24 hours, $p<0.001$; for night, $p=0.001$) and between group 2 and group 3 (for 24 hours, $p<0.001$; for night, $p=0.009$), but group 1 and group 2 did not differ significantly in this respect ($p>0.05$).

Conclusion: These findings suggest that subjects with high-normal BP have increased sympathetic activity and decreased parasympathetic activity, possibly making them more liable to hypertension.

Key words: Autonomic nervous system; blood pressure; electrocardiography, ambulatory; heart rate; hypertension.

Amaç: Bu çalışmada, kan basıncı (KB) normal sınırlarda olan ve Avrupa Hipertansiyon Derneği ve Avrupa Kardiyoloji Derneği (ESH/ESC) kılavuzuna göre KB optimal, normal ve yüksek-normal olarak sınıflandırılan kişilerde otonomik aktivite farklılıkları araştırıldı.

Çalışma planı: Çalışmaya, klinik, morfometrik, biyokimyasal, elektrokardiyografik ve ekokardiyografik özellikleri benzer bulunan ve KB normal sınırlarda olan 294 kişi (135 erkek, 159 kadın; yaş dağılımı 16-75) alındı. Olgular KB'ye göre şu gruplara ayrıldı: Grup 1 (n=113) optimal KB (<120/80 mmHg), grup 2 (n=104) normal KB (120-129/80-84 mmHg), grup 3 (n=77) yüksek-normal KB (130-139/85-89 mmHg). Tüm olgulara 24 saatlik Holter takibi yapılarak, 24 saat, gündüz ve gece süresince kalp hızı değişkenliği (KHD) parametreleri araştırıldı. Ayrıca, normalleştirilmiş düşük (LF_n) ve yüksek (HF_n) frekans güçleri ve KHD parametrelerinin logaritmik (Log) değerleri de hesaplandı.

Bulgular: Yirmi dört saatlik Holter takibinde grupların kalp hızı değerleri benzer bulundu. Grup 1 ve 2 ile karşılaştırıldığında, grup 3'te LF/HF ($p<0.001$) ve LF_n ($p=0.001$) değerleri anlamlı derecede yüksek, HF_n ($p=0.001$), pNN50 ($p=0.001$) ve rMSSD ($p=0.005$) değerleri anlamlı derecede düşük bulundu. Üç grup arasında gündüz KHD parametreleri arasında anlamlı farklılık görülmedi; ancak, gece LF/HF, LF_n ve HF_n değerleri anlamlı farklılık gösterdi. Yirmi dört saatlik ve gece için hesaplanan Log LF/HF değerleri grup 1 ile grup 3 (24 saat için $p<0.001$; gece için $p=0.001$) ve grup 2 ile grup 3 (24 saat için $p<0.001$; gece için $p=0.009$) arasında anlamlı farklılık gösterirken, grup 1 ile grup 2 arasında bu açıdan anlamlı farklılık görülmedi ($p>0.05$).

Sonuç: Bu sonuçlar, yüksek-normal KB olan kişilerde sempatik aktivitede artış, parasempatik aktivitede ise azalma olduğunu; bu durumun bu kişileri hipertansiyona daha yatkın hale getirdiğini göstermektedir.

Anahtar sözcükler: Otonomik sinir sistemi; kan basıncı; elektrokardiyografi, ambulatuvar; kalp hızı; hipertansiyon.

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Blood pressure regulation is maintained by multiple regulatory physiologic mechanisms. Autonomic nervous system is one of the most important regulation mechanisms of blood pressure (BP).[1,2] Hypertension is a good example for this condition. Although several studies have shown that hypertension is a multifactorial disease, autonomic dysfunction is of special importance because of being both a reason and a consequence of hypertension.[3,4] It is well-known that high BP is associated with increased sympathetic activity and autonomic circadian rhythm abnormalities.[5-8] Subjects with high-normal BP or prehypertension have a higher risk for hypertension than those with normal BP. Prehypertension is considered to be a precursor of stage 1 hypertension and a predictor of excessive cardiovascular risk.[9-11] It has been shown that patients with high-normal BP have faster heart rates even after adjustment for body mass index.[12] Autonomic dysfunction is another important factor for the progression of hypertension. Although correlation between prehypertension and sympathetic overactivity is well-studied, data on autonomic activity differences between normal and high-normal BP levels are rare.

In the present study, we aimed to investigate autonomic activity differences in individuals having normal and high-normal BP levels as defined by the ESH/ESC guidelines (European Society of Hypertension and European Society of Cardiology).[9]

SUBJECTS AND METHODS

Study group. Subjects who presented for general health examination were diagnosed and classified according to the ESH/ESC guidelines after detailed history taking and physical examination.[9] Only the subjects whose BP was less than 140/90 mmHg were selected for the study. Thus, a total of 294 subjects (135 males, 159 females; age range 16 to 75 years) were enrolled into the study. The subjects were classified into the following study groups according to the BP levels: group 1 (n=113): optimal BP (<120/80 mmHg); group 2 (n=104): normal BP (120-129/80-84 mmHg); and group 3 (n=77): high-normal BP (130-139/85-89 mmHg).

The following parameters were determined as the exclusion criteria: acute or chronic renal dysfunction, diabetes mellitus, metabolic syndrome, hypertension (≥140/90 mmHg), white coat hypertension (elevated office BP+normal BP out of office) and masked hypertension (normal office BP+elevated BP out of office), heart failure (EF <%50), valvular heart disease, cardiomyopathies, atrial fibrillation, sick sinus syndrome, supraventricular and ventricular tachycardias, aortic disease (Marfan's syndrome, coarctation of the aorta, aortic aneurysms or aortic surgery, etc.), history of coronary artery disease or proven coronary artery disease on coronary angiography or noninvasive tests, familial hyperlipidemia, asthma or chronic obstructive lung disease, pregnancy or oral contraceptive use, use of medications that might affect BP, connective tissue disorders, neurological problems, malignancies, psychiatric diseases, endocrinologic diseases, smoking, alcohol use, drug abuse, and use of medications for hormonal treatment within the last six months.

All the subjects gave written informed consent and the study was approved by the local ethics committee.

Blood pressure measurements. Subjects were instructed not to consume drinks containing caffeine throughout 2.5 hours and not to perform excessive physical activity prior to BP measurements. Blood pressure was measured three times for each subject with a standard mercury sphygmomanometer on the right arm in the sitting position after a 10-minute rest. Phase I and V Korotkoff sounds were used to determine systolic and diastolic BP, respectively. In each subject, measurements were performed in the same room and at the same time of the day by a paramedic. The average of three measurements was used for the analyses.

Echocardiographic examination. All the subjects underwent standard transthoracic echocardiography in the left lateral decubitus position by using a Vivid 7 Pro machine with a 2.5 Mhz probe (General Electric, Florida, USA). Standard transthoracic views were used to determine end-diastolic and end-systolic volumes, stroke volume index, left ventricular ejection fraction, transmitral E and A wave velocities, E/A ratio, deceleration time, isovolumetric relaxation and contraction times, ejection time, left ventricular mass, left ventricular mass index, and myocardial performance index.

Heart rate variability. Heart rate variability (HRV) parameters were derived from the recordings of 24-hour Holter monitoring and analyzed as recommended previously.[12,13] A three-channel, 24-hour Holter recording was obtained from each subject using the Del Mar-Impresario system and software (Del Mar Impresario Medical Systems, Irvine, CA, USA).

Time-domain HRV parameters included the following measures:

- rMSSD (msec): Square root of the mean of the squares of differences between successive RR intervals.

Table 1. Characteristics of the three blood pressure groups

	Group 1 (n=113) (Mean±SD)	Group 2 (n=104) (Mean±SD)	Group 3 (n=77) (Mean±SD)
Age (years)	39±11	41±11	43±12
Height (cm)	165±9	167±7	167±7
Weight (kg)	78.4±14.5	79.5±16.0	81.0±11.7
Body mass index (kg/m^2)	28.9±6.1	28.4±5.6	29.1±4.6
Waist (cm)	92.6±15.7	93.9±14.0	97.8±11.5
Hip (cm)	92.3±12.9	93.9±11.8	95.6±11.7
Waist/Hip ratio	1.00±0.09	0.99±0.09	1.02±0.10

Group 1 optimal (<120/80 mmHg), group 2 normal (120-129/80-84 mmHg), and group 3 high-normal (130-139/85-89 mmHg) blood pressure.

- SDNN (msec): Standard deviation of all normal RR intervals in 24-hour Holter recording. It is correlated with total power (TP) assessed as one of the frequency-domain measures.

- SDNN index (SDNNi (msec): Mean of the standard deviations of RR intervals in all 5-minute segments of 24-hour recording.

- pNN50 (%): Percentage of differences between successive RR intervals that are greater than 50 msec.

Frequency-domain HRV parameters included the following measures:

- Total power (TP) (msec^2): The energy in the heart period power spectrum from 0 to 0.40 Hz.

- Low frequency (LF) and high frequency (HF) powers (msec^2): The energy in the heart period power spectrum between 0.04 and 0.15 Hz and 0.15 and 0.40 Hz, respectively.

- LF/HF ratio: Ratio of low to high frequency power.

- LF and HF were also measured in normalized units, which represent the relative value of each power component in proportion to the total power minus the very low frequency (VLF) component. Normalized LF (LF_n) was calculated as LF power in normalized units LF/(total power-VLF)x100, and normalized HF (HF_n) as HF power in normalized units HF/(total power-VLF)x100.[13]

Frequency-domain measures were calculated using the fast Fourier transform to break down the time series to its underlying periodic function.

rMSSD reflects parasympathetic activity as the HF power and HF_n in frequency-domain data. LF/HF and LF_n reflect sympathovagal balance. SDNNi reflects both sympathetic and parasympathetic activity and is related to total power in frequency-domain data.[13]

We evaluated HRV parameters at day (06:00 to 22:59) and night (23:00 to 05:59) periods. To compare the differences between these periods, time-domain and frequency-domain HRV parameters were obtained for both day and night periods.

For detection of day-night fluctuations in sympathovagal balance and parasympathetic activity, LFn_{day}/LFn_{night} ratio was calculated.

We also calculated the logarithmic values of all HRV parameters.

In our study, we mainly used LF/HF ratio, Log LF/HF ratio and LF_n parameters for indirect evaluation of sympathetic activity, and HF_n for indirect evaluation of parasympathetic activity.[13]

Statistical analysis. All statistical analyses were performed using the SPSS version 15 software package. Data with normal distribution were expressed as mean±standard deviation (SD). One-way ANOVA with Bonferroni-adjusted post-hoc test was used in the evaluation of the differences between the BP groups. Data with non-normal distribution were expressed as median and range and were compared using the Kruskal-Wallis or Mann-Whitney U tests. A *p* value of less than 0.05 was accepted as statistically significant.

RESULTS

Clinical and morphometric measurements (Table 1), biochemical, electrocardiographic and echocardiographic (Table 2) findings were within normal limits in the study group; and there were no differences among the three BP groups.

On 24-hour Holter monitoring, maximum, minimum, and mean heart rates were similar in the three groups (Table 3). Among frequency-domain and time-domain analysis parameters, LF/HF, LF_n, and HF_n ($p<0.001$, $p=0.001$, $p=0.001$, respectively) and pNN50 and rMSSD ($p=0.001$, $p=0.005$, respectively) showed significant differences among the groups (Table 3). Differences in the remaining HRV parameters (SDNN,

Table 2. Echocardiographic measurements

	Group 1 (n=113)		Group 2 (n=104)		Group 3 (n=77)	
	Median (Range)	Mean±SD	Median (Range)	Mean±SD	Median (Range)	Mean±SD
End-diastolic volume (ml)		104.2±30.9		107.8±28.7		109.1±25.1
End-systolic volume (ml)		34.6±12.8		38.6±16.3		36.4±12.7
Stroke volume index (ml/m^2)		38.4±10.9		36.9±8.8		38.2±8.9
Left ventricular						
Ejection fraction (%)		67.7±5.3		65.7±5.5		67.4±6.5
Mass (g)		156.7±43.9		163.0±47.6		173.6±45.6
Mass index (g/m^2)		84.2±22.1		84.8±24.1		90.9±21.6
Transmitral E wave (m/sec)		0.83±0.21		0.88±0.18		0.86±0.20
E/A		1.22±0.29		1.19±0.34		1.11±0.31
Deceleration time (m/sec)		215±60		227±82		227±64
Relaxation time (m/sec)	61.2 (49.8-70.6)		66.5 (55.4-75.4)		60.9 (49.8-66.5)	
Contraction time (m/sec)	40.2 (31.3-49.2)		40.2 (31.3-48.7)		40.2 (31.3-49.2)	
Ejection time (m/sec)		280±33		287±38		292±41
Tei index	0.39 (0.30-0.44)		0.38 (0.32-0.44)		0.34 (0.28-0.42)	

Group 1 optimal, group 2 normal, and group 3 high-normal blood pressure.

SDNNi, VLF, TP, HF_{day}/HF_{night}, $LF/HF_{day}/LF/HF_{night}$) were insignificant (p>0.05).

Table 4 shows the frequency-domain HRV parameters (LF/HF, LF_n, and HF_n) of the day and night periods. There were no significant differences between the groups with respect to frequency-domain parameters on day recordings (p>0.05); however, LF/HF, LF_n, and HF_n values obtained in the night period were significantly different between the groups. The remaining day and night frequency-domain and time-domain HRV parameters did not differ significantly between the groups (p>0.05).

Comparisons between Log LF/HF values of the three BP groups obtained during the 24-hour period and night period showed significant differences between group 1 and group 3 and between group 2 and group 3, but group 1 and group 2 did not differ significantly in this respect (Fig. 1).

For the 24-hour period, patients in group 3 had higher sympathetic activity (increased LF/HF and LF_n values) and decreased parasympathetic activity (low HF_n value). For the night period, group 1 had lower LFn and higher HFn values than the other groups (p=0.005). Group 1 also had a higher LFn_{day}/LFn_{night} ratio (p=0.022; Table 3).

DISCUSSION

In this study, we found that HRV parameters, in particular LF_n, HF_n, and rMSSD, were different among patients with normal BP levels, suggesting higher sympathetic activity as demonstrated by increased

Table 3. Heart rate and heart rate variability measures obtained from 24-hour Holter monitoring

	Group 1 (n=113)		Group 2 (n=104)		Group 3 (n=77)		
	Median (Range)	Mean±SD	Median (Range)	Mean±SD	Median (Range)	Mean±SD	
Heart $rate_{max}$		129±17		127±19		127±17	NS*
Heart $rate_{min}$		53±6		53±8		55±8	NS*
Heart $rate_{mean}$		76±9		75±9		77±9	NS*
Frequency-domain analysis							
LF/HF		2.26±1.39		2.23±1.31		3.39±2.20	<0.001*
LF_n		0.63±0.14		0.64±0.14		0.71±0.13	0.001*
HF_n		0.36±0.14		0.35±0.14		0.28±0.13	0.001*
Time-domain analysis							
pNN50 (%)	9.1 (0.0-49.4)		8.2 (0.4-49.4)		3.8 (0.1-35.9)		0.001**
rMSSD (msec)	36.9 (12.0-135.3)		37.4 (18.3-142.0)		29.9 (14.0-95.1)		0.005**
LFn_{day}/LFn_{night}	1.7 (1.1-3.1)		1.1 (1.1-1.4)		0.7 (0.5-1.0)		0.022**

*One-way ANOVA; **Kruskal-Wallis test. NS: Not significant. Group 1 optimal, group 2 normal, and group 3 high-normal blood pressure. LF_n: Normalized low frequency; HF_n: Normalized high frequency.

Table 4. Frequency-domain heart rate variability parameters during day (06:00 to 22:59) and night (23:00 to 05:59) periods

	Group 1 (n=113) (Mean±SD)	Group 2 (n=104) (Mean±SD)	Group 3 (n=77) (Mean±SD)	*p**
Day				
LF/HF	3.60±1.99	3.89±2.16	4.09±1.54	NS
LF_n	0.73±0.12	0.74±0.12	0.78±0.08	NS
HF_n	0.26±0.12	0.25±0.12	0.21±0.08	NS
Night				
LF/HF	2.17±1.67	2.14±1.34	3.15±1.97	0.002
LF_n	0.61±0.16	0.74±0.12	0.71±0.11	0.005
HF_n	0.38±0.16	0.25±0.12	0.28±0.11	0.005

*One-way ANOVA; NS: Not significant. Group 1 optimal, group 2 normal, and group 3 high-normal blood pressure. LF_n: Normalized low frequency; HF_n: Normalized high frequency.

LF_n value, and lower parasympathetic activity as demonstrated by decreased HF_n and rMSSD values in patients having a high-normal BP level compared to patients in group 1 and group 2.

It is well-known that one of the etiologic factors of hypertension is increased sympathetic activity. Sympathetic overactivity results in increased heart rate and BP.[1,14-16] It has also been shown that the sympathetic activity levels do not remain in a steady state when BP increases to hypertensive levels.[15] For this reason, normotensive subjects do not have an equal tendency to develop hypertension in the end. Rather, subjects with borderline BP levels for hypertension have a higher risk to develop hypertension.[9,10,15]

In our study, we investigated autonomic differences between subjects with optimal, normal, and high-normal BP levels as defined by the ESH/ESC criteria.[9] Our results showed that there were no autonomic function and autonomic circadian rhythm differences between subjects having optimal and normal BP levels for the daytime period. However, autonomic functions of the subjects with a high-normal BP level differed significantly from those having optimal or normal BP levels for the 24-hour and nighttime periods. High-normal BP levels were associated with increased sympathetic and decreased parasympathetic activity.

The role of decreased parasympathetic activity is of great importance in the development of hypertension. Moreover, decreased LFn_{day}/LFn_{night} ratio is another important factor for diastolic BP at high-normal BP levels. This finding suggests that there is a blunted fluctuation in sympathetic activity between day and night periods in the high-normal BP group. In other words, this group has characteristics of nondipping sympathetic activity. Nondipping and blunted

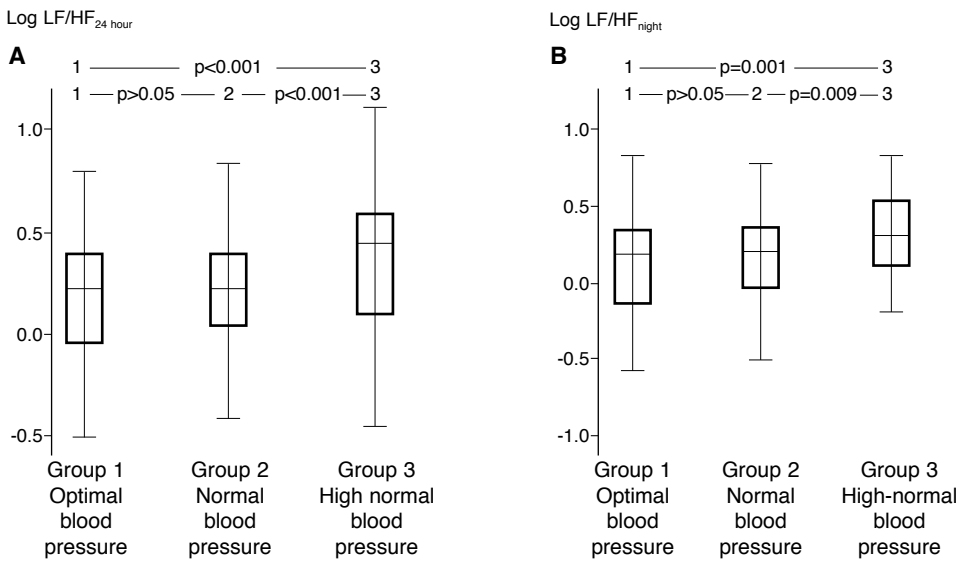

Figure 1. Differences between the three blood pressure groups with respect to **(A)** log $LF/HF_{24\ hour}$ and **(B)** log LF/HF_{night} values (One-way ANOVA, Bonferroni post-hoc test).

fluctuation in sympathetic activity may result from various pathologic conditions, including high BP, insulin resistance, diabetes mellitus, and psychiatric disorders.[6,7,17-19]

There are several studies on the pathophysiologic mechanisms of high BP related with oversympathetic activity.[6,15,16,20,21] Thornton et al.[22] have shown that the blunted reflex response of heart rate and lumbar sympathetic nerve activity to volume expansion could be the cause of impaired cardiopulmonary volume receptor function. Moreover, enhanced afferent arteriolar reactivity to angiotensin II and catecholamines is also related to autonomic BP regulation.[22-25]

Although the adverse effects of prehypertension have been well-documented, the beginning level of this pathological circuit and the time to initiate drug therapy remain unclear.[9,10]

In our study, subjects with optimal and normal BP levels did not have significant differences with respect to autonomic activity, but subjects with high-normal BP exhibited autonomic characteristics different from the other BP groups. This suggests that changes in autonomic activity may have triggering effects on the progression of normal to high-normal BP and on the pathological stages of hypertension.

As several factors are effective in the regulation of BP, it is not possible to speculate that every subject with high-normal BP would inevitably become a candidate for hypertension. Yet, increased alertness to autonomic abnormalities may be helpful to determine which subjects are more likely to develop hypertension.

Limitations. Because of technical limitations, we could not perform Holter monitoring and ambulatory BP monitoring simultaneously, which would enable us to compare simultaneous changes in BP and HRV parameters.

In conclusion, subjects with high-normal BP have distinct autonomic characteristics from those with normal or optimal BP levels, suggesting that high-normal BP may be a precursor of hypertension and patients with high-normal BP may need close clinical evaluation and follow-up.

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