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Spectral analysis and dynamics of heart rate and blood pressure in hypertensive patients

Victor-Dan Moga [1], Ioana Cotet [1], Andrei Beceanu [1] *, Mariana Moga [2], Florin Vidu [2], Attila Frigy [3], Rodica Avram [1]

[1] University of Medicine and Pharmacy "V.Babes", Cardiology Clinic, Emergency County Hospital, Timisoara, Romania
[2] IT Department of the of the Emergency County Hospital, Timisoara, Romania
[3] Department of Internal Medicine IV, University of Medicine and Pharmacy of Tirgu Mures, Romania

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Abstract

Hypertension represents an important condition that affects the adult population worldwide; it contributes significantly to morbidity and mortality from stroke, heart failure, coronary heart disease and renal failure. Heart rate variability (HRV) reflects the dynamic interplay between ongoing perturbations of circulatory function and the compensatory response of short-term cardiovascular control systems. A variety of linear, non-linear, periodical and nonperiodical oscillation patterns are present in heart rate fluctuations in healthy and hypertensive subjects. The aim of this study was to demonstrate that even in the early stages, the autonomic tone is involved in the complex pathophysiology of hypertension with consequences in the outcome of patients. In 47 hypertensive patients (23 men, 24 women, mean age 54.2 years), ECG signal analysis and heart rate variability (HRV) measurements were performed for short time epochs (5 minutes epochs). Also, a beat-to-beat finger photoplethysmographic waveform system, included in an ABPM system has been used for continuously recording blood pressure. Entropy analysis has been used for the study of heart rate dynamics. HRV in time domain showed reduced values independently of age, gender and severity of hypertension. Compared to the linear parameters of HRV, the nonlinear parameters, showed a much earlier impairment in hypertensive patients. We have highlighted the complexity of heart rate modulation in hypertension and its relationship with the entropy of RR intervals in hypertensive and normotensive subjects. Even in the early stages of the disease, the autonomic tone is involved in the complex mechanisms of cardiovascular coupling regulation.

Keywords: hypertension, heart rate variability, nonlinear analysis

Background

Hypertension represents an important condition that affects the adult population worldwide; it contributes significantly to morbidity and mortality from stroke, heart failure, coronary heart disease and renal failure [1]. The incidence of hypertension remains worldwide

* Correspondence to: Andrei BECEANU,
University of Medicine and Pharmacy "V. Babes", Cardiology Department, Emergency County Hospital Timisoara,
Iosif Bulbuca street, 10, Timisoara, TM, Romania.
Tel.: +40 730036601, e-mail: andreibeceanu@gmail.com

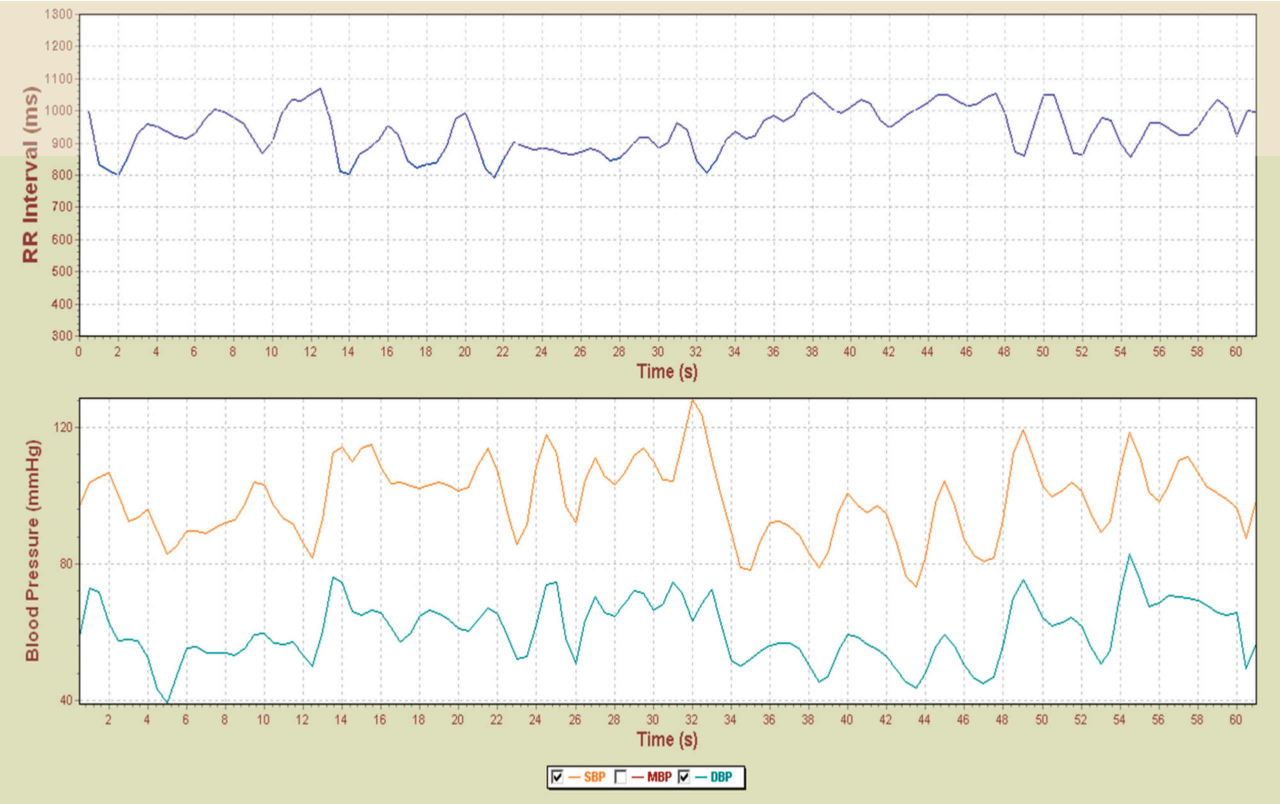

Figure 1. Time series of RR intervals (ms) and blood pressure (mmHg) in an adult normotensive subject.

high despite the development of pharmacological approach and the implementation of numerous prophylactic programs. Overall, approximately 20% of the world's adults are estimated to have hypertension, when hypertension is defined as BP in excess of 140/90 mmHg. The prevalence dramatically increases in patients older than 60 years: in many countries, 50% of individuals in this age group have hypertension. Worldwide, approximately 1 billion people have hypertension, contributing to more than 7.1 million deaths per year [2]. Previous studies suggest that the autonomic nervous system plays an important role in blood pressure regulation and in the development of hypertension [3]. Early identification of individuals prone to hypertension may allow early interventions, like lifestyle modifications, regular exercises and weight loss, targeted at reducing the risk of developing hypertension, and reducing sympathetic nervous system activation [4]. Heart rate (HR) is one of the most important physiological variables, and HR variability (HRV) reflects the dynamic interplay between ongoing perturbations of circulatory function and the compensatory response of short-term cardiovascular control systems. Linear and nonlinear methods are used for quantification of HRV [1, 5]. Blood pressure (BP) and heart rate (HR) are two main parameters that reflect global characteristics of the cardiovascular system. Several studies have shown that blood pressure and heart rate change not only in relation to behavioral and environmental factors but also as a result of regular fluctuations unrelated to external stimuli [6]. The sympatho-vagal balance is altered in numerous pathophysiological processes. It is the case of essential hypertension (Guzzetti et al. 1988), even in the presence of arterial pressure values still in the high normal range (Lucini et al. 2002). The ability of decreased heart rate variability to predict incident hypertension has not been well studied, and there are no studies of whether hypertension leads to changes in heart rate variability [7]. Blood pressure variability includes rhythmic and non-rhythmic fluctuations that, with the use of spectral analysis, appear as clear peaks or broadband power, respectively

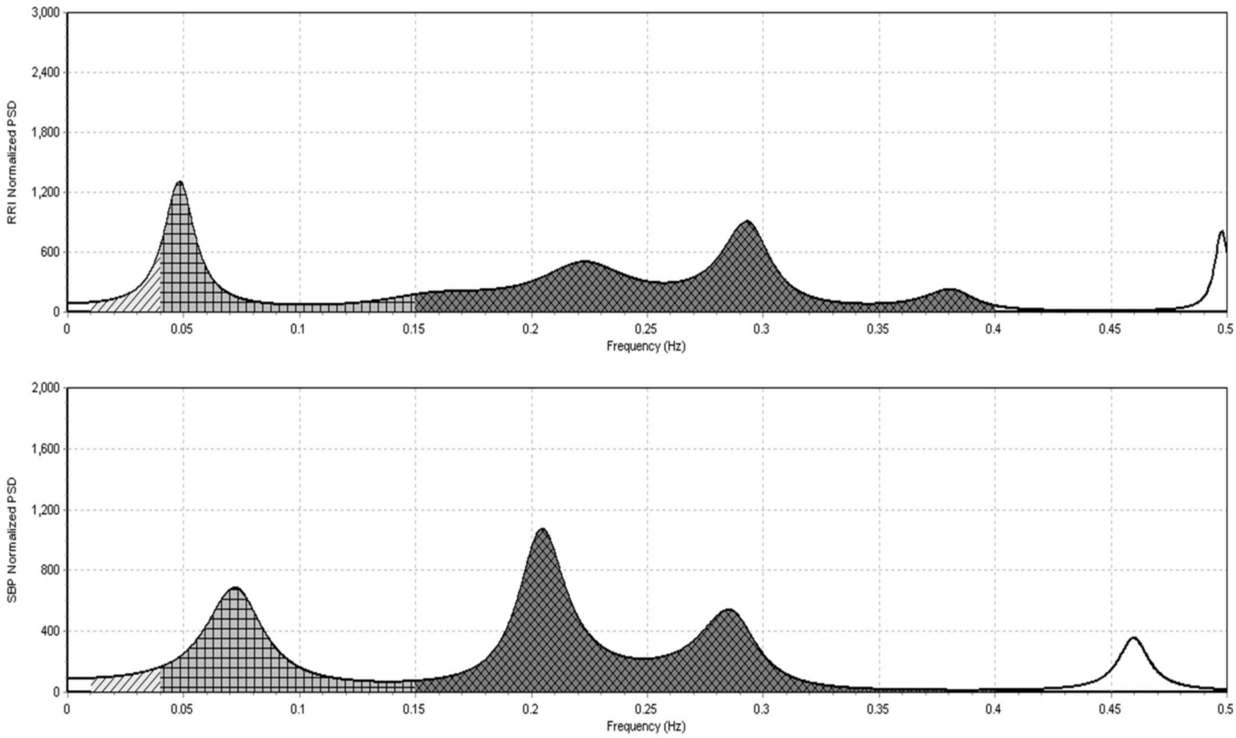

Figure 2. Power spectrum of RR intervals (top) and systolic blood pressure (bottom).

[8]. However, these two parameters have a dynamic behavior. This dynamic behavior of BP implies that attention should be directed not only to the average BP value, which is the reference set point, but also to the BP and cardiovascular fluctuations occurring around this average. The early studies of Stephen Hales opened the hypothesis of beat-to beat variability of the hemodynamic parameters like heart rate and blood pressure. It has been recognized that the instantaneous heart rate, blood pressure and other hemodynamic parameters fluctuate on a beat-to-beat basis [9]. Cardiovascular fluctuations can be studied through blood pressure (BP) beat-to-beat and heart rate (HR) monitoring and calculation of the variance (or standard deviation) of their values (Figure 1). Frequency domain analysis has also been used to subdivide the variability of BP and HR into different frequency components and to quantify the power at each specific frequency [8].

The development of various techniques of signal recording and analysis, like continuous recording, beat-to-beat analysis, fast algorithms like Fast Fourier Transform (FFT) or autoregressive method (AR) has led to more sophisticated approaches to rhythmic circulatory phenomena and to their more frequent investigation by power spectral analysis. Originally, three BP and HR rhythmic oscillations were identified, all with a period shorter than 1 minute and with the appearance in the spectrum as individual peaks (Figure 2), with a frequency around 0.2 to 0.4 Hz, a frequency similar to that of normal respiratory activity, defined as high-frequency (HF); (2) oscillations with a frequency of approximately 0.1 Hz, defined as mid-frequency (MF) and corresponding in the case of BP to the classic Mayer waves; and (3) oscillations with a frequency between 0.02 and 0.07 Hz, defined as low-frequency (LF) and probably related to a variety of cardiorespiratory phenomena and mechanisms [8, 10].

Heart rate variability (HRV) has become a universal tool to study the neural control of the heart, i.e. the delicate interaction between sympathetic and vagal influences on heart rate in health and disease. HRV can be quantified by the simple calculations of the mean and standard deviation of RR-intervals in the time domain. Furthermore, in the frequency domain, spectral analysis of HRV reveals two distinct frequency regions in the modulation of heart rate in humans. A high fre-

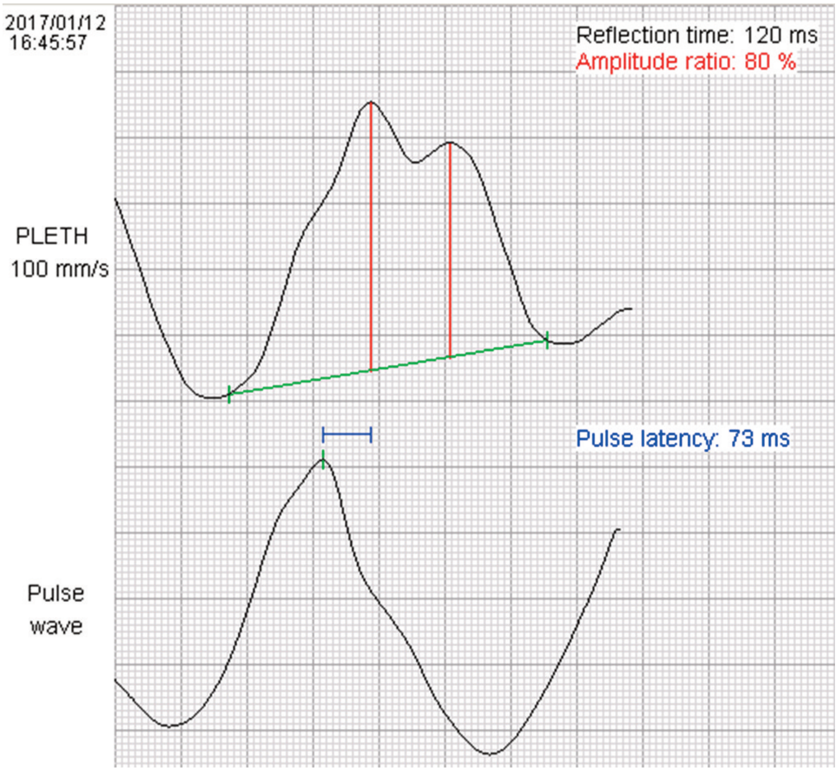

Figure 3. Reflexion time and pulse latency on a photopletismography arterial pulse wave.

quency region (0.15-0.4 Hz) which is a marker of vagal modulation, and a low frequency region (0.04-0.15 Hz), which reflects predominantly sympathetic modulation and baroreflex activity [11]. Recent studies have shown that BP and HR variability includes not only rhythmic oscillations but also non-rhythmic fluctuations that appear in the spectrum not as clearly defined peaks but as powers spread over a broad frequency region [8]. Nonlinear analysis methods, like entropy and detrended fluctuation analysis of RR intervals could identify the poor outcome even in apparently stable patients, like in hypertension [12, 13]. In the early 80's, in a study of Mancia et al, no agreement has been reached as to whether blood pressure variability is different in normotensive and hypertensive subjects and whether it undergoes a modification with aging [14]. A variety of linear, non-linear, periodical and nonperiodical oscillation patterns are present in heart rate fluctuations [15, 16]. Physiological processes are complex phenomena, outcomes of multiple inputs including autonomic nervous system and humoral controls. Measure of entropy quantifies the unpredictability of fluctuations in a time series, reflecting the likelihood that 'similar' patterns of observations will not be followed by additional 'similar' observations. Therefore, a time series containing many repetitive patterns has relatively small entropy; a less predictable process (with more disorder) has higher entropy [17]. Entropy is a newly developed measure of the complexity of heart rate variability (HRV), and correlates highly with changes in systolic blood pressure and could also represent a possible prediction of hypotension in some specific conditions [18]. Digital plethysmography provides noninvasive, continuous, and real-time measurement of arterial pressure with infrared light transmitted through a digit (finger or toe) [19]. With advancing age, arterial stiffness and wave reflections increase and elevate systolic and pulse pressures. An elevated central pulse pressure is generally ascribed to increased wave reflection and portends an unfavorable prognosis [20]. On plethysmography (PPG) the waveform represents the pulsatile peripheral blood flow, which reflects both peripheral and central hemodynamics and is also a useful noninvasive measure of vascular dysfunction [19].

In the Framingham study, Mitchell et al. [20], found in 188 men and 333 women changes in pulse wave velocity (PWV) and augmentation index (AI). Recent studies emphasize the potential information embedded in the PPG waveform signal and it deserves further attention for its possible applications beyond pulse oximetry and heart-rate calculation. The appearance of the PPG pulse is commonly divided into two phases: the anacrotic phase is the rising edge of the pulse, whereas the catacrotic phase is the falling edge of the pulse as shown in Figure 3.

Some parameters obtained from the PPG curve could be used in the assessment of vascular resistance and arterial stiffness. Therefore, the main aim of this study was to ascertain how and which of the variability and complexity parameters of the heart rate variability are different in hypertensive patients compared to normotensive patients. A second aim was to establish the relationship between heart rate and parameters describing the pulse of peripheral arteries.

Methods

The study was performed at the Cardiology Clinic of the Emergency County Hospital Timis, University of Medicine and Pharmacy "V. Babes "Timisoara, Romania. In the study group (23 men, 24 women, mean age 54.2 yrs) have been included hypertensive patients with stage III (moderate) and IV (severe) essential hypertension. All hypertensive patients have been on antihypertensive medication. ACE inhibitors and beta-blockers had been the main drugs used. Twenty-four hours before the study drug intake was stopped. A control group of twenty normotensive subjects (11 men, 9 women, mean age 46.7 yrs) was selected to compare the clinical data and autonomic parameters. ECG signal analysis and heart rate variability (HRV) measurements have been done for short time epochs (5 minutes epochs) using an ECG recorder, Cardiax V 3.50.4 ECG system by IMED Co Ltd, Hungary, and a beat-to-beat finger photoplethysmographic waveform system included in a Holter ABPM system (Meditech CardioVisions v.1.21.2). Short periods of continuous ECG and blood pressure monitoring has been performed and more than 90 % of the signals and measurements were eligible for the study. Artefacts and noise were manually removed from the signals. High frequency noise was removed with a 45 Hz low-pass filter and a 3 Hz high pass filter adjusted for wandering baseline. The signal processing algorithm consisted on Fast Fourier Transform algorithm with Hanning filter and autoregressive method, with AR order established at 16 (Figure 4).

All subjects were in sinus rhythm. Analysis of heart rate variability was performed (1) in time domain, and mean RR intervals (RR, ms), standard deviation of all normal RR intervals (SDNN, ms) have been measured, and in (2) frequency domain, with assessment of the power spectrum in very low frequency (VLF, 0.01–0.05 Hz), low frequency (LF, 0.05 -0.15 Hz) and high frequency (HF, 0.15-0.50 Hz) range. The LF/HF ratio was considered as a global indicator of the autonomic tone imbalance. Complementary, a Kubios v. 2.1, software (http://kubios.uku.fi/) was used for linear and nonlinear analysis of the RR series.

Spectral analysis was performed on linearly resampled (1 Hz) time series using Welch's method. The 256-point fast Fourier transform was repeatedly computed with 50% overlap between adjacent segments. Then, spectral power of each segment was computed and averaged. Hanning window was applied to avoid spectral leakage. Subsequently, spectral powers in the low frequency (LF) band (0.04–0.15 Hz) and high fre-

Figure 4. Recorded PPG pulse wave in an adult hypertensive patient.

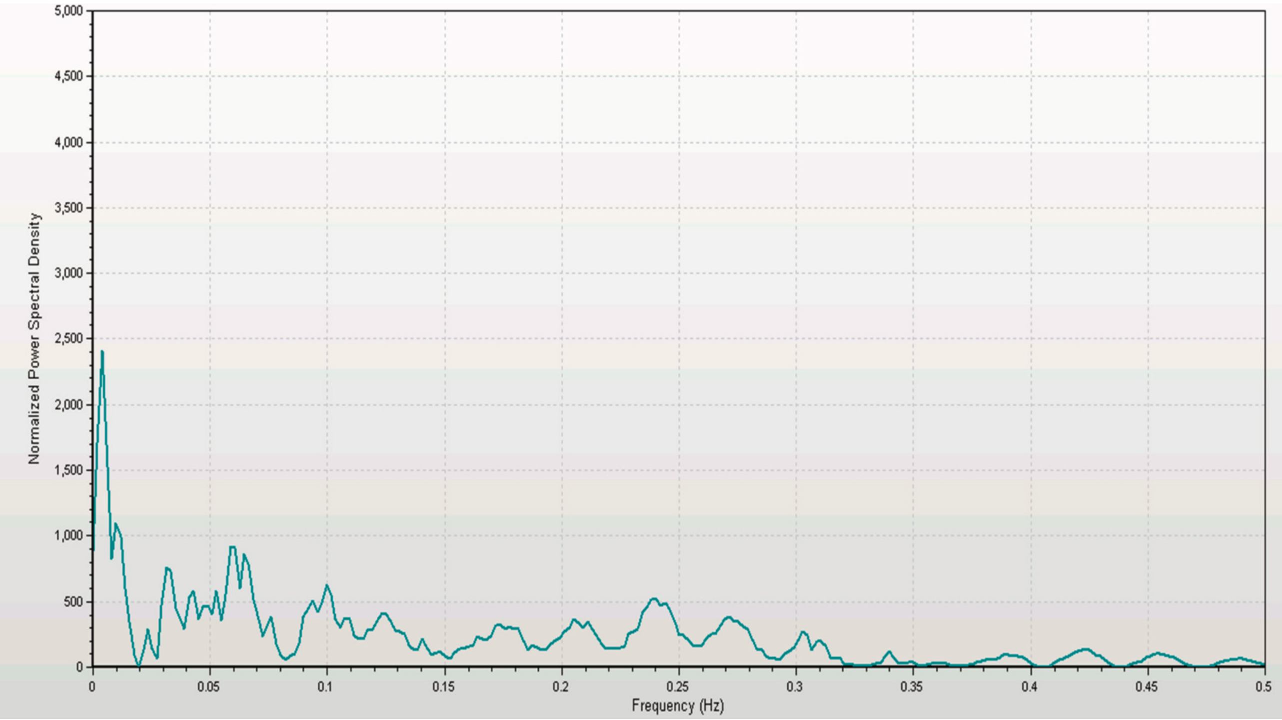

Figure 5. Short-term recordings of RR intervals heart rate variability (HRV). Power spectrum. 1024 data points, Hanning Window, normalized units (n.u.)

quency (HF) band (0.15–0.40 Hz) were obtained by integration. Approximate and Sample entropy (SampEn), detrended fluctuation analysis, have been used for the study of heart rate dynamics in both groups. SampEn was developed to reduce the bias caused by the self-matching in approximate entropy which is a mathematical approach to quantifying the complexity and regularity of a system. Detrended fluctuation analysis (DFA) has been introduced to evaluate the fractal correlation properties of R-R interval dynamics and to characterize the features of HR dynamics that may not be easily detectable by traditional methods of analysis. Breakdown of fractal organization into beat-to-beat R-R interval dynamics indicates increased cardiac vulnerability and a higher risk of mortality in patients with and without structural heart disease [12]. The PPG curve offers some specific parameters like pulse latency and reflection time (Figure 3). Trends of heart rate (b/min) and blood pressure (mmHg) have been recorded for both groups. Left ventricular ejection fraction (LVEF, %) has been measured echocardiographic by an independent operator – by which method.

Statistical analysis

For statistical analysis, we have used Graph Pad Prism® for Windows v.5.03. All numeric variables were expressed as mean and the statistical analysis was performed using Student's t-test and correlation analysis by Pearson method. A p value < 0.05 was considered statistically significant.

Results

Hypertensive patients had a higher heart rate compared to healthy subjects, also hypertensive women had higher heart rate compared to men, (mean heart rate 87 b/min vs. 80 b/min), but the differences were not statistically significant. Independently from gender, patients with moderate hypertension (HTN) had preserved left ventricular ejection fraction (LVEF =58 % in men and 61% in women). In the hypertensive group, those with longer hypertensive history and ischemic heart disease had a lower left ventricular ejection compared to the general hypertensive population (LVEF 48 % vs. 68 %, $p< 0.005$).

Table 1. Main clinical characteristics of the study and the control group.

	Hypertension	Control	P
N	47 (W:23)	20	0.05
Age (yrs.)	54.2	46	0.05
Mean Heart Rate (b/min)	84	75	0.001
LVEF (%)	60	85	0.0001
Systolic Blood Pressure (mmHg)	170	117	< 0.005
Diastolic Blood Pressure (mmHg)	107	66	< 0.005
Mean Arterial Pressure (mmHg)	111	83	0.005
Pulse Pressure (mmHg)	57	51	0.29

The main clinical characteristics are presented in Table 1.

Heart rate variability

The autonomic tone imbalance in essential hypertension was assessed using linear and nonlinear parameters. HRV in time domain showed reduced values independently to age, gender and severity degree of hypertension. Spectral analysis showed a high power spectral density (PSD) in the low frequency domain (LF: 0.05–0.15 Hz) reflecting the high sympathetic tone activity in hypertensive patients and the more parasympathetic reserve.

The value of mean RR intervals (ms) was similar to the normotensive subjects despite the relatively higher heart rate (Table 2). Time domain measure like standard deviation of RR intervals (SDNN, ms) had decreased values compared to control group.

In an age-gender relationship, hypertensive women have lower mean RR intervals and lower SDNN compared to the male hypertensive subjects (Table 3). The same differences occurred for the spectral analysis.

Spectral analysis of heart rate variability in moderate hypertension patients was characterized by decreased values compared to normotensive subjects (LF 1170 ms^2/Hz vs. 1432 ms^2/Hz), respective in the high frequency band (HF: 726 ms^2/Hz vs 1360 ms^2/Hz), so the LF/HF ratio was higher compared to the control group (Figure 3). Hypertensive patients had a higher sympathetic activity, correlated to the higher heart rate. In severe hypertension the autonomic imbalance was highly increased (Table 4).

Table 2. Mean time domain and frequency domain parameters in hypertensive patients.

	Hypertension	Control	P
Mean RR (ms)	824	741	0.30
SDNN (ms)	126	167	0.11
LF (ms^2/Hz)	1170	1432	0.30
HF (ms^2/Hz)	726	1360	0.09
LF/HF	2.17	1.05	0.07

Table 3. HRV parameters in hypertensive women compared to men.

	Men (23)	Women (24)	P
Mean HR (b/min)	79	86	0.02
Mean RR (ms)	863	787	0.04
SDNN (ms)	137	114	0.10
LF (ms^2/Hz)	1331	984	0.18
HF (ms^2/Hz)	854	579	0.001
LF/HF	2.67	1.67	0.12

Nonlinear analysis

Compared to the linear parameters of HRV, the nonlinear parameters, proved a much earlier impairment in hypertensive patients (Table 5). Entropy parameters as measure of the nonlinear analysis of heart rate dynamics had lower values compared to control subjects.

Measures of entropy are suitable for detecting changes in neural outflow to the heart. Higher SampEn values were obtained for healthy subjects than for hypertensive subjects, which is in agreement with the idea of loss of HRV in pathological conditions.

Discussions

Hypertension remains worldwide, one of the leading cause for morbidity and mortality. The pathogenetic mechanisms are still unclear. Population-based studies have reported reduced heart rate variability in patients with long-term arterial hypertension, despite treatment with antihypertensive drugs. In the ARIC study decreased HRV was observed in the hypertensive population, and even in normotensive population low HRV predicted hypertension after a follow-up of nine years.

An important reduction of spectral HRV parameters, mainly in the high frequency range was observed in hypertensive women. This reflects a high sympathetic tone associated to a reduced parasympathetic activity. Numerous papers published in the last decades highlight the role of the autonomic imbalance in hypertension and the role of reduced HRV in women. The exact mechanism remains unclear but genetic factors and a specific vulnerability of women could be challenging.

Table 4. Heart rate variability parameters in severe hypertensive patients.

	Moderate HTN	Severe HTN	P
Mean RR (ms)	823	828	
SDNN (ms)	122	126	
LF (ms^2/Hz)	1018	2656	
HF (ms^2/hz)	956	969	
LF/HF	1.16	2.35	

Table 5. Nonlinear parameters of HRV and heart rate dynamics in hypertensive patients. P<0.05 is considered significant.

	Hypertension	Control	P
ApEn	1.02	1.28	0.39
SampEn	0.94	1.33	0.29
DFA α_1	0.69	1.08	0.0001

Entropy based measures, such as Sample Entropy (SampEn), have been widely used for quantifying the Heart Rate Variability (HRV) for cardiac risk stratification purposes, with the hypothesis that decreasing entropy points to a perturbation of the complex physiological mechanisms or disease [21]. Entropy-based measures might provide useful indicators of pathological changes in cardiac activity and be suitable for the early detection of autonomic dysfunction in cardiac as well as non-cardiac patients [22].

Application of new signal processing techniques based on nonlinear dynamics provided supplementary information (i.e. hidden underlying mechanisms) about systems involved in cardiovascular function and pathology [22]. In a healthy sample with no evidence of cardiovascular disease and a low burden of risk factors, Mitchell et al found a marked age-related increase in aortic stiffness [20]. The pulsatile PPG signal reveals the HR, hence, could be used to monitor HRV [5]. Heart rate variability and nonlinear dynamic parameters DFA α_1 like entropy and detrended fractal analysis was applied to the ECG signals obtained from hypertensive patients (Table 2). In concordancy to other previuos studies [23] we didn't observe significant differences in the 24-h mean, LF power between normotensive and hypertensive subjects, but HF power was significant lower in the hypertensive group. The reduction in the parasympathetic reserve could be an explanation for the autonomic imbalance expressed by an increased LF/HF power ratio. In our study, hypertensive patients, mainly severe hypertensive patients had significant ($p<0.05$) lower values for nonlinear parameters, like approximate entropy (ApEn) and sample entropy (SamEn). High entropy characterizes a healthy cardiovascular system [11, 17]. In a former study, G. Parati [6] showed that in hypertensive patients spectral analysis can be applied to 24-hour blood pressure and heart rate tracings, and this finding has been recently confirmed. The data obtained by analyzing of systolic blood pressure and RR intervals by short term recordings demonstrate that blood pressure and RR interval oscillations at frequencies ranging from 0.025 to 0.5 Hz occur in normotensive and hypertensive patients. Even in a limited and selected group of patients it is difficult to identify vulnerable hypertensive patients [10]. It seems adequate to perform nonlinear analysis of the RR intervals in hypertensive patients to identify vulnerable patients. Not all parameters will have spectacular changes but approximate entropy (ApEn) and detrended fluctuation analysis parameter (DFA α_1) confirm the capacity to identify at risk patients even in apparently stable conditions, like in essential hypertension [1, 24].

Conclusions and limitations

The aim of the study was to offer data about the complex mechanisms involved in essential hypertension. The direct effect of high values of systolic and diastolic blood pressure and an important left ventricular hypertrophy will lead to altered heart rate variability, indicating a disturbance in cardiac autonomic balance in essential hypertension [25]. The most important aspect of this study is that even in early stages of essential hypertension autonomic mechanisms are involved being detectable by noninvasive methods. Autonomic imbalance is an important mechanism involved in the pathogenesis of essential hypertension. Beside the well-known heart rate variability parameters, it seems that new parameters like entropy and nonlinear parameters of heart rate dynamics can offer important data on pathophysiology and prognosis in hypertension. Our study proved that the severity of the autonomic imbalance is correlated to the severity of hypertension and occurs even in the early stages.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

References

1. Marek Malik, A. John Camm – Heart Rate Variability – Futura Publishing Company, Inc, 1995
2. Albert W Dreisbach et al. - Epidemiology of Hypertension -
3. Kolasinska-Kloch W et al, - Circadian heart rate variability in patients with primary arterial hypertension - Przegl Lek 59 (9), 752-755. 2002.
4. R Virtanen et al, - Reduced heart rate variability in hypertension: associations with lifestyle factors and plasma renin activity - Journal of Human Hypertension (2003) 17, 171–179
5. Ping Shi - Photoplethysmography in noninvasive cardiovascular assessment https://dspace.lboro.ac.uk/dspace-jspui/bitstream/2134/5399/1/Thesis_SHI, P_2009.pdf
6. G. Parati et.al - Sequential spectral analysis of 24-hour blood pressure and pulse interval in humans - Hypertension 1990, 16:414-421
7. Melillo et al. - Heart rate variability and target organ damage in hypertensive patients - BMC Cardiovascular Disorders 2012, 12:105
8. Gianfranco Parati, J. Philip Saul, Marco Di Rienzo, Giuseppe Mancia - Spectral Analysis of Blood Pressure and Heart Rate Variability in Evaluating Cardiovascular Regulation . A Critical Appraisal - Hypertension. 1995; 25: 1276-1286
9. Solange Akselrod et al - Power Spectrum Analysis of Heart Rate Fluctuation: A Quantitative Probe of Beat-to-Beat Cardiovascular Control - SCIENCE, VOL. 213, 10 JULY 1981
10. Omboni S, Parati G, Di Rienzo M, Wieling W, Mancia G - Blood pressure and heart rate variability in autonomic disorders: a critical review - Clin Auton Res. 1996 Jun;6(3):171-82.
11. Ahsan H Khandoker et all - Identifying diabetic patients with cardiac autonomic neuropathy by heart rate complexity analysis - BioMedical Engineering OnLine 2009, 8:3
12. Sirkku M. Pikkujamsa, Timo H. Makikallio, K. E. Juhani Airaksinen, Heikki V. Huikuri - Determinants and interindividual variation of R-R interval dynamics in healthy middle-aged subjects - Am J Physiol Heart Circ Physiol 280: H1400–H1406, 2001.
13. Darrel P. Francis et all. - Physiological basis of fractal complexity properties of heart rate variability in man - Journal of Physiology (2002), 542.2, pp. 619–629
14. Mancia et al. - Variability in Blood Pressure and Heart Rate in Humans - Circulation Research/Vol. 53, No. 1, July 1983
15. AE Aubert, F Beckers, B Seps - Non-linear Dynamics of Heart Rate Variability in Athletes: Effect of Training - Computers in Cardiology 2002;29:441−444
16. A. L. Goldberger, S. M. Pincus: Physiological Time-Series Analysis: What does Regularity Quantify? Am J Physiol, Vol. 266 (Heart Circ. Physiol.), pp. H1643-H1656, 1994
17. Tatjana Loncar-Turukalo et al, - Entropy and Gaussianity - Measures of Deterministic Dynamics of Heart Rate and Blood Pressure Signals of Rats - Acta Polytechnica Hungarica, Vol. 5, No. 1, 2008
18. Yamanaka N, Aoyama T, Ikeda N, Higashihara M, Kamata K - Characteristics of heart rate variability entropy and blood pressure during hemodialysis in patients with end-stage renal disease - Hemodial Int. 2005 Jul;9(3):303-8
19. Steven M. Helschien et al - Monography - www.level1diagnostics.com
20. Gary F. Mitchell et al - Changes in Arterial Stiffness and Wave Reflection With Advancing Age in Healthy Men and Women The Framingham Heart Study - Hypertension. 2004;43:1239-1245
21. R Goya-Esteban et al. - Characterization of Heart Rate Variability Loss with Aging and Heart Failure Using Sample Entropy - Computers in Cardiology 2008;35:41−44.
22. Mathias Baumert et al.- Entropy Analysis of RR and QT Interval Variability during Orthostatic and Mental Stress in Healthy Subjects - Entropy 2014, 16, 6384-6393; doi:10.3390/ e16126384OPEN
23. Hoyo J. ey al - Autonomic nervous system activity in essential hypertension: a comparison between dippers and non-dippers - J Hum Hypertens. 1997 Oct;11(10):665-71.
24. Darrel P. Francis et all. - Physiological basis of fractal complexity properties of heart rate variability in man - Journal of Physiology (2002), 542.2, pp. 619–629 http://emedicine.medscape.com/article/1928048-overview#aw2aab6b4
25. Kaftan A.H, Kaftan O. - QT intervals and heart rate variability in hypertensive patients - Jpn Heart J. 2000 Mar;41(2):173-82

