Original article
UDC: 616.12:616.071:615-085:656.254

Computer Analysis of Cardiovascular Signals: Contribution to Diagnosis of Cardiovascular Disease

Nina JAPUNDŽIĆ-ŽIGON

INSTITUTE OF CLINICAL PHARMACOLOGY,
PHARMACOLOGY AND TOXICOLOGY,
MEDICAL FACULTY UNIVERSITY OF BELGRADE,
YUGOSLAVIA

In the last decade development of computerized methods for registration of cardiovascular (CV) signals allowed application of mathematical algorithms for analysis of blood pressure (BP) and electrocardiogram (ECG) signals. It has been shown that BP and HR (derived from ECG) both oscillate in a complex manner comprising short-term (period up to 1 min duration) and long-term (period up few hours) periodic oscillations as well as non-periodic oscillations that depict neurohumoral cardiovascular control. BP and HR analysis in time and frequency domain enhanced the understanding of physiological mechanisms that underlie these variabilities. New approaches for assessing spontaneous baro-reflex sensitivity have been developed. Moreover, estimation of imbalance between the linearity and non-linearity contribution to HR dynamics, either in time domain or in frequency domain was found to have a prognostic value in critically ill patients.

KEY WORDS: *Cardiovascular signals; Computer analisys*

INTRODUCTION

In the past few decades the pivotal role of neural mechanisms in cardiovascular pathophysiology has been postulated. Very soon it has become clear that the role of the autonomic nervous system (ANS) in the pathogenesis of cardiovascular disease should be assessed within the framework of the dynamics of the sympatho-vagal interactions that govern the instantaneous performance of the cardiovascular system. However, until recently, such an approach was not possible due to methodological constraints. Owing to the development of applied computer sciences that permitted continuous registration of cardiovascular parameters and application of mathematical algorithms to their analysis, powerful tools for assessment of spontaneous cardiovascular variability became available. Thus, the regulatory mechanisms that underlie cardiovascular beat-to beat variability could be approached in a dynamic manner.

ASSESSMENT OF RHYTHMIC CHANGES OF BLOOD PRESSURE AND HEART RATE VARIABILITIES AND THEIR PHYSIOLOGICAL SIGNIFICANCE

Figure 1. Illustrate a short-lasting digitalized recording of systolic and diastolic blood pressure derived from a pulse wave (recorded non-invasively by Fin-a-press device, 18) as well as the heart rate (HR) derived from an electrocardiogram (ECG). One may observe that BP and HR permanently oscillate around their means in a very complex manner. In order to identify constituting oscillatory components of BP and HR variabilities, spectral analysis methodologies based on fast Fourier transform algorithm and autoregressive modeling were proposed. The spectra of BP and HR obtained by either methodological approach were comparable and revealed that BP and HR oscillatory activity is clustered around three main frequency components: very-low frequency (VLF: 0.004-0.07 Hz), low frequency (LF:0.07-0.15 Hz) and high frequency (HF:0.15-0.5 Hz) range. Subsequent research revealed that each of these frequency "peaks" is a resultant of complex interaction of more than one regulatory mechanism involved in the control of circulation and homeostasis.

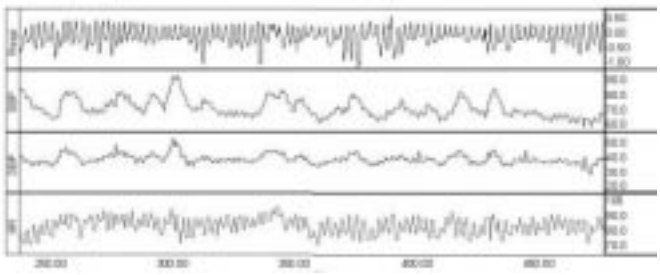

Figure 1. Digitalized recording of respiration (respi), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in a healthy supine human

The dominant oscillation of the HR spectrum is the HF-HR component that is located in the frequency range of respiration (fig. 2). In animals and humans it is almost abolished by interventions that exclude vagal influences on the heart such as atropinisation and

Address correspondence to:
Prof Nina Japundžić-Žigon, Medical Faculty, Department of Clinical Pharmacology, University Belgrade, Dr Subotića 1, Belgrade, Yugoslavia
E-mail: zigon@eunet.yu

Accepted for publication: 20. 04. 2001.

sino-aortic denervation (1,7,11). Thus the HF-HR component has been attributed to the respiratory sinus arrhythmia (RSA) a well-known vagal phenomenon that couples the heart beats to respiration (fig. 3). The physiological meaning of this coupling is not well understood though it was suggested that it serves to improve the efficiency of gas exchange during respiration (9). Nonetheless, RSA is well pronounced in children and healthy young adults, it declines with age and finally disappear in elderly and disease (10).

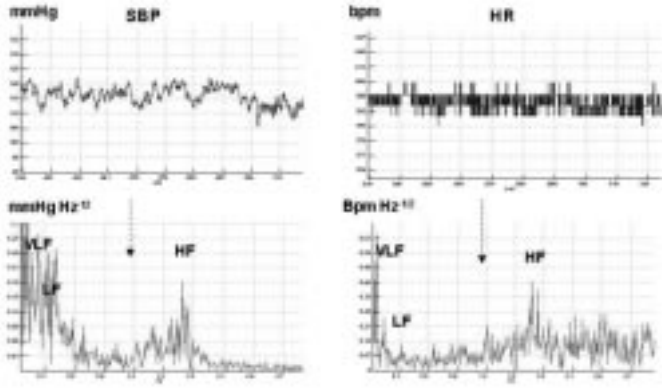

Figure 2. Digitalized recording of systolic blood pressure (SBP), heart rate (HR) and their corresponding spectra (bottom) in one conscious Wistar rat.

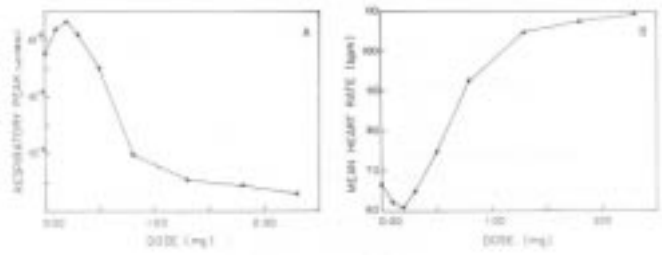

Figure 3. Two dose-response curves to increasing doses of atropine obtained by plotting the value of the integral of the high-frequency component of the heart rate spectrum (left) and the heart rate (right) as functions of dose. Note the sensitivity of the HF-HR component as a marker of vagal outflow to the heart (1).

The changes of intrathoracic pressure induced by respiratory movements perturb circulation in thorax and create the respiratory oscillation of BP or HF-BP spectral component (fig. 2). The aspiratory effect of inspiration (negative intrathoracic pressure) distends the heart and large thoracic vessels, increases the heart filling and decreases BP while in expiration the recoiling of thorax increases the cardiac output and BP. Although the respiratory oscillation of BP is purely mechanically generated, the arterial baro-reflex was found to oppose it by modifying both vagal and sympathetic outflow to the heart (RSA) and the resistance vessels, respectively. Thus, it has been proposed that the HF spectral components of the HR should be used as a marker of cardiac vagal efferent activity (1,4,7,15,16) while the HF-BP component could be useful in assessing hemodynamic parameters such as venous return and CO (11,12).

Identification of slower rhythms in HR and BP spectra was a more difficult task because the slower rhythms are closely located in the spectra. The slower rhythms in the HR spectrum comprise less than 30% of the overall HR variability. The LF-HR oscillation is affected by both the vagus and the sympathicus while the VLF-HR oscillation has been associated with autonomic response to the renin-angiotensin system activation (vasoconstriction). However, only in stressful situations the sympathetic component was found to dominate over vagal influences in the lower frequency range of the HR spectrum. Therefore the upright posture seems to be appropriate for assessing sympathetic contribution to the HR in humans (orthostatic stress increases sympathetic activity to the heart, 16).

The VLF and LF oscillations in the BP spectrum comprise more than 60 % of the total spectral power (overall variability) and have been shown to originate from the oscillatory activity of the resistance vessels located in different arterial beds: VLF-BP is associated with mesenteric and renal vascular bed while LF-BP oscillation is related to muscular vascular bed (12). Under stressful situations such as hemorrhage, the increase in efferent sympathetic activity to blood vessels enhances the LF-BP component precisely around 0.35 Hz in rats reflecting the activation of the arterial baro-receptor reflex. This increase can be prevented by blockade of (1 adrenegic receptors (7). Other vasoconstrictor systems such as angiotensin and vasopressin were also found to modulate the amplitude of LF-BP component as well as the amplitude of the VLF-BP component (7,11,13).

Research in humans has provided evidence about the usefulness of spectral methodologies in diagnosis and prognosis of cardiovascular and autonomic disease. They indicate that the reduction of the HF-HR spectral component should be considered as an upsetting prognostic sign in cardiovascular disease as it reflects reduction of vagal outflow to the heart and an impairment of the cardio-respiratory relationship (16). This finding also points out to sympathetic domination on the heart. In fact some authors found a concomitant increase of the LF-HF spectral component. For instance, in subjects suffering from myocardial infarction or chronic heart failure, the reduction of HF-HR component and an increase of the LF-HR component may indicate oncoming life-threatening arrhythmias that wind up in sudden death (16). These finding suggest that treatment should be focused in the restoration of vagal drive to the heart and to the protection of the heart from sympathetic activation. Furthermore, in subjects suffering from autonomic neuropathies such as in diabetes mellitus (15) and in chronically haemodyalized patients (3), a significant reduction of all spectral BP and HR components was found even before the appearance of signs and symptoms of disease. In the spectra

of borderline hypertensive subjects, the power of the BP spectrum is shifted toward lower frequencies (VLF-BP component is significantly increase while the LF-BP component is reduced) most probably due to the impairment of the arterial baro-receptor reflex (5,19,20).

In addition to the short-term BP oscillations, long-lasting recordings of BP revealed ultra low or ultradian and circadian oscillations. The physiological significance of these oscillations is not yet elucidated. However, studies in animals (telemetry) and humans (holter monitoring) suggest that the functioning arterial baro-receptor reflex oppose them (16,17).

METHODS FOR ASSESSMENT OF SPONTANEOUS BAROREFLEX SENSITIVITY

The baroreceptor reflex is the most important, fast acting neural reflex that responds to external perturbations and integrates sympathetic and parasympathetic drive to the heart and the blood vessels. It is therefore responsible for instantaneous, beat-to-beat cardiovascular homeostasis. Baro-receptors located in the arch of aorta and carotid sinus sense changes in arterial pressure and transmit these information to the CNS (autonomic centers) that act fast to adjust the sympatho-vagal outflow to the circulation in order to maintain BP in homeostatic range. The impairment of the baro-reflex function occurs in disease. Until recently, the baro-reflex function could be only estimated in the laboratory animals by evaluating the HR response to BP changes induced by strong vasodilators or vasoconstrictors. Now, novel non-invasive methods for assessing the spontaneous baro-reflex function have been introduced. These are transfer function analysis or the so-called (coefficient in the frequency domain, and the sequence technique in time domain. The two methods have been validated in sino-aortic denervated animals as well as in subjects suffering from cardiovascular and autonomic disease (4,17).

Transfer function analysis (fig. 4) comprises the cross-spectrum of BP and HR signals, squared coherence and phase lag spectrum calculated in each frequency band. Analysis of the phase relationship between the frequency bands of BP and HR spectra confirmed that the phase delay of LF-HR to LF-BP component corresponds to the baro-reflex induced delay in sympathetic response of the HR to BP changes, whereas insignificant delay in HF bands match the fast vagal cardiac response to changes in BP. The gain of the baro-receptor reflex assessed by transfer function can thus be estimated separately for the sympathicus ((LF coefficient) and the vagus nerve ((HF coefficient; fig 7). However the (coefficient cannot discern non-baro-reflex from baro-reflex BP and HR couplings; it does not indicate whether the oscillations of BP and HR in the specific frequency band are uni-(non-baro-reflex) or bi-directionally (baro-reflex) modulated.

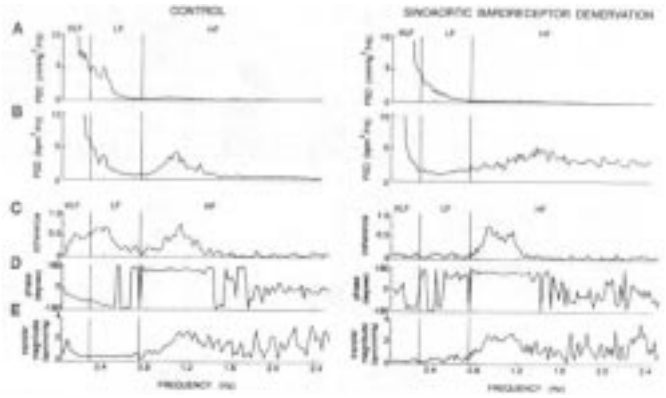

Figure 4. Power spectra densities of mean arterial pressure (A), heart rate (B) and their corresponding coherence (C), phase (D), and transfer magnitude (E) spectra in one conscious intact (control) rat and sinoaortic baro-receptor denervated rat (4)

The sequence technique (fig. 5) detects SBP and RR interval pairs in which BP and RR nterval steeply raise or decrease (at least 3 consecutive pairs of values). The pairs of detected points are used to calculate tg (of the BP and HR linear relationship. The calculated number of such pairs - the baro-reflex index (BRI) is also a measure of baro-receptor reflex effectiveness in controlling circulation. The sequence technique focuses on BP-HR changes in a wider frequency content than transfer function and cannot estimate separately sympathetic and vagal branch of the baro-reflex . Nevertheless the sequence technique has an important advantage in some clinical situations in which distinction of the baro-reflex stimulation from baro-reflex deactivation is important. This is the case in the sleep apnea syndrome. Thus (coefficient in the frequency domain and the sequence technique in time domain provide complementary information and should be used both when estimating the spontaneous baro-receptor reflex function (17).

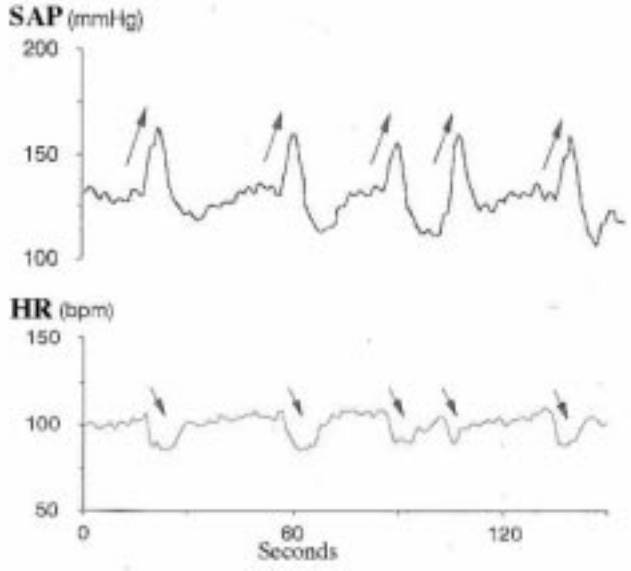

Figure 5. Episodes of the spontaneous baro-reflex. Note the bi-directional systolic blood pressure (SBP) and heart rate (HR) couplings (arrows)

ASSESSMENT OF NON-RHYTHMIC CHANGES AND THEIR SIGNIFICANCE

Most investigators focused their research on the detection of spectral peaks because they believed that peaks reflect single regulatory mechanisms to cardiovascular control. However, spectra of HR and BP reveal non-periodic variations which appear as powers spread over a broadband frequency (fig 2). It is now clear that these "noise-like variability" reflects cardiovascular control mechanisms, too (2, 21). The methods for their identification and quantification comprise the calculation of fractal dimensions of HR time series and Lyapunov exponent. Using these indices, it has been documented that the origin of HR spectrum chaotic behaviour lies probably in the vagus nerve since cholinergic, but not adrenergic blockade reduces HR non-linearity. In healthy adults, a balance between chaotic and periodic dynamics exists. In illness reduction of noise-like variability or the so-called HR decomplexification has been reported (6). In chronic heart failure HR decomplexification have been shown to parallel the decrease in vagal activity and to posses prognostic value. Nevertheless, disease may be associated to an increase in non-linearity such as in cardiac fibrillation (fig. 6; 14). Therefore, in predicting the outcome of cardiovascular disease both periodic and non-periodic behaviour should be analysed. A methodolgical bridge between them are scatter plots of Poincare. They are obtained by plotting RR interval against its predecessor interval (RRi vs. RRi-1). Four different shapes of plots have been described and associated to health and disease (fig. 7).

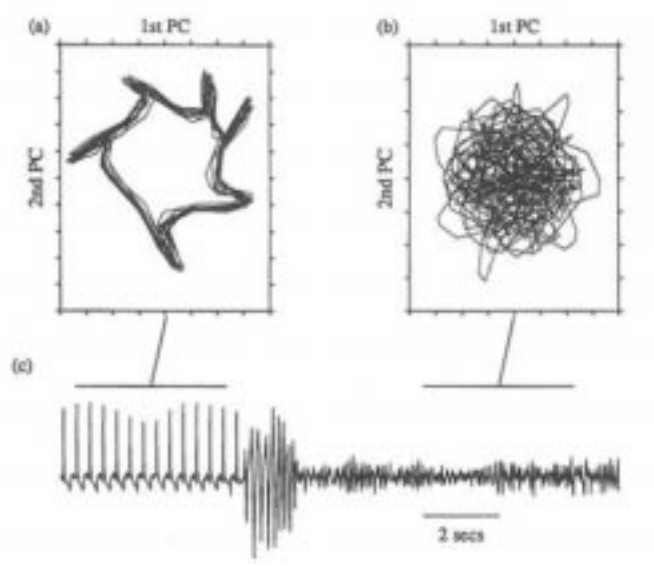

Figure 6. The fractal dimension (trajectory) of 4 seconds of atrially paced rhythm (a). The trajectory of 4 seconds of fibrillations (b) and the corresponding ECG signal (c) (14)

While the source of cardiac chaotic behaviour seems to lie in the vagus nerve influences (6), the source of BP chaotic dynamics is probably the results of resistance vessels' smooth muscle inherent dynamics induced by Ca++ fluxes (21). In isolated blood vessel preparations calcium channel blockers reduce aperiodic behaviour (8). It was further shown that the level of arterial pressure and thus baro-receptor reflex regulates the switch between aperiodic and periodic fluctuations of blood vessels.

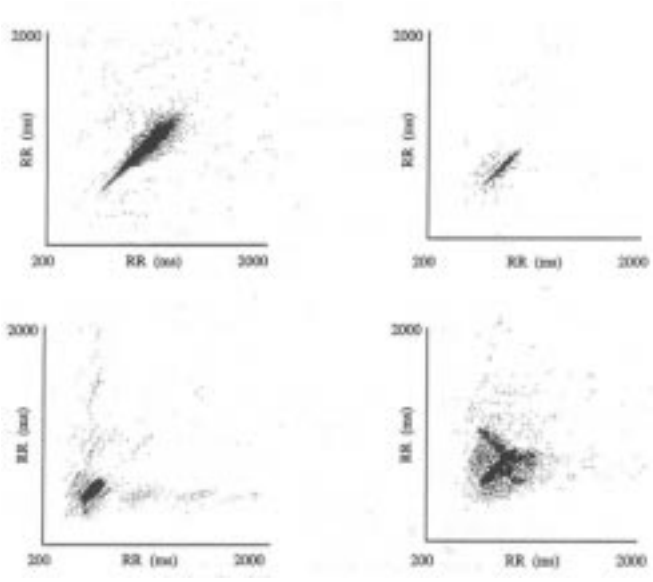

Figure 7. Four different patterns of Poincare plot: commet pattern (a), torpedo pattern (b), fan pattern (c) and complex pattern (d)

REFERENCES

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Cohen RJ. Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220-2.
2. Braun C, Kowallik P, Freking A, Hadeler D, Kniffki K-D, Meesman M. Demonstration of nonlinear components in heart rate variability of healthy persons. Am J Physiol 1998; (Heart Circ.Physiol. 275): H1577-H1584.
3. Cavalcanti S, Severi S, Chiari L, Avanzolini G, Enzmann G, Bianco F et al. Autonomic nervous function during haemodialysis assessed by spectral analysis heart-rate variability. Clin Sci 1997;92:351-9.
4. Cerutti C, Barres C, Paultre C. Baroreflex modulation of blood pressure and heart rate variabilities in rats: assessment by spectral analysis. Am J Physiol 1994; (Heart Circ.Physiol. 266): H1993-H2000.
5. Girard A, Laude D, Japundzic N, Elghozi J-L. Effects of chronic beta adrenoceptor blockade on variability in blood pressure and heart rate: a non-invasive study. J Hypertens 1991;9:S350-S351.
6. Golstein B, Fisher D, Kelly MM, Mickelsen D, Ruttiman U, Pollack MM. Decomplexification in critical illness and injury: relationship between heart rate variability, severity of ilness, and outcome. Crit Care Med 1998;26:352-357.
7. Gonzales JG, Cordero Valeriano JJ, Rodriguez MF. Autonomic mediation of short-term cardiovascular oscillations after acute hemorrhage in conscious rats. J Auton Nerv Syst 1995;55:123-30.
8. Griffith TM, Edwards DH. Fractal analysis of the role of smooth muscle Ca2+ fluxes in genesis of chaotic arterial pressure oscillations. Am J Physiol 1994;(Heart Circ. Physiol 35):H1801-H1811.
9. Hayano J, Yasuma F, Okada A, Mukai S, Fujinami T. Respiratory sinus arrhythmia. A phenomenon improving pulmonary gas exchange and circula-

tory efficiency. Circulation 1996;94:842-7.

10. Hughson RI, Maillet A, Dureau G, Yamamoto Y, Gharib C. Spectral analysis of blood pressure variability in heart transplant patients. Hypertension 1995;25:643-50.
11. Japundzic N, Grichois M-L, Zitoun P, Laude D, Elghozi J-L. Spectral analysis of blood pressure and heart rate in conscious rats: effects of autonomic blockers. J Auton Nerv Syst 1990;30:91-100.
12. Japundzic-Zigon N. Physiological mechanisms in regulation of blood pressure fast frequency variations. Clin Exper. Hypertension 1998;20:359-88.
13. Japundzic-Zigon N. Effects of nonpeptide vasopressin V1a and V2 antagonists on the fast blood pressure oscillations in conscious rats. Clin and Exp Hypertension 2001;23, in press.
14. Kaplan DT, Cohen RJ. Is fibrillation chaos? Circullation Res 1990;67:886-92.
15. Pagani M, Malfatto G, Pierini S, Casati R, Masu AM. Poli M, et al. A spectral analysis of heart rate variability in assessment of autonomic diabetic neuropathy. J Auton Nerv Syst 1988;23:143-53.
16. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral Analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. Hypertension 1995;25:1276-86.
17. Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: form the cardiovascular laboratory to daily life. J Hypertens. 2000;18:7-19.
18. Pinna GD, Maestri R, Mortara A. Estimation of arterial blood pressure variability by spectral analysis: comparison between Finapres and invasive measurements. Physiol Meas 1996;17:147-69.
19. Siche JP, Longere P, De Gaudemaris R, Ricachi M, Comparat V, Maillon JM. Variability in arterial blood pressure at rest depends on the sensitivity of the baroreflex. J Hypertens. 1993;11:S176-S177.
20. Takalo R, Korhonen I, Turjanmaa V, Majahalme S, Tuomisoto M, Uusitalo A. Short-term variability of blood pressure and heart rate in borderline and mildly hypertensive subjects. Hypertension 1994;23:18-24.
21. Wagner CD, Persson PB. Chaos in the cardiovascular system: an update. Cardiovasc Res 1998;40:257-64.