Signal Processing for Heart Rate Variability: Part I

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Abstract: *Over the last century, it has been established that the shapes and frequencies of ECG waves can reveal abnormalities in the heart's anatomy or function. Beyond the peaks and valleys of an ECG recording, there lies a treasure of information about the heart rate patterns that can identify patients at high risk of autonomic disorders and cardiac problems. The heart rate variability (HRV) is a reliable reflection of many physiological factors modulating the normal rhythm of heart, provides a powerful means of observing the interplay between the sympathetic and parasympathetic nervous systems. Despite the intensive research efforts, clinical use of cardiovascular variability analysis is still limited, as a number of topics remain relatively unresolved. This is largely due to the general complexity of the human physiology that is reflected in the signals. This complexity gives rise to large inter-subject variability and disposes the signal to measurement artifacts and noise due to other physiological activities. The most influencing biological artifacts in ECG recording are the ectopic beats. This paper gives a comprehensive survey and general backgrounds of research and development of time-domain and frequency-domain analysis techniques of HRV and the advancements in the methods used for ectopic beat replacement. Moreover, currently there is considerable interest in the possibility of measuring baroreflex sensitivity (BRS) by noninvasive methods to improve the clinical applicability and versatility of BRS assessment. The present study also shed light on the various approaches to analyze BRS.*

Keywords: *HRV, Lomb transform, Ectopic beats, BRS, Spectral analysis*

1. Introduction

Endogenous biomedical signals from physiological systems are acquired for a number of reasons including diagnosis, post surgical intensive care monitoring, neonatal monitoring, guide therapy and research *etc.* The pattern of variability of these physiological signals contains the valuable information about the physiological system, representing an important means for clinical diagnosis. The science of variability has been developed from inter-disciplinary work of mathematicians, physicians and clinicians.

HRV refers to the beat-to-beat alterations in heart rate and a decrease in its value or abnormalities in its patterns have been used as a measure for predicting the future coronary events. Thus, variability present in the time intervals between R-wave peaks in the ECG, serves as a means for exposing cardiac dysfunction. It is thought that the HRV is the result of interaction among complex feedback mechanisms in the cardiovascular system. Therefore, as the feedback mechanisms are degarded by diseases, the HRV diminishes. Now a day, HRV has become a central topic in physiological signal analysis, serving as a vital noninvasive indicator of cardiovascular and autonomic system function, with direct connections to respiratory, central nervous and metabolic dynamics. During the past 30 years, a *medline* search reveals more than 12000 papers on different aspects on HRV, covering physiological modeling and interpretation, diagnostic tools in major pathological states such as ischemia and myocardial infraction, heart failure, hypertension, diabetics and other pathologic involving autonomic and central nervous system, in ambulatory patient monitoring in intensive care unit and anesthesia level measurement, in sports and space medicine as well as for the detections of stress level and environment effect. The clinical relevance of HRV was first appreciated in 1965 when Hon and Lee [1] noted that fetal distress was preceded by alterations in interbeat intervals before any appreciable change occurred in the heart rate itself. Burton and Taylor [2] completed the foundation for the analysis of the short-term cardiovascular variability in 1940, with the discovery of the third main oscillatory component, with a period slower than 0.05 Hz. In the last three decades, the easy access to powerful computers has brought about a revolutionary change in computing powers and the hypothesis arose that cardiovascular rhythms might be capable of providing quantitative markers of cardiovascular control mechanisms [3]-[7]. Although patterns of HRV hold considerable promise for clarifying issues in clinical applications, the inappropriate quantification and interpretation of these patterns may obscure critical issues or relationships and may impede rather than foster the development of clinical applications. ESC & NASPE Task Force was created and charged with reviewing the problems of HRV measurement, physiologic interpretation, and clinical use [1]. HRV related cardiological issues reiterate the significance of HRV in assessing the cardiac heath [5],[8]-[13].

One of the traditional methods to quantify the overall variability of heart rate is the time-domain method [1],[14]-[16]. Goldberger *et al.* [17] and Mäkikallio *et al.* [18] suggests that the time domain measures cannot detect subtle changes in heart rate dynamics and are suitable only for long-term recordings. In recent studies, low SDNN (standard deviation of the average RR intervals) has shown to predict mortality in post-acute myocardial infracted patients [15],[19]-[20].

Kitney and Rompleman [21],[22] described the thermoregulatory influence on HRV reflected in very low frequency band. Akselrod *et al.* [5] reported that HRV power spectrum reflect beat-to-beat cardiovascular control. DeBoer *et al.* [23] evaluated the interval spectrum and spectrum of counts and established their equivalence for HRV. Berger *et al.* [24] proposed an improved algorithm for the derivation of a heart rate signal from the ECG. Shin *et al.* [25] explored the HRV by using complex demodulation. Bianchi *et al.* [26] described time-variant power spectrum analysis for the detection fo transient episodes in HRV signal. Kamath and Fallen [27] presented a detailed literature review on methodological issues relevant to signal processing, computational and clinical applications of power spectrum analysis of HRV. Parati *et al.* [28] presented a critical appraisal of the commonly used spectral analysis techniques and they also provided an insight into the problems that affect the physiological and clinical interpretations of the data provided by spectral analysis of BP and HRV. Clayton *et al.* [29] compares the autoregressive and Fourier transforms based techniques for estimating RR-interval spectra. Attapattu and Mitrani [30] suggested a telemedicine application to remotely track the HRV of patients in a clinical research environment. Persson *et al.* [31] used time and frequency domain techniques for accessing BRSand Di Reinzo *et al.* [32] examined the advancements in estimating the baroreflex function. Boardman *et al.* [33] proposed an optimum model order not less that p=16, of autoregressive models for HRV. Nazeran *et al.* [34],[35] uses time and frequency domain methods for the analysis of HRV signal for the detection of sleep disordered breathing in children and developed a user friendly integrated software for the same. Singh *et al.* [36] studied the effects of RR-interval segment duration on HRV spectrum estimation and proposes the segment length of 256 samples with 50% overlapping and they further proposed the sampling frequency of 4 Hz of the RR-interval time series for spectral analysis of HRV [37] and the same group [38] proposed an improved windowing technique to overcome the effects of window bias for HRV power spectrum estimation. Further, they studied the effects of aging on blood pressure and heart rate variations in healthy subjects using time and frequency domain analysis [13]. Mateo *et al.* [39] applied the IPFM model for HRV analysis. Most of the FFT based or AR based methods of spectral estimation requires a re-sampled RR-interval series. But this re-sampling operation induces a distortion in the spectral estimates. Clifford and Tarassenko [40] quantified the errors in spectral estimates of HRV due to beat replacement and re-sampling. Shin *et al.* [41] and Moody [42] used Lomb transform for the direct power spectral estimation of unevenly sampled cardiac event series. In this method [43]-[46] there is no need of re-sampling the RR-interval series before spectral estimation thus all the drawbacks which are associated with the re-sampling operation are removed in this method. Thong and others [47] developed a Lomb-Welch periodogram for non-uniform sampling and the same group [48] studied the effect of Nicotine on HRV using Lomb-Welch periodogram.

Signal processing offers a wide spectrum of theories, methods and algorithms for addressing a variety of problems ranging from noise reduction, delineation of events, spatiotemporal dynamics estimation. Algorithmic results are discussed to show not only the potential performance but also the limitations of the processing resources at our disposal.

2. Origin of HRV

The HRV is originated based upon the interaction between SMP and PSMP branches of autonomic nervous system (ANS). SMP stimulation, occurring in response to stress, exercise and heart disease, causes an increase in HR by increasing the firing rate of sino-atrial node. PSMP activity, primarily resulting from the function of internal organs, trauma, allergic reactions and the inhalation of irritants, decreases the firing rate of packmaker cells and the HR, providing a regulatory balance in physiological autonomic function [9]. The separate rhythmic contributions from SMP and PSMP autonomic activity modulate the RR-interval series derived from the electrocardiogram (ECG), at distinct frequencies. SMP activity is associated with the low frequency range (0.04-0.15 Hz) while PSMP activity is associated with the higher frequency range (0.15-0.4 Hz) of modulation frequencies of the HR.

3. HRV Modulators

3.1 Respiration

The variation of heart rate (HR) with respiration often known as sinus arrhythmia is primarily mediated by the vagal innervations of the heart. This phenomenon has been studied extensively, and although it is not fully understood, its physiological determinants have been unveiled [49]-[50]. The HR gets accelerated during inspiration and slows down during expiration. These variations in the HR with respiration can be mediated using the slow-deep breathing test [51].

3.2 Exercise

The exercise training increases the HR and this effect can only be of vagal origin. Further, the meta-boreceptors within the muscle also get stimulated and contribute to an afferent input, which further increase HR. Many other mechanisms are also involved in increasing the HR with exercise, including reflexes from lung inflation and possible inhibition of the baroreflex [51].

3.3 Reflexes

The stimulus response sequences like the thermoregulatory systems, homeostatic control systems *etc.*, are known as reflexes. Although in some reflexes, we are aware of the stimulus and/or the response, many reflexes regulating the internal environment occur without any conscious awareness [52]. Many reflexes in the cardiovascular and central nervous systems simultaneously stimulate the vagal and SMP centers.

The overall autonomic function is controlled by a central command from the brain. The ANS operates as a feedback system, and many reflexes regulate HR, which may increase and/or decrease the SMP or PSMP activity [51]. All circulatory reflexes interact in a complex way and it may, thus, be difficult to differentiate between the actions of different control systems [51].

3.4 Myocardial Infarction

Acute myocardial infarction (MI) patients have reduction in PSMP cardiac control [53]. The increase in SMP activity decreases the fibrillation threshold and predisposes to ventricular fibrillation (VF), whereas an increase in vagal activity increases the threshold and appears to have a protective effect against life threatening arrhythmias [54]-[55]. The degree of respiratory sinus arrhythmia shows a linear relation with PSMP cardiac control [56] and thus can be used as a prognostic tool in patients, who have had a MI. It was shown that, the HRV decreases with the recent MI [57].

3.5 Nervous System

Disorders of the central and peripheral nervous system have effects on HRV. The vagally and sympathetically mediated fluctuations in HR may be independently affected by some disorders. All normal cyclic changes in HR are reduced in the presence of severe brain damage [58] and depression [57]. The significance of HRV analysis in psychiatric disorders arises from the fact that one can easily detect a sympatho-vagal imbalance, if it exists in such pathologies. It is proved that, in physically healthy depressed adults the HRV does not vary from healthy subjects [59].

3.6 Cardiac Arrhythmia

A complex system like cardiovascular system cannot be linear in nature and by considering it as a nonlinear system, can lead to better understanding of the system dynamics. Recent studies have also stressed the importance of nonlinear techniques to study HRV in issues related to both health and disease. The progress made in the field using measures of chaos has attracted the scientific community to apply these tools in studying physiological systems, and HRV is no exception. There have been several methods of estimating invariants from nonlinear dynamical systems being reported in the literature. Recently, Fell *et al.* [60] have tried the nonlinear analysis of ECG and HRV signals, respectively. Owis *et al.* [61] have used nonlinear dynamical modeling in ECG arrhythmia detection and classification. Acharya *et al.* [62] have classified the HRV signals using nonlinear techniques, and artificial intelligence into different groups. Dingfie *et al.* [63] have classified cardiac arrhythmia into six classes using autoregressive (AR) modeling.

3.7 Diabetes

The decreased beat-to-beat variability during deep breathing in diabetic neuropathy was first reported by Wheeler and Watkins [64]. In studies comparing cardiac autonomic function tests and HRV indices, show that, in diabetic patients without abnormal function tests, HRV was lowered [65]. It was concluded that cardiac (PSMP) autonomic activity was diminished in diabetic patients before clinical symptoms of neuropathy become evident [9], [146].

3.8 Renal Failure

In patients with renal failure, autonomic function tests have been done [66], followed by HRV indices [67]. Although autonomic function tests revealed predominant impairment of the PNS [68], spectral analysis exhibited a strong reduction in the HR power spectrum at all frequency ranges, both sympathetically and parasympathetically [69]. The 5-min HRV of 20 chronic renal failure (CRF) patients were analyzed. Results revealed that calcium is negatively correlated to the mean of RR intervals and normalized HF power after hemodialysis. A model of baroreflex control of BP was proposed in terms of a delay differential equation and was used to predict the adaptation of short-term cardiovascular control in CRF patients [70]. They showed that in CRF patients, the mean power in the LF band was higher and lower in the HF bands than the corresponding values in the healthy subjects.

3.9 Gender and Age

It is proved that, the HRV depends on the age and sex also. The HRV was more in the physically active young and old women [71]. The HRV for healthy subjects was studied by Bonnemeir *et al.* [72] and found that the HRV decreases with age and variation is more in the case of female than men. Previous studies have assessed gender and age-related differences in time domain, frequency domain and nonlinear indices of HRV [73]. There also seemed to be a significant difference between day and night hours when studying HRV using time and frequency domain methods [73]. The amount of HRV is also influenced by physiologic and maturational factors. Maturation of the SMP and vagal divisions of the ANS results in an increase in HRV with gestational age and during early postnatal life [74]. HRV decreases with age [62]. This decline starts in childhood [75]. Infants have a high SMP activity that decreases quickly between ages 5 and 10 years [76]. The influence of provocation on HRV is more pronounced at younger ages [75]. In adults, an attenuation of rspiratory sinus arrhythmia with advancing age usually predominates [77]. It was shown that compared to men, women are at lower risk of coronary heart disese [78]. Time-domain studies have clearly shown that HRV decreases with increasing age, the decline being generally attributed to age-related reduction in PSMP activity [79]. SMP activity also declines with age, but at a slower rate [11]. Singh *et al.* [13] studied the aging effect on time and frequency domain HRV.

3.10 Drugs

HRV can be significantly influenced by various groups of drugs. The influence of medication should be considered, while interpreting HRV. On the other hand, HRV can be used to quantify the effects of certain drugs on the ANS. The effects of beta-blockers and calcium channel blockers on the HRV have been studied in post infarction and hypertensive patients [80],[81]. With spectral analysis, it is possible to unravel the SMP and PSMP activities of these drugs and thus explain thier protective effects in cardiac diseases. Guzzetti *et al.* [82] studied the effect of atenolol in patients with essential hypertension. They found not only an increase in HF fluctuations, but also a decrease in the sympathetically mediated LF oscillations.

3.11 Smoking

Studies have shown that smokers have increased SMP and reduced vagal activity as measured by HRV analysis. Smoking reduces the HRV. One of the mechanisms by which smoking impairs the cardiovascular function is its effect on ANS control [83],[84]. Altered cardiac autonomic function, assessed by decrements in HRV, is associated with acute exposure to environmental tobacco smoke (ETS) and may be part of the patho-physiologic mechanisms linking ETS exposure and increased cardiac vulnerability [85]. Zeskind and Gingras [86] proved that, the vagal modulation of the heart had blunted in heavy smokers, particularly during a PSMP maneuver. Blunted autonomic control of the heart may partly be associated with adverse event attributed to cigarette smoking [9], [11].

3.12 Alcohol

HRV reduces with the acute ingestion of alcohol, suggesting SMP activation and/or PSMP withdrawal. Malpas *et al.* [87] have demonstrated vagal neuropathy in men with chronic alcohol dependence using 24 hrs HRV analysis. ECG indices of vagal activity have been reported to have significantly lower indices of cardiac vagal nerve activity than normal volunteers, in acute alcoholic subjects [87], [88].

4. Signal Acquisition

The ECG is the most appropriate signal to study short-term and long-term HRV because it offers the most accurate representation of the electrical events of cardiac system. In particular, the QRS complex of the ECG sharply defines the onset of ventricular electrical depolarization. It is closest to the time occurrence of pacemaker potentials, which in turn are modulated by the autonomic outflow. The simplicity and noninvasiveness in ECG recording have been exploited to study HRV in a wide variety of species, from fish and reptiles to mammals [7], [89], [90], [91].

Depending on the specific indication for analysis of HRV, either long-term (24-hour) or short-term (5-minute) recordings are made. HRV increases with increased periods of observation, and it is important to distinguish ranges on the basis of duration of recording. The Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE)[1] provided frequency ranges for each parameter of HRV obtained during short- and long-term recordings. Frequency domain methods are preferable for short-term recordings. Recording should last at least ten times the duration of the wavelength of the lowest frequency under investigation. For example, recordings should be approximately 1-minute for short-term evaluation of the HF and 2-minutes for evaluation of LF. The authors of the ESC/NASPE Task Force recommend standardization at 5-minute recordings for short-term analysis of HRV [1].

5. Ectopic Beats in HRV

Ambulatory ECG recording is exposed to many physiological and technical disturbances. Technical artifacts may result from poorly fastened electrodes or be motion artifacts during ambulatory recording. Ectopic beats, arterial fibrillation and ventricular tachycardia are examples of physiological artifacts in ECG recording. Ectopic beats are generated by additional electrical impulses imposed by local pacemakers. Ectopic beats (in terms of timing) are defined as those which have intervals less than or equal to 80% of the previous sinus cycle length [40], [92]. The decision whether an ectopic beat should be corrected or not usually forms the most difficult step in the artifact removal. In computerized artifact detection, relatively simple artifact detection criteria supported by additional visual verifications are still being used [93]. In literature, the effect of different ectopic editing methods on HRV parameters have been studied [49], [93]-[97].

6. Quantification of HRV

The concept, trends and the methods of developments of HRV signal processing can be traced over the past three decades. Such an examination sheds light on the respective influences of medical (clinical) and signal processing concerns and on the ways the problems were stated and addressed. Our aim in this part of work is: i) to investigate traditional HRV measures and to identify where difficulties still lie, ii) to point out the advancements made and iii) to explore new and innovative approaches for the quantification of HRV signals.

6.1 Linear Techniques

6.1.1 Time-domain measures

HR fluctuations were quantified by number of methods. Perhaps the simplest to perform are the time domain measures. These measures of HRV are based on either statistical or geometrical analysis of the HR or RR intervals between successive normal-normal QRS complexes [98]. With these methods HR at any point in time or between successive normal complexes can be estimated.

The following statistical indices are recommended by the Task Force of the European Society of Cardiology and North American Society of Pacing Electrophysiology [1]: i) SDNN, ii) SDANN, iii) RMSSD, iv) SDNN, v) SDSD, vi) NN50 count, vii) NN50%. Another time domain measure of HRV is the triangular index; a geometric measure obtained by dividing the total number of all NN intervals by the height of histogram of all NN intervals on a discrete scale with bins of 7.8125 ms [99]

6.1.2 Frequency-domain measures

The time domain measures will convey the information about the overall variability in time series or the maximum amplitude of variability but not contain any information about the periodic fluctuations of the HR. Frequency domain analysis provides information of how power distributes as a function of frequency. As per the recommendations of Task Force [1] the power spectrum of a healthy subject can usually be divided into four major frequency bands. The range of the spectral components usually used is: HF component 0.15-0.4 Hz, LF component 0.04-0.15 Hz, VLF component 0.003-0.04 Hz, and ULF component <0.003 Hz. The total power in autonomic band from 0-0.5 Hz is represented by the total area under the power spectral curve, and the power of individual frequency bands are represented by the area under the proportion of the curve related to each band. The ratio between the LF and HF components (LF/HF ratio) has been found to reflect the sympatho-vagal balance of the HR fluctuation [100],[101].

FFT and AR methods of spectral estimation

The two most common methods for frequency-domain HRV metric estimation are auto-regressive (AR) spectral estimation and Fourier techniques [29],[33]. These methods are used to transform HR signals into the frequency domain. In most instances, the two methods provide comparable results. The FFT spectra are characterized by discrete peaks for several frequency components. However, FFT requires strict periodicity of the data and a priori selection of the number and frequency range of the oscillatory components. The advantages of the FFT method are the simplicity of the algorithm and high processing speed. On the other side the AR method yields smoother spectral components which can be distinguished independently of pre-selected frequency bands and provides an accurate estimation of PSD even on a small number of samples on which the signal is supposed to maintain stationarity. When the analysis is focused on broadband powers, the AR method suitably describes the spectrum only if an appropriately high model order is used; which is empirically selected on the basis of the investigator's expertise or by comparing the AR power spectra with that computed from other techniques. The basic disadvantage of AR method is the need to verify the suitability of the chosen model and its complexity. Changing the model-order across different physiological conditions and/or patients may introduce a new variable into the computation of power spectrum. A fixed model-order has been proposed as a practical rule for AR spectral estimation [28], [33], [102]. In clinical applications the AR method is criticized on the ground that in using the same model order for all the subjects irrespective of their autonomic behavior [103]. Under this condition the FFT based methods are widely used for their easy applicability, computational speed and direct interpretation of results is more preferable.

The regular PSD estimators implicitly assume equidistant sampling and, thus, the RR-interval series should be converted to equidistantly sampled series by some suitable interpolation method prior to PSD estimation using either FFT or AR method. If the power spectrum is computed from the irregularly time-sampled signal, implicitly assuming it to be evenly sampled, additional harmonic components are generatd in the spectrum. Thus, to avoid spectral distortions, RR-interval series were transformed into evenly sampled signals using interpolation.

Lomb transform method of spectral estimation

The instantaneous HR time series used as the bases of spectral analyses are sampled at intrinsically irregular intervals. As it was seen in the previous section to apply FFT or AR techniques to HR time series requires that the series be re-sampled at uniform intervals [46]. This has been achieved by re-sampling the RR-interval time series [12],[104]. But the re-sampling process induces a distortion in the spectral estimates of even a noise-free time series due to the low-pass filtering effect. If the time series contains inappropriate or missing samples (as, for example, in HR time series with ectopic beats or noise), the re-sampling is further complicated by the need to infer probable values as replacements, with the likelihood of further alteration of frequency content [46].

Lomb transform (LT) was proposed for PSD estimation of raw RR-interval series without any re-sampling. Laguna *et al.* [41] found that the Lomb method for estimating the PSD of unevenly sampled signals produces a better estimate of the PSD of an RR tachogram than re-sampling and using a conventional FFT. Lomb-Scargle transform has been proposed [41],[44] for HRV studies, thus entirely avoided the problems associated with re-sampling and sample replacement.

The Lomb normalized transform (spectral power as a function of angular frequency $\omega = 2\pi f > 0$) is defined using equation (1):

$$P_N(\omega) = \frac{1}{2\sigma^2}\left\{\frac{[\Sigma_j (h_j - \bar{h}) \cos\omega(t_j - \tau)]^2}{\Sigma_j \cos^2\omega(t_j - \tau)} + \frac{[\Sigma_j (h_j - \bar{h}) \sin\omega(t_j - \tau)]^2}{\Sigma_j \sin^2\omega(t_j - \tau)}\right. \qquad (1)$$

where h and σ^2 are the mean and variance of the series h_j, and τ is a frequency dependent time delay, defined to make the transform insensitive to time shift [43] and is computed using equation (2).

$$\tan(2\omega\tau) \frac{\Sigma_j \sin 2\omega t_j}{\Sigma_j \cos 2\omega t_j} \quad (2)$$

This method has one drawback in terms of its large computational complexity that reduces the speed of the algorithm. This reduction in speed further puts a restriction in terms of length of the record to estimate. Thus based upon this limitation a fast Lomb transform (FLT) [43] has been proposed for HRV studies [105]. With FLT a significant increase in the speed is attained and this increase in speed also removes a restriction in terms of length of record to be estimated, *i.e.* with FLT method one can analyze 10^6 input data points. But the FLT method induces an amplitude distortion in the spectral estimates; this restricts to use this method in HRV studies. Thus, an average Lomb transform (ALT) was proposed for accurate assessment of RR interval series. The ALT of a non-uniformly sampled real-valued data sequence $\{x(t_n)\}$ of length N is defined [47],[48] using equation (3).

$$P_x(f) = \frac{1}{N}\left\{ \frac{[\sum_{n=1}^{N}(\bar{x}(t_n) - x) \cos(2\pi f(t_n - \tau))]^2}{\sum_{n=1}^{N} \cos^2(2\pi f(t_n - \tau))} + \frac{[\sum_{n=1}^{N}(\bar{x}(t_n) - x) \sin(2\pi f(t_n - \tau))]^2}{\sum_{n=1}^{N} \sin^2(2\pi f(t_n - \tau))} \right. \quad (3)$$

Since this method is used for handling the long non-uniformly sampled RR-interval records, so for averaging the long record is segmented into three overlapped segments of same time duration. Finally, power averaging transform of these overlapped windowed segments is obtained. Thus in terms of spectral smoothness, resolution and accuracy of spectral estimates, the ALT method of spectral estimation for non-uniformly sampled data gives superior performance in comparison to its other two variants (LT and FLT) in HRV studies.

7. Baroreflex Sensitivity

Baroreflex sensitivity (BRS) assesses autonomic reflex integrity. It is an index of reflex vagal activity. Arterial baroreceptors play a central role in controlling short-term blood pressure responses to the continuous perturbations produced by various stimuli by setting reflex change in HR. The change in HR in response to change in blood pressure (BP) provides valuable information about BRS in healthy subjects as well as in diseased conditions [106]. In literature there are variety of methods have been used for the evaluation of BRS like i) Phenylephrine method [106], [107] ii) Spontaneous method [108]-[112] iii) Sequence method [108], [208] iv) Spectral method [108],[112]-[115].

8. Future Challenges

There is a family of possible risk factors now known for cardiovascular disease and the role of age, gender, diabetes, smoking, hypertension and cholesterol has been established. The assessment of heart health needs to incorporate the heart rate turbulence, erratic rhythm, and other measures of HRV for effective diagnostic procedures. The general complexity of the human physiology has imposed several limitations giving rise to large inter-subject variability and disposes the signal to the measurement artifacts and noise. Moreover, in the last decades, much attention was dedicated to linear methods, but the complex origin of the signal makes these traditional linear analysis approaches often inadequate and limited. Due to this reasons there is an urgent need to identify where the problem still lie, to point out the advance made, and to propose new innovative approaches for deciphering the hidden dynamics of HRV signals. In the next extension of this paper, we will consider the time-frequency domain techniques for signal processing of HRV. The nonlinear techniques will be reviewed within a unified conceptual framework.

9. Conclusion

HRV, the changes in the beat-to-beat HR calculated from the electrocardiogram, is a key indicator of an individual's cardiovascular condition. Assessment of HRV has been shown to aid clinical diagnosis and intervention strategies. This paper has been devoted to signal processing as applied to HRV signals. In this study some trends in HRV signal processing methods and research in progress along with the critical issues like editing of ectopic beats and BRS have been sketched. However the another challenge will be to deal with the changes in signal features brought about by the movement of external actions in controlled and ambulatory situations. The potential for further breakthroughs in HRV signal processing methods are examined in Part-II, which follows.

References

1. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability - standards of measurement, physiological interpretation and clinical use", *European Heart Journal*, vol. 17, pp. 354-381, 1996.

2. I. Korhonen, "Methods for the analysis of short-term variability heart rate and blood pressure in frequency domain", *Ph.D. Thesis, Technical Research Centre of Finland,* Espoo: VTT Publications 316, 1997.

3. A. Malliani, M. Pagani and F. Lombardi, "Physiology and clinical implications of variability of cardiovascular parameters with focus on heart rate and blood pressure", *American Journal of Cardiology,* vol. 73, pp. 3C-9C, 1994.

4. B. Sayers, "Analysis of heart rate variability", *Ergonomics,* vol. 16, no. 1, pp. 17-32, 1973.

5. S. Akselrod, D. Gordon, F.A. Ubel, D.C. Shannon, A.C. Barger and R.J. Cohen, "Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control", *Science,* vol. 213, pp. 220-222, 1981.

6. P.K. Stein, M.S. Bosner, R.E. Kleiger and B.M. Conger, "Heart rate variability: A Measure of Cardiac Autonomic Tone", *American Heart Journal,* vol. 127, no. 25, pp. 1376-1381, 1994.

7. G.G. Berntson, J.T. Bigger, D.L. Eckberg, P. Grossman, P.G. Kaufmann, M. Malik, H.N. Nagaraja, S.W. Porges, J.P. Saul, P.H. Stone and M.W. van der Molen, "Heart rate variability: Origins, methods, and interpretive caveats", *Psychophysiology,* vol. 34, pp. 623-648, 1997.

8. Schwartz PJ, Priori SG (1990) Sympathetic nervous system and cardiac arrythmias", *In D.P. Zipes, J. jalife (eds.) Cardiac electrophysiology. From cell to bedside.* W.B. Saunders, Philadelphia, pp. 330-343.

9. U.R. Acharya, K.P. Joseph, N. kannathal, C.M. lim and J.S. Suri, "Heart Rate Variability: a review", *Med Bio Eng. Comp.,* vol. 44, pp. 1031-1051, 2006.

10. P.K. Stein, M.S. Bosner, R.E. Kleiger and B.M. Conger, "Heart rate variability: A measure of cardiac autonomic Tone", *American Heart Journal,* vol. 126, no. 25, pp. 1376-1381, 1994.

11. M.A. Conny, L.A.A. Kollee, C.W. Hopman, G.B.A. Stoelinga and H.P. Van Geijn, "Heart rate variability", *Annals of Internal Medicine,* vol. 118, pp. 436-447, 1993.

12. R.D. Berger, S. Akselrod, D. Gordon and R.J. Cohen, "An efficient algorithm for spectral analysis of heart rate variability", *IEEE Trans Biomed Eng,* vol. 33, pp. 900-904, 1986.

13. D. Sing, K. Vinod, S.C. Saxena and K.K. Deepak, "Spectral evaluation of aging effects on blood pressure and heart rate variations in healthy subjects," Journal of Medical Engineering Technology, vol 30, no. 3, pp. 145-150, 2006

14. D. J. Ewing, J.M.M Neilson, and P. Travis, "New method for assessing cardiac parasy empathetic activity using 24 hours electrocardiograms," British Heart Journal, vol. 52, pp. 396-402, 1984.

15. J.T. Bigger Jr., P. Albrect, R.C. Steinman, L.M. Rolniztky, J.L. Fleiss, and R.J. Cohem, "Comparison of time and frequency domain-based measures of cardiac parasympathetic activity in holter recordings after myocardial infarction," American Journal of Cardiology, vol. 64, pp. 536-538, 1989.

16. R. E. Kleiger, P. K. Stein, M. S. Bosner, and J. N. Rottman, "Time domain measurements of heart rate variability," Cardiology Clinics, vol. 10, pp 487-498, 1992.

17. A. L. Goldberger, "Non-linear dynamics for clinicians chaos theory, fractals, and complexity at the bedside," Lancet, vol. 347, pp. 1312-1314, 1996.

18. T. H. Makikallio Ristimae, K. E. Airaksinen, C. K. Peng A. L. Goldberger, and H. V. Huikuri, "Heart rate dynamic in patients with stable angina pectoris and utility of fracta and complexity measures," American Journal of Cardiolog vol. 81, pp. 27-31, 1998.

19. R. E. Kleiger, J. P. Miller, J. T. Bigger Jr., and A. J. Moss "Decreased heart rate variability and its association wit increased mortality after acute myocardial infarction," American Journal of Cardiology, vol. 59, pp. 256-262 1987.

20. H. Tsuji, F. J. Venditti Jr., E. S. Manders, J. C. Evans, M G. Larson, C. L. Feldman, and D. Levy, "Reduced hea rate variability and mortality risk in an elderly cohort: Th Framingham Heart Study," Circulation, vol. 90, pp. 878-883, 1994.

21. R. I. Kitney and O. Rompelman, Eds., "The Beat-by-be Investigation of Cardiovascular Function," Oxfor Clarendon Press, 1987.

22. R. I. Kitney and O. Rompelman, Eds., "The study of hea rate Variability," Oxford: Clarendon Press, 1980.

23. R. W. De Boer, J. M. Karemaker, and J. Stracke "Comparing spectra of a series of point events particular for heart rate variability data," IEEE Transaction Biomedical Engineering, vol. BME-31, PP. 384-387, 198

24. R. D. Berger, S. Akselrod, D. Gordon, and R. J. Cohe "An efficient algorithm for spectral analysis of heart ra variability," IEEE Transactions on Biomedical Engineerir vol. BME-33, PP. 900-904, 1986.

25. S. Shin, W. N. Tapp, S. S. Reisman, and B. H. Natelsc "Assessment of autonomic regulation of heart ra variability by the method of complex demodulation," IE Transactions on Biomedical Engineering, vol. 36, no. pp. 274-282, 1989.

26. A. M. Bianchi, L. Mainardi, E. Petrucci, M. G. Signori M. Mainardi, and S. Cerutti, "Time-variant pow spectrum analysis for detection of transient episodes HRV signal," IEEE Transactions on Biomedical Engineeri vol. 40, no. 2 , pp. 136-144, 1993.

27. M. V. Kamath and E. L. Fallen, "Power spectral analy of heart rate variability: A noninvasive signature of card autonomic function," Critical Reviews in Biomedi Engineering, vol. 21, no. 4, pp. 245-311, 1993.

28. G. Parati, J. P. Saul, M. Di Rienzo, and G. Manc "Spectral analysis of blood pressure and heart r variability in evaluating cardiovascular regulation. A crit approach," Hypertension vol. 25, pp. 1276-1286, 19

29. R. H. Clayton, S. W. Lord, J. M. McComb, and A. Mur "Comparison of autoregressive and Fourier transform ba techniques for estimating RR interval spectra," Proceedings of the IEEE International Conference Computers in Cardiology, Lund, Sweden, September 7 pp. 379-382, 1997.

30. S. A. Atapattu and R. D. Mitrani, "A telemedic application utilizing data socket to remotely track the h rate variability of patients in a clinical resea

environment,' in Proceedings of IEEE Conference ITAB-IT IS 2000, November 9-10, pp. 71-73, 2000.

31. P. B. Pesson, M. DiRienzo, P. Castiglioni, C. Cerutti, M. Pagani, N. Honzikova, S. Akselrod, and G. Parati, 'Time versus frequency domain techniques for assessing baroreflex sensitivity," Journal of Hypertension, vol. 19, no. 10, pp. 1699-705, 2001.

M. Di Rienzo, P. Castiglioni, G. Mancia, A. Pedotti, and G. Parati, "Advancements in estimating baroreflex function: Exploring the different aspects of autonomic control of the heart through the sequence technique," IEEE Engineering in Medicine and Biology, Vol. 20, no. 2, pp. 25-32, 2001.

33. A. Boardman, F. S. Schlindwein, A. P. Rocha, and A. Leite, "A study on optimum order of autoregressive models for heart rate variability," Physiological Measurement, vol. 23, pp. 325-336, 2002.

34. H. Nazaren, Y. Pamula, A. Gradziel, K. Ung, S. Vijendra, and K. Behbehani, "Computer based analysis of HRV for detection of sleep disordered breathing in children," in Proceedings of the 25th Annual International Conference of the IEEE EMBS, vol. 1, no. 17-21, pp. 338-341, 2003.

35. H. Nazaren, V. Magdum, B. Vikram, P. Nava, and E. Haltiwanger, "A user friendly integrated software environment for HRV analysis of sleep disordered breathing," in Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico, September 17-21, 2003, pp. 2378-2381.

36. D. Singh, K, Vinod, S. C. Saxena, and K. K. Deepak, "Effects of RR segment duration on HRV spectrum estimation," Physiological Measurement, vol. 25, pp. 721-735, June 2004.

37. D. Singh, K. Vinod, S. C. Saxena, "Sampling frequency of the RR-interval time-series for spectral analysis of the heart rate variability," Journal of Medical Engineering and Technology, vol. 28, no. 6, pp. 263-272, 2004.

38. D. Singh, K. Vinod, S. C. Saxena, and K. K. Deepak, "An improved windowing techniques for HRV power spectrum estimation," Journal of Medical Engineering and Technology, vol. 29, no. 2, pp. 95-101, 2005.

39. J. Mateo and P. Laguna, "Improved heart rate variability signal analysis from the beat occurrence times according to the IPFM model," IEEE Trans. On Biomed. Engg, vol. 47, no. 8, 2000.

40. G. D. Clifford and L. Tarassenko, "Quantifying errors in spectral estimates of HRV due to beat replacement and resampling," IEEE Transactions on Biomedical Engineering. Vol. 52, No. 4, pp. 630-638, 2005.

41. K. S. Shin, H. Minamitani, S. Onishi, H. Yamazaki, and M. H. Lee, "The direct power spectrum estimation of unevenly sampled cardiac event series," in Proceedings of the 16th Annual International Conference of the IEEE EMBS, vol. 2, pp. 1254-1255,1994.

42. G. B. Moody, "Spectral analysis of heart rate variability without resampling," IEEE Transactions on Biomedical Engineering, BME-33, PP. 900-904, 1986.

43. N. R. Lomb, "Least-squares frequency analysis of unequally spaced data," Astrophysical and Space Science, vol. 39, pp. 447-462, 1976.

44. J. D. Scargle, "Studies in astronomical time series analysis II: Statistical aspects of spectral analysis of unequally spaced data," Astrophysical Journal, vol. 263, pp. 835-853, 1982.

45. W. H. Press and G. B. Rybiciki, "Fast algorithm for spectral analysis of unevenly sampled data," Astrophysical Journal, vol. 338, pp. 277-280, 1989.

46. P. Laguna, G. B. Moody, and R.G. Mark, "Power spectral density of unevenly sampled data by least-square analysis: performance and application to heart rate signals," IEEE Transaction on Biomedical Engineering, pp. 698-715, 1998.

47. Tran Thong, James Mcnames, and Mateo Aboy, "Lomb-Welch periodogram for nonuniform sampling," in Proceedings of the IEEE EMBS, vol. 1, pp. 271-274, 2004.

48. Tran Thong, I. O. Yung, D. P. Zajdel, R. M. Ellingson, J. Mc Names, M. Aboy, and B. S. Oken, "HRV analysis of effect of Nicotine using Lomb-Welch periodogram," in Proceedings of the 26th Annual International Conference of the IEEE EMBS, September 1-5, vol. 1, pp. 294-297, 2004.

49. E. Toledo, M. G. Rosenblum, J. Kurths and S. Akselrod, "Cardiorespiratory synchronization: Is it a real phenomenon?" in Proc. IEEE Computer in Cardiology, vol. 26, pp. 237-240, 1999.

50. E. Pyetan and S. Akselrod, "Do the high frequency indexes of HRV provide a faithful assessment of cardiac vagal tone? A critical theoretical evaluation," IEEE Transactions on Biomedical Engineering, vol. 50, no. 6, pp. 777-783, 2003.

51. R. Hainsworth, "The control and physiological importance of heart rate," in Heart Rate Variability, M. Malik and A.J. Camm, Futura, Pub Co., 1995.

52. A.J. Vander, J.H. Sherman and D.S. Luciano, Human physiology: The mechanisms of boody function," 6th edn., New Delhi: McGrow-Hill, 1994.

53. M. Rothschild, A. Rothschild and M. Pfeifer, "Temporary decrease in cardiac parasympathetic tone after acute myocardial infarction," Am J Cardiol, vol. 18, pp. 637-639, 1988.

54. P.J. Schwartz, M.T. La Rovereand and E. Vanoli, "Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification," Circulation, vol. 85, (Suppl I), pp. 177-191, 1992.

55. J. M. Wharton, R.E. Coleman H.C. Strauss, "The role of the autonomic nervous system in sudden cardiac death," Trends Cardiovasc Med, vol. 2, pp. 65-71, 1992.

56. P.G. Katona and F. Jih, "Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control," J Appl Physiol, vol. 39, pp. 801-805, 1975.

57. R.M. Carney, J.A. Blumenthal, P.K. Stein, L. Watkins, D. Catellier, L.F. Berkman, S.M. Czajkowski, C. O' Connor, P.H. Stone and K.E. Freedland, "Depression, heart rate variability, and acute myocardial infarction," Circulation, vol. 104, pp. 2024, 2001

58. R.I. Lowensohn, M. Weiss and E.H. Hon, "Heart-rate variability in brain-damaged adults," Lancet, vol. 1, pp. 626-628, 1977.

59. K. Sayar, H. Gu lec and L. Ak, "Heart rate variability in depressed patients," Bull Clin Psychopharmacol, vol. 12, pp. 130-133, 2002.

60. J. Fell, K. Mann, J. Roschke and M.S. Gopinathan, "Nonlinear analysis of continuous ECG during sleeps I. Reconstruction," Biol Cybernat, vol. 82, pp. 477-483, 2000.

61. M.I. Owis, A.H. Abou-Zied, A.B.M. Youssef ABM and Y.M. Kadah, "Study of features on nonlinear dynamical modeling in ECG arrhythmia detection and classification," IEEE Trans Biomed Eng. Vol. 49, no, 7, pp. 733-736, 2002.

62. U.R. Acharya, N. Kannathal, O.W. Seng, L.Y. Ping and T. Chua, "Heart rate analysis in normal subjects of various age groups," Biomed Online J USA, vol. 3, no. 24, 2004.

63. D. Ge, N. Srinivasan and S.M. Krishnan, "Cardiac arrhythmia classification using autoregressive modeling," BioMedEng Online, vol. 1, no. 1, pp. 5, 2002.

64. T. Wheeler and P.J. Watkins, "Cardiac denervation in diabetes," Br Med J, vol. 4, pp. 584-586, 1973.

65. M.A. Pfeifer, D. Cook, J. Brodsky, D. Tice, A. Reenan, S. Swedine et al, "Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man," Diabetes, vol. 3, pp. 339-345, 1982.

66. D.J. Ewing and R. WinneR, "Autonomic function in patients with chronic renal failure," on intermittent haemodialysis. Nephron, vol. 15, no. 6, pp. 424-429, 1975.

67. J. Forsstrom, E. Heinonen, I. Valimaki and K. Antila "Effects of heamodialysis on heart rate variability in chronic renal failure," Scand J Clin Lab Invest, vol. 46, pp. 665-670, 1986.

68. C. Zoccali, M. Ciccarelli and Q. Maggiore, "Defective reflex control of heart rate in dialysis patients: evidence for an afferent autonomic lesion," Clin Sci, vol. 63, pp. 285-292, 1982.

69. S. Axelrod, M. Lishner, O. Oz, J. Bernheim and M. Ravid, "Spectral analysis of fluctuations in heart rate: an objective evaluation of autonomic nervous control in chronic renal failure," Nephron, vol. 45, pp. 202-206, 1987.

70. C. Lerma, A. Minzoni, O. Infante and M.V. Jose, "A mathematical analysis for the cardiovascular control adaptations in chronic renal failure," Artif Organs, vol. 28, no 4, pp. 398-409, 2004.

71. K.P. Davy, C.A. Desouza, P.P. Jones and D.R. Seals, "Elevated heart rate variability in physically active young and older adult women," Clin Sci, vol. 94, pp. 579-584, 1998.

72. H. Bonnemeier, U.K.H. Wiegand, A, Brandes, N. Kluge, H.A. Katus, G. Richardt and J. Potratz J, "Circadian profile of cardiac autonomic nervous modulation in healthy subjects: Differing Effects of aging and Gender on heart rate variability," J Cardiovasc Electrophysiol, vol. 14, pp. 8791-799, 2003.

73. D. Ramaekers, H. Ector, A.E. Aubert, A. Rubens, F. van de and Werf F, "Heart rate variability and heart rate in healthy volunteers: Is the female autonomous nervous system cardioprotective?," Eur Heart J vol. 19, pp. 1334-1341, 1993.

74. C.M. Van Ravenswaaij, J.C. Hopman, L.A. Kollee, J.P. Van Amen, G.B. Stoelinga and H.P. Van Geijn, "Influences on heart rate variability in spontaneously breathing preterm infants," Early Hum Dev, vol. 27, pp. 187-205, 1991.

75. J.B. Schwartz, W.J. Gibb and T. Tran, "Aging effects on heart rate variation," J Gerontol, vol. 46, pp. M99-M106, 1991.

76. J.P. Finley, S.T. Nungent and W. Hellenbrand, "Heart rate variability in children, spectral analysis of developmental changes between 5 and 25 years," Can J Physiol Pharmacol, vol. 65, pp. 2048-2052, 1987.

77. L.A. Lipsitz, J. Mietus, G.B. Moody and A.L. Goldberger, "Spectral characteristics of heart rate variability before and during postural tilt: relations to aging and risk of syncope,' Circulation, vol. 81, pp. 1803-1810, 1990.

78. P.W. Wilson and J.C. Evans, "Coronary artery prediction" Am J Hypertens, vol. 6, pp. 309S-313S, 1993.

79. K. Umetani, D.H. Singer, R. McCraty and M. Atkinson, 'Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades," Journal of the American College of Cardiology, vol. 31, pp. 593-601, 1998.

80. S. Bekheit, M. Tangella, A. el-Sakr, Q. Rasheed, W. Craelius and N. el-Sherif, "Use of heart rate spectral analysis to study the effects of calcium channel blockers on sympathetic activity after myocardial infarction," Am Heart J, vol. 119, pp. 79-85, 1990.

81. P. Coumel, J.S. Hermida, B. Wennerblom, A. Leenhardt, P. Maison-Blanche and B. Cauchemez, "Heart rate variability in left ventricular hypertrophy and heart failure and the effects of beta-blockade," Eur Heart J, vol. 12, pp. 412-422, 1991.

82. S. Guzzetti, E. Piccaluga, R. Casati, S. Cerutti, F. Lombardi, M. Pagani et al, "Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability," J Hypertens, vol. 6, pp. 711-117, 1988.

83. J. Hayano, M. Yamada, Y. Sakakibara et al, "Short, long-term effects of cigarette smoking on heart rate variability," Am J Cardiol, vol. 65, pp.84-88,1990.

84. D. Luchini, F. Bertocchi, A. Maliani et at., "A controlled study of the autonomic changes produced by habitual cigarette smoking in healthy subjects," Cardiovasc Res, vol. 31, pp. 633-639, 1996.

85. C.A. III Pope, D.J. Eatough, D.R. Gold, Y. Pang, K.R. Nielsen, P. Nath, R.L. Verrier and R.E. Kanner, "Acute exposure to environmental tobacco smoke and heart rate variability," Environ Health Perspect, vol. 109, no. 7, pp. 711-716, 2001.

86. P.S. Zeskind and J.L. Gingras, "Maternal cigarette-smoking during pregnancy disrupts rhythms in fetal heart rate," J Pediatr Psychol, vol. 31, no. 1, pp. 5-14, 2006.

87. S.C. Malpas, E.A. Whiteside and T.J. Maling, "Heart rate variability and cardiac autonomic function in men with chronic alcohol dependence," Br Heart J, vol. 65, pp. 84-88, 1991.

88. J. Rossinin, M. Vitsalo, J. Partanen et al, "Effects of acute alcohol ingestion on heart rate variability in patients with documented coronary artery disease and stable angina pectoris," Am J Cardiol, vol. 79, pp. 487-491, 1997.

89. M. Malik and A.J. Camm, Eds., "Heart Rate Variability," Armonk, NY: Futura, 1995.

90. J. Altimiras, "Understanding autonomic sympathovagal Balance from short-term heart rate variations. Are we analyzing noise?," Comparative Biochemistry and Physiology Part A, vol. 124, pp. 447-460, 1999.

91. P. Castiglioni, "Evaluation of heart rhythm variability by heart or heart period: Differences, pitfalls and help from logarithms," Medical & Biological Engineering & Computing, vol. 33, pp. 323-330, 1995.

92. M.V. Kamath and F.L. Fallan, "Correction of the heart rate variability signal for ectopic and missing beats," in Heart Rate Variability, M. Malik and A.J. Camm, Futura, pp. 75-85, 1995.

93. P. Tikkanen, "Characterization and applications of analysis methods for ECG and time interval variability data," Ph. D Thesis, Oulu University, 1999.

94. N. Lippman, K. Stein and B. Lerman, 'Comparison of methods for removal of ectopic in measurement of heart rate variability," American Journal of Physiology, vol. 267, pp. H411-H418, 1994.

95. C.L. Birkett, M.G. Kienzle and G.A. Myers, "Interpolation over ectopic beats increase low frequency power in heart rate variability spectra," Computers in Cardiology, IEEE Computer Society Press, pp. 257-259, 1991.

96. M.A. Peltola, T. Seppanen, T.H. Makikallio, and H.V. Huikuri (2004), "Effects and significance of premature beats on Fractal correlation properties of R-R interval dynamics," Annals of Noninvasive Electrocardiology, vol. 9, no. 2, pp. 127-135, 2004.

97. M.A. Salo, V. Heikki and T. Seppanen, "Ectopic beats in heart rate variability analysis: effects of editing on time and frequency domain measures,' Annals of Noninvasive Electrocardiology, vol. 6, no. 1, pp. 5-17, 2001.

98. R.E. Kleiger, P.K. Stein, M.S. Bosner and J.N Rottman, "Time domain measurement of heart rate variability," in Heart Rate Variability, M. Malik and A.J. Camm, Futura, Pub Co., 1995.

99. D. Singh, "Analysis and interpretation of heart rate and blood pressure variability," Ph.D. dissertation, Indian Institute of Technology, Roorkee, 2004.

100. D.L. Eckberg, "Sympathovagal balance," Circulation, vol. 96, pp. 3224-3232, 1997.

101. M. Pagani, F. Lombardi, S. Guzzetti, O. Rimoldi, R. Furlan, P. Pizzinelli, G. Sandrone, G. Malfatto, S. Dell 'Orto, and E. Piccaluga, "Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog," Circulation Research, vol. 59, pp. 178-193, 1986.

102. M. Di Rienzo, P. Castiglioni, G. Mancia, G. Parati, and A. Pedotti, " 24 hour sequential spectral analysis of arterial blood pressure and pulse interval in free moving subjects," IEEE Transactions on Biomedical Engineering, vol. 36, pp. 1066-1074, 1989.

103. G.D. Pinna, R. Maestri, and A. DiCesare, "Application of time series spectral analysis theory: Analysis of cardiovascular variability signals," Medical and Biological Engineering and Computing, vol. 34, pp. 142-148, 1996.

104. J.P. Martinez, R. Almeida, S. Olmos, A.P. Rocha, and P. Laguna, "A wavelet-based ECG delineator: Evaluation on standard databases," IEEE Transactions on Biomedical Engineering, vol. 51, no. 4, pp. 570-581, 2004.

105. B.S. Saini, "Signal processing of heart rate variability," Ph. D Thesis, NIT Jalandhar, 2009.

106. T. Laitinen, J. Hartikainen, E. Vanninen, L. Niskanen, G. Geelen and E. Lansimies, "Age and gender dependency of Baroreflex sensitivity in healthy subjects," J Appl Physiol, vol. 84, no. 2, pp. 576-83, 1998.

107. E. Vanoli and P.B. Adamson, " Baroreflex sensitivity: methods, mechanism, and prognostic value," PACE, vol.17, pp. 434-445, 1994.

108. M.V. Pitzalis, F. Mastropasqua, F. Massari, C. Forleo, A. Passantino, R. Colombo, P. Totaro and P. Rizzon, "Effects of hydrophilic and lipophilic beta-blockers on heart rate variability and baroreflex sensitivity in normal subjects," Pacing Clin Electrophysiol, vol. 21, no. 3, pp. 559-67, 1998.

109. G. Bertinieri G, M. Di Rienzo, A. Cavallazzi, A.U. Ferrari, A. Pedotti and G. Mancia, "Evaluation of baroreceptor reflex by blood pressure monitoring in unanesthetized cats," Am J Physiol, vol. 254, pp: H377-H383, 1998.

110. G. Parati, M. Di Rienzo, G. Bertinieri, G. Pomidossi, R. Casadei, A. Groppelli, A. Pedotti, A. Zanchetti and G. Mancia, "Evaluation of the Baroreceptor-heart rate reflex by 24-hour intraarterial blood preasure monitoring in humans," *Hypertension*, vol 12, pp. 214-219, 1988.

111. J. Parlow, J. P. Viale, G. Annat, R. Hughson and L. Quintin, "Spontaneous cardiac baroreflex in humans. Comparison with drug-induced responses," *Hypertension*, vol 25, no 5, pp. 1058-1068, 1995.

112. D. Laude, J. L. Elghozi, A. Girard, E. Bellard, M. Bouhaddi, P. CAstiglioni et al., "Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study)," *Am J Physiol Regul Integr Comp Physiol*, vol 26, no 1, pp. R226-R231, 2004.

113. R. Zhang, K. Iwasaki, J. H. Zuckrman, K. Behbehani, C. G. Crandall and B. D. Levine, "Mechanism of blood pressure and R-R variability: insights from ganglion blockade in humans," *J Physiol*, vol 543, pp. 337-348, 2002.

114. A. Cevese, G. Gulli, E. Polati, L. Gottin and R. Grasso, "Baroreflex and oscillation of heart period at 0.1 Hz studied by alpha-blockade and cross-spectral analysis in healthy humans," *J Physiol*, vol 531, pp. 235-244, 2001.

115. P. Castiglioni, M. Di Rienzo, A. Veicsteinas, G. Parati and G. Merati, "Mechanisms of blood pressure and heart rate variability: an insight from low-level paraplegia," *Am J Physiol Regul Integr Comp Physiol*, vol 292, no 4, pp. R1502-1509, 2007.