International Journal of Neurorehabilitation
ISSN: 2376-0281

Kamal, Int J Neurorehabilitation Eng 2014, 1:3
DOI: 10.4172/2376-0281.1000133

Research Article Open Access

Novel Method for Assessment of Autonomic Function in Health and Disease: An Application to Epilepsy

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Abstract

Objective: Impaired autonomic function has been associated with an increased risk of mortality in patients with epilepsy. Autonomic dysfunction involving both sympathetic and parasympathetic systems has also been demonstrated in Epileptic disease using cardiovascular reflex tests based on heart rate to various stimuli. The aim of this study is to propose novel approach using Volterra kernel for system identification of nonlinear relationship between input stimulus (lowering and raising leg) and the output (HRV signals) using entrainment method based on lowering and raising leg of patients to assess in qualitative and quantitative methods the autonomic function of healthy subjects and patients with epilepsy disease and provide medical indices for assessment and neurorehabilitation of autonomic system in Epilepsy

Methods: Forty eight patients with Epilepsy and forty eight of healthy subjects age matched controls participated in this study from July to September 2010 at Johns Hopkins Hospital, Baltimore, Maryland, and the Medical Center, Cookeville, Tennessee, United States of America. All subjects signed consent to participate in the research prior to their inclusion in the study and the consent of ethical committee was obtained and approved the study protocol. The study design was to carry out experimental procedure of lowering and raising a leg at different frequency rate whiles the subject in supine. By applying an algorithm and considering the process of lowering and raising a leg as stimulus input and the Heart Rate Variability signal (HRV) as output for system identification, a mathematical model is expressed as integral equations, whose input-output behavior is nearly identical to that of the system in both healthy subjects and epilepsy disease patients. The model for each group contains the linear part (first order kernel) and nonlinear part (second order kernel).

Results: A difference equation model was employed to represent the system for both control subjects and patients with Epilepsy disease .The results show significant difference in first and second kernel for both groups. Both the first kernel and second kernel of epileptic patients show low variation with respect to healthy subjects. Introducing Normalized Mean Square Errors (NMSE) of first order and second order kernel prediction of both groups may be considered as medical index for to assess the autonomic nervous system in health and disease

Conclusion: Using first order kernel and second order kernel, it is possible noninvasively to differentiate and assess autonomic function qualitatively and quantitatively in both groups. Future studies are needed to investigate model quantitative indices using this methodology to assess the autonomic nervous system in health and disease.

Keywords: Autonomic function; Volterra kernel; Entrainment; System identification

Introduction

Impaired autonomic function has been associated with an increased risk of mortality both in patients with heart disease and in randomly selected general populations. Autonomic dysfunction involving both sympathetic and parasympathetic systems has also been demonstrated in Epileptic Patients using cardiovascular reflex tests based on heart rate to various stimuli [1-11]. However, the clinical significance and pathophysiology of these findings in Epilepsy are poorly understood. The application of power spectral analysis of heart rate variability (HRV), Peripheral Blood Flow (PBF) and their coherence to assess the autonomic function to epileptic patients especially in short term, is limited. In fact, the mortality rate among patients suffering from epilepsy is three times higher than among the general population [3,4]. The increasing risk of sudden death is directly related to the cause of epilepsy itself. The incidence of sudden death varies in different epilepsy populations. Most sudden deaths are related to temporarily to seizures [5] and many also occur during sleep [6]. It is generally agreed that cardiac respiratory changes occurring around the time of a clinical seizure [7]. The exact mechanisms of cardiac respiratory changes which led to sudden death are unknown. However, theories propounded on the mechanism of sudden death have concentrated on autonomic dysfunction and have included cardiac arrhythmia and apnea [8]. Conventional time and frequency domain analysis techniques based on the linear fluctuation of heart rate insufficient in outline the changes in heart rate dynamics [12-23], therefore, new methods based on nonlinear dynamics have been introduced to quantify complex heart rate dynamics and complement conventional measures of its variability. One aim of this study is to propose another approach using Volterra kernel for system identification of nonlinear relationship between input stimulus (lowering and raising leg) and the output (HRV signals) to assess the autonomic function of healthy subjects and Epileptic patients and provide insight into the autonomic dysfunction of Epilepsy patients compared with healthy subjects. Also, in this study, we propose simple experimental procedure to stimulate the autonomic nervous system by subjecting both groups to stimulus based on lowering and raising a leg as shown in Figure 1 [16].

This proposed study may help in screening the autonomic neuropathy noninvasively specially for Epileptic patients, as well as

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Received September 10, 2014; **Accepted** November 25, 2014; **Published** December 03, 2014

Citation: Kamal AK (2014) Novel Method for Assessment of Autonomic Function in Health and Disease: An Application to Epilepsy. Int J Neurorehabilitation 1: 133. doi:10.4172/2376-0281.1000133

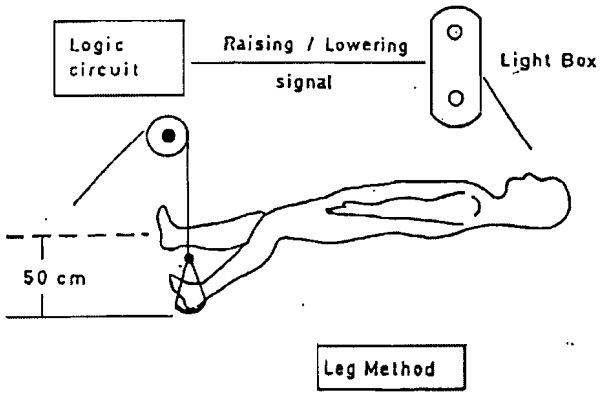

Figure 1: The Leg Method experiment.

introducing new medical Biomarkers by producing, evaluating and comparing the impulse transfer function (first order kernel) and second order kernel diagrams for system nonlinear identification between the input stimulus (Raising and lowering leg) and the output (HRV signals) for both groups of normal subjects and Epileptic patients.

Patients

The study was performed in summer 2011(12 July-9 September 2011) at Johns Hopkins university hospital, Baltimore, Maryland and Regional Medical Center, Cookeville, TN, USA.

The study group of patients was composed of forty eight newly diagnosed male epilepsy patients (60.3±1.43 years) who had generalized tonic-clonic seizures (GTCS) and were not taking medication. For each patient, one healthy age and sex matched control on no medication was selected. For both controls and patients, biochemical tests as well as. Physical test were obtained to be certain no evidence of cardiovascular or other diseases.

None of patients had clinical signs of autonomic dysfunction, history of myocardial infarction, arterial hypertension, diabetes or pulmonary disease. We checked the patients and the controls during the study with any administered drugs that could affect the HRV parameters. Eight patients who were smoking were excluded from the study. Therefore, the final group consisted of 48 male patients with epilepsy who have GTCS (mean 60.3± 1.43 years) and 48 healthy age and sex matched controls (mean 58.6± 1.57 years). All subjects agreed to participate in the research with signing a consent letter prior to their inclusion in the study and the consent of ethical committee was obtained and approved the study protocol. With each subject lying supine on a bed and physiological measuring devices are connected. The breathing signal is measured using a thermistor placed on the nose. The ECG is taken from wrists and the ankle (lead II) for the duration of experiments. All measurements are interfaced to laptop PC and stored in CD. The second phase of experiments entail that all subjects asked to raise and lower one of their legs at comfortable different frequency as explained in Experimental procedure section and the entire signal measured in this position. The duration of measurements is 10 min.

Experimental Procedure and Method

The experiments were carried out noninvasively as shown in Figure 1 for forty eight healthy subjects (mean age 58.6 years) and forty eight untreated patients with Epilepsy (mean age 60.3 years). The patient was placed on a bed with room temperature of 22 C and rested for 10 minutes then he requested in this supine position to raise and lower his led according to 7 periods of time (frequencies) namely: 5s, 10s, 15s , 20s , 25s, 35s and 40s. Both the duration of experiments (10 min) and periods of time covered the frequency response of the system for exact identification of the system using algorithm by Fakhouri [22]. This algorithm proposed another approach using system identification of the input-output relationship of any physical or physiological system. This is performed by means of a mathematical model which can be expressed either by a set of differential equations (parameters and static estimation) where the topology of the system is assumed known or by integral equations (non-parametric, weighting function, kernel or functional) which needs little or no prior assumptions about the system. This provides a powerful tool for identification of system whose underlying processes are not well understood. So, by using this algorithm [22], it is possible to identify HRV signal-Raising and lowering leg system in terms of the functional Volterra series in which the form of integral equation is fixed and the identification method reduces to the determination of the values within the integral, called kernel. Further details will be found in [22]. The subject's signal was recorded for 10 minutes for every period of time mentioned above. These signals include Electrocardiogram (ECG) measured in Lead II sampled at rate of 1000 Hz, HRV (derived from ECG) and stimulus input pulse measured using strain gage mounted on the leg so that electrical pulse produced with the period of time matching to the time of rising and lowering of leg as shown in Figure 1. HRV signals and stimulus input signals were processed through digital filter with bandwidth in the range of 0-1.5 Hz which covered the spectrum of HRV signal stimulated by the periods of lowering and raising a leg and sampled at 3.8 Hz with 1024 points stored for each signal. Figure 2 illustrated the derivation of HRV signal from ECG. The technique used in this study to produce HRV signals based on the hardware described by Cohen et al. developed by the author for interfacing to laptop computer. This technique based on hardware device to detect R-R intervals using threshold circuit and interfaced the R-R intervals to software program to reconstruct the heart rate variability signals which is now suitable for sampling and processing as shown in Figure 2. [16]

Results

Following Fakhouri's algorithm [24], it is possible to compute the first kernel (impulse response) and second order kernel (mesh diagram) for both groups. Figures 4 and 5 show the first order kernel for a typical control subject and a typical untreated patient with Epilepsy disease. While Figure 5 illustrates a typical second order kernel of control subject and Figure 6 shows a typical second order kernel of Epileptic patient. Table 1 shows comparison of averaged Normalized Mean Square Errors of HRV Variability (NMSE) ± Standard Deviation (in %) of first order and second order rejection as well as test of significance (p values) for both two groups

Discussion

The specific duration of 10 min for test experiments is vital to get the satisfactory results as well as to get exact identification of the system. However, this period (10 min) is selected to minimize the complain of

		Model order		
	First order (NMSE)	Second order(NMSE)		P value
Control Subjects	(48)	24.43 ± 11.45	16.75 ± 9.76	< 0.05
Epileptic Patients	(48)	37.50 ± 9.53	24.46 6.34	0.001

Table 1: Comparison of averaged Normalized Mean Square Errors (NMSE) of first order and second order kernel prediction of both groups.

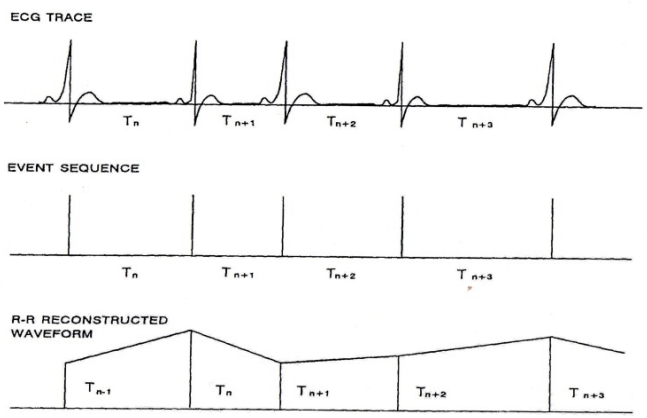

Figure 2: Heart Rate Variability signal Generation.

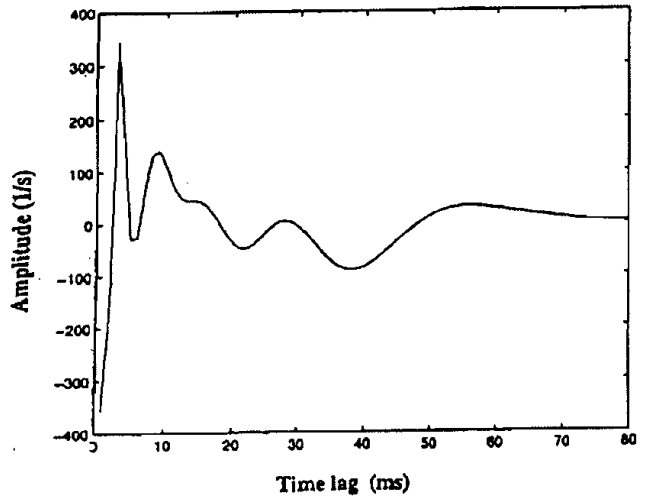

Figure 3: A typical response of the linear part of the system (first order kernel) for control subject.

some patients of their fatigue by raising and lowering their time for longer period than 10 min.

Figure 3 and Figure 4 demonstrate a typical response of the linear part of the system (first order kernel) for both control subject and Epileptic patient respectively. This response exhibits the oscillatory and under damped nature of the system for control subjects and less oscillatory amplitudes for Epileptic patients. Also, for mesh diagram as shown in Figures 5 and 6 where the amplitudes of Figures 6 belong to typical Epileptic patient with autonomic dysfunction is greatly reduced compared with Figure 5 for control subject. This may be attributed to the nature of the system being less sensitive to stimulus [25-28] i.e., the lowering and raising the leg causes fewer variations in heart rate reflected in lower response for Epileptic patients as shown in Figure 6 compared with control healthy subject as shown in Figure 5.

Actually, the appearance of low amplitudes of second order kernel of Figure 6 (mesh diagram) for A typical Epileptic patient suggests correlation between autonomic function and this diagram which may be used as indicator of the dysfunction of autonomic nervous system in Epileptic patients [29-31]. Table 1 summarizes the average NMSE (Normalized Mean Square Errors) of the model prediction for 48 control subjects and 48Epileptic patients. Table 1 indicated the significance of second order model of the system in describing the nonlinearity and complexity of relationship between stimulus and HRV. Referring to Table 1,which indicates that the quantitative medical index , NMSE, for

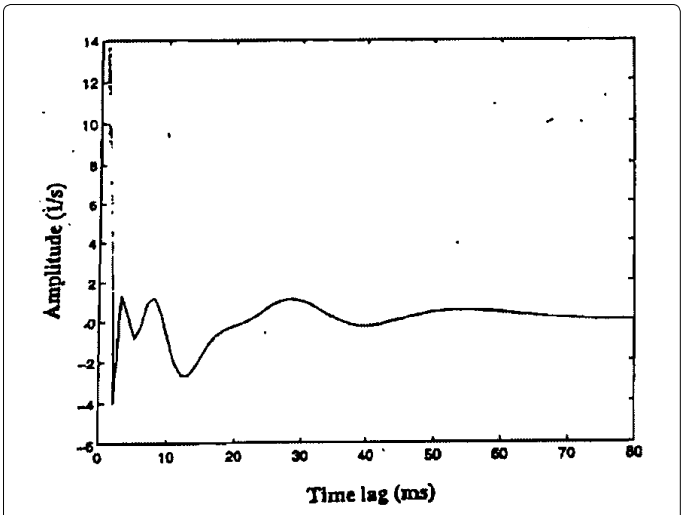

Figure 4: A typical response of the linear part of the system (first order kernel) for Epileptic patient.

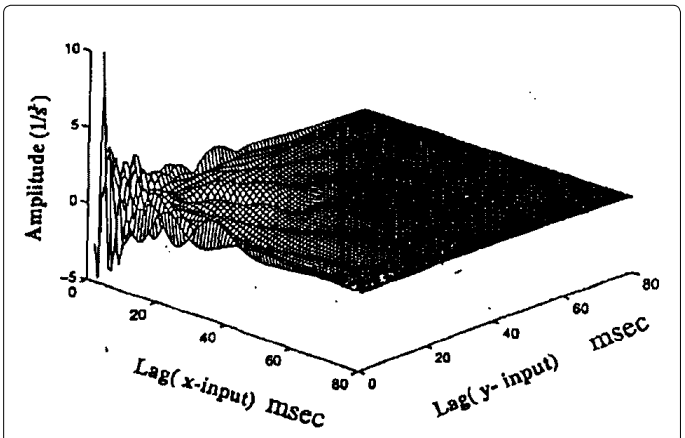

Figure 5: A typical response of the non linear part of the system(second order kernel) for control subject.

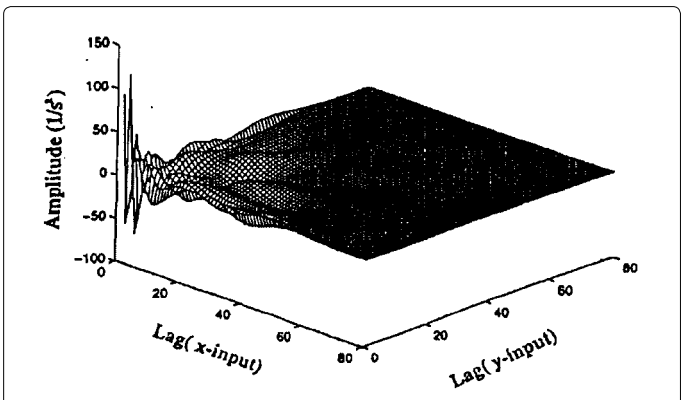

Figure 6: A typical response of the linear part of the system(first order kernel) for Epileptic patient.

first order and second order for Epileptic patients is greater than control subjects ($p<0.005$ and 0.001 respectively).

In fact, NMSE index represents the errors related to conveying the stimulus to HRV via brainstem. As NMSE index increases, increase reflected autonomic malfunction. The nonlinear characteristics involved in the modulation of HRV were confirmed by comparing the prediction NMSE achieved by the linear and nonlinear models. The prediction index NMSE is increased in Epileptic patients than Control healthy subjects especially for second-order terms showing that NMSE may be used as Biomarker for screening and to differentiate the autonomic function for both groups. However, we do not see the nonlinear analysis techniques as a replacement of the linear methods but rather as a completion of the model. The linear methods have an advantage over the nonlinear methods in that they are more suitable when shorter data sets are used. Spectral analysis is also superior in visually representing autonomic modulation. The interpretation of the spectral components is more intuitive and easier to understand. However, they cannot quantify the presence or absence of nonlinear behavior. These results may give model quantitative medical index (NMSE) to assess the autonomic nervous system in health and disease and helping autonomic function neurohabitation. In summary, the application of the nonlinear model based approach to quantify linear and nonlinear dynamics involved in the autonomic control of heart rate constitutes a useful, insightful and comprehensive approach for screening, detection and assessment of abnormal autonomic function in epileptic patients [19,32-39]. This noninvasive method could also be useful for evaluating autonomic dysfunction in other disease conditions, such as diabetes, Parkinson disease.

Conclusion and Future Work

This study pointed to the following

1. The possibility of separating the linear and nonlinear part of autonomic nervous control system using Algorithm developed to extract the linear and nonlinear part of Volttera kernel.
2. Significance of including the nonlinearity part of autonomic control system in Epilepsy to differentiate between Epileptic patients and control subjects qualitatively (From Figures) and quantitatively (From NMSE index)

However, further study is required to investigate more epileptic patients as well as using other quantitative methods to identify the prognosis of Epilepsy with duration of the disease such as Approximate Entropy Method.

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