# Assessment of autonomic function in epileptic patients

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## ABSTRACT

**الأهداف:** استخدام التحليل الطيفي لتقييم النشاط الحيوي الذاتي لدى مرضى الصرع ومقارنتهم مع المرضى السليمين، بالإضافة إلى تقييم جدوى استخدام طرق معالجة المؤشرات الحيوية ( signal processing ).

**الطريقة:** أُجريت هذه الدراسة في مستشفى جونز هوبكينز، بالتيمور، ماريلاند، ومركز كوكفيل الصحي، كوكفيل، تينيسي، الولايات المتحدة الأمريكية وذلك خلال الفترة من يوليو 2007م إلى سبتمبر 2007م. شارك في هذه الدراسة مجموعتين وهما: المجموعة المُصابة وشملت 48 مُصاباً بنوبات الصرع التوترية والإرتجاجية والذين لا يتعاطون أي نوع من الأدوية، ومجموعة التحكم الغير مُصابة وشملت نفس العدد والجنس. وافق كل المشاركين على الانضمام إلى الدراسة قبل البدء بها، كما وافقت لجنة القيم والأخلاق على هذه الدراسة. لقد قامت الدراسة بقياس المؤشرات الحيوية التالية: مؤشر تدفق الدم المحيطي، ومؤشر التنفس، ومؤشر تغير معدل نبض القلب والذي تم أخذه من مخطط كهربية القلب، وتم قياس كل هذه المؤشرات أثناء وقوف المشاركين واستلقائهم.

**النتائج:** أشارت الدراسة بأن قيم الترابط المنطقي التي سجلها مرضى الصرع كانت أقل بكثير من القيم التي سجلتها مجموعة التحكم. ولقد حدث هذا الاختلاف في حزمات التردد العليا والدنيا لطيف التطابق المنطقي بين تغير معدل نبض القلب وكلاً من تدفق الدم المحيطي والتنفس وذلك خلال وضعيتي الاستلقاء والوقوف.

**خاتمة:** أشارت الدراسة إلى جدوى تطبيق تحليل طيف التطابق المنطقي والتحكم الذاتي على مرضى الصرع ومقارنة ذلك بالأشخاص السليمين، حيث يساهم ذلك في تقييم الوظائف الحيوية الذاتية لدى مرضى الصرع، ونحن بحاجة إلى المزيد من الدراسات والاختبارات حول طرق تحليل ومعالجة المؤشرات الحيوية.

**Objectives:** To use spectral analysis to assess the autonomic activity of epileptic patients compared with normal patients, and to assess the clinical usefulness of the applied methods of signal processing.

**Methods:** Forty-eight patients with generalized tonic-clonic seizures and who were not taking any medications, and 48 age and gender matched controls participated in this study from July to September 2007 at Johns Hopkins Hospital, Baltimore, Maryland, and the Medical Center, Cookeville, Tennessee, United States of America. All subjects consented to participate in the research prior to their inclusion in the study, and the local ethics committee approved the study protocol. The study design was to measure peripheral blood flow (PBF) and respiration signals as well as the heart rate variability (HRV) signals derived from the ECG during supine and standing positions.

**Results:** The results clearly indicate that in patients with epilepsy, the coherence values are less than in the control group in both low frequency and high frequency bands at coherence spectra between HRV and PBF as well as HRV and respiration in both the supine and standing position.

**Conclusion:** Autopower and coherence spectra analysis for patients with epilepsy compared to normal subjects seems useful in the assessment of autonomic function for epileptic patients. Further studies are needed using other tests and methods of signal analysis.

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The short-term power spectral analysis of the heart rate variability (HRV) signal has been used to assess autonomic control of heart rate. Many applications of this methodology have been reported, especially in diabetes and chronic heart failure.[1,2] However, the application of power spectral analysis of HRV, peripheral blood flow (PBF) and their coherence to assess the autonomic function of epileptic patients, especially in the short-term, is limited. The mortality rate among patients suffering from epilepsy is 3 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 seizures and are unwitnessed,[5] and many also occur during sleep.[6] It is agreed that cardiac respiratory changes occur around the time of a clinical seizure.[7] The exact mechanisms of cardiac respiratory changes that leads 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] The effect of autonomic dysfunction involvement in sudden death in epileptic patients is significant since any seizure discharges mediated through the cortical, limbic, and hypothalamic systems[9] can induce an autonomic imbalance and alter autonomic discharges causing cardiac arrhythmia's.[10] The HRV and PBF signals in healthy subjects manifest a balance between sympathetic and parasympathetic systems. Strong variability in HRV signal and PBF signal indicates healthy individuals with well-adjusted autonomic control. Conversely, weak variability in HRV and PBF indicates an unstable autonomic system. Reduced HRV has emerged as a strong indicator of risk related to adverse events in patients with a range of diseases.[11-13] Actually, HRV and PBF analysis using autopower and coherence spectra can provide insight into the dynamics of autonomic function, and can help in obtaining medical indices to assess autonomic function in health and disease. Previous studies of autonomic function of epileptic patients were based on only HRV signal with the exclusion of other signals such as PBF.[14] This study will include other signals to obtain a comprehensive assessment of autonomic function in epileptic patients using power and coherence spectra. The aim of this study is to assess the autonomic function of epileptic patients who have generalized tonic-clonic seizures (GTCS) not taking any medication related to epilepsy, by evaluating the power spectra and coherence of several signals including HRV, PBF, and respiration signals.

**Methods.** *Patients.* The study was performed between July and September 2007 at the Johns Hopkins University Hospital, Baltimore, Maryland, and the Regional Medical Center, Cookeville, Tennessee, United States of America. The study group of patients were composed of 48 newly diagnosed male epilepsy patients (22±1.43 years) that had GTCS and were not taking any medication. For each patient, one healthy age, and gender matched control on no medications was selected. For both controls and patients, biochemical tests as well as physical tests were obtained to be certain of no evidence of cardiovascular or other diseases. None of the 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 for 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 and GTCS (mean 22±1.43 years) and 48 healthy age and gender matched controls (mean 22±1.57 years). All subjects agreed to participate in the research by signing a consent letter prior to their inclusion in the study, and the approval of the local ethical committee was obtained for the study protocol.

With each subject lying supine on a bed and physiological measuring devices connected, the breathing signal was measured using a thermistor placed on the nose. The ECG was taken from the wrists and the ankle (lead II). An infrared plethysmograph was placed on the finger to indicate PBF signal simultaneously for the duration of the experiments. All measurements were interfaced to a laptop PC and stored on CD. The second phase of the experiments entailed all subjects standing up, and all the signals measured in this position. The duration of measurements in both supine and standing positions was 10 minutes.

***Generation of HRV signal and estimation of coherence function.*** **Figure 1** illustrates the derivation of HRV signals from the ECG. The technique used in this study to produce HRV signals is based on the hardware circuits to detect R-R interval and produce HRV signals. The HRV signals were then passed through 2, 12 bit A/D converters at a 10 Hz sampling rate and then interfaced to a laptop PC. The A/D converters were designed so that the first conversion would occur when the first R wave of the ECG was detected. The stored HRV signals of 48 epileptic patients and 48 control subjects were then transferred to a spectral package prepared at the Tennessee Technical University, stored on PC to

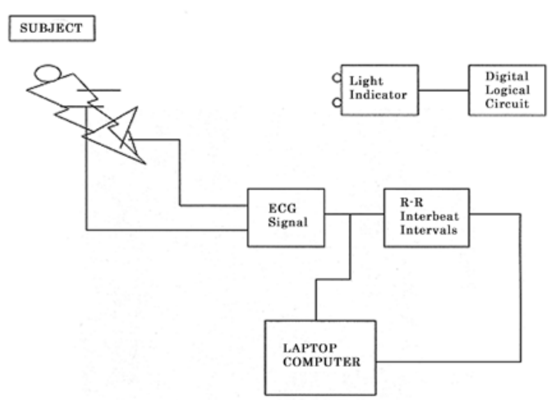


**Figure 1 -** Block diagram of measurement and recording of physiological signals (ECG, PBF and respiration). ECG -electrocardiogram, PBF - peripheral blood flow.

produce auto-power spectrum, cross power spectrum, and coherence spectrum between different signals including HRV, respiration signal, and PBF in supine and standing positions. Using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) a rank sum test, a nonparametric analog of independent samples t-test, was applied to the data of both groups. Results are considered significantly different at 0.001.

**Results.** **Table 1** shows the ratio of standing to supine position for both the epileptic patients (n=48), and the healthy control subjects (n=48). The healthy subjects exhibit a higher ratio than epileptic patients, as most of healthy subjects (34 subjects) have a standing ratio between 1.4-1.59, while most of the epileptic patients (33 patients) have a lower standing ratio between 1-1.29. **Table 1** indicates that as a whole, the healthy control subjects enjoyed a higher standing ratio with respect to epileptic patients. **Figures 2 and 3** represent the typical HRV spectrum for control subjects and epileptic patients in the supine and standing positions. Similar figures were obtained for PBF. The power spectra of the HRV signal for supine and standing positions for healthy subjects demonstrates high components in blood pressure (0.1 Hz) and respiration (0.25 HZ), especially upon standing. On other hand, the power spectra of HRV signals of the epileptic patients demonstrates lower oscillations in both supine and standing positions compared with the power spectra of healthy subjects. **Figure 4** shows the typical coherence spectrum between HRV and PBF for normal subjects and epileptic patients in the supine position. The coherence values between the 2 signals for normal subjects in **Figure 4** are high, demonstrating the high correlation between the frequency contents of both HRV and PBF signals. Noting that, the coherence values become lower in epileptic patients. **Figure 5** shows the coherence spectrum between HRV and PBF signals in normal subjects and epileptic patients upon standing, demonstrating the lower values of coherence for epileptic patients and indicating no strong correlation between the frequency contents of HRV and PBF for this group. **Figure 6** demonstrates the influence of breathing on HRV signal in the coherence spectrum for control subjects and epileptic patients in the supine position. The values of coherence are very high for control subjects around the breathing frequency and decline for epileptic patients. **Figure 7** represents the typical coherence spectrum between HRV and respiration signals for normal subjects and epileptic patients in the standing position, and shows lower values of coherence for epileptic patients upon standing and less influence of breathing on HRV signals.

**Table 1 -** Number of subjects (control and epileptic patients) exhibiting amplitude entrainment upon standing.

| Ratio of amplitudes THM (standing)/ THM (Supine) | Number of healthy subjects | Number of epileptic patients |
|---|---|---|
| <1 | 0 | 0 |
| 1-1.29 | 0 | 33 |
| 1.3-1.39 | 4 | 12 |
| 1.4-1.59 | 34 | 3 |
| 1.6-1.79 | 6 | 0 |
| >1.8 | 4 | 0 |
| **Total** | **48** | **48** |

THM - Traube Herring Meyer

**Discussion.** The present study investigated if differences in autonomic cardiovascular control could appear between epileptic patients and control subjects during a situation of orthostatic stress (standing position), which is a natural stimulus leading to sympathetic excitation and vagal withdrawal in the heart.

Comparison of **Figure 2** and **Figure 3** show the significant change of amplitude of blood pressure oscillation at frequency 0.1 Hz in power spectrum of HRV signal for both control subjects and epileptic patients in the supine and standing positions. This ratio is known as the Traube Herring Meyer (THM) ratio,[14] and is calculated and represented in **Table 1**, which indicates that most control subjects exhibit a higher THM ratio upon standing with respect to epileptic patients. This is a clear indication of the little effect of standing as a natural stimulus to the autonomic system of epileptic patients compared to control subjects, especially for the ability of the autonomic system to convey the stimulus signal to the heart.[13-16] A comparison between **Figures 4 & 5** illustrates the low coherence values of HRV and PBF for epileptic patients with respect to healthy control subjects in both supine and standing positions. Once again, this may indicate that the autonomic system of epileptic patients (both sympathetic and parasympathetic) cannot convey the control oscillations (thermoregulatory oscillation at 0.03 Hz, blood pressure oscillation at 0.1 Hz, and respiration oscillation at nearly 0.25Hz) as manifested in coherence spectrum between HRV and PBF signals.

Investigating **Figures 6 and Figure 7**, the coherence values for the epileptic group are lower than in the control group at both supine and standing positions. The control group exhibits high values of coherence in both coherence spectrum between HRV and respiration (**Figure 6**) in the supine position, or between HRV and respiration (**Figure 7**) in the standing position. However, the epileptic group shows less coherence values, especially around respiration oscillation (nearly around

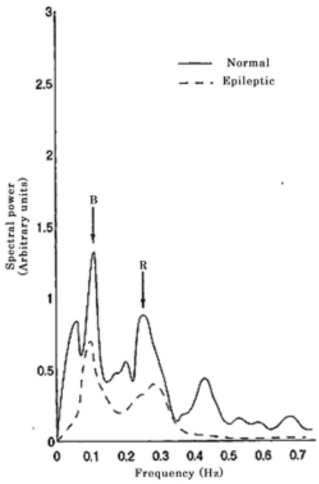


**Figure 2 -** Typical auto-power spectrum of HRV signals of normal subjects and epileptic patients in supine position. HRV - heart rate variability, R - respiration rate, B - blood pressure oscillation.

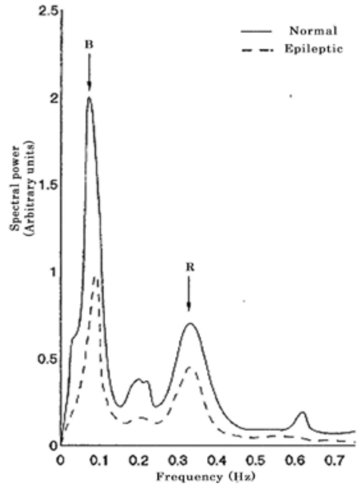


**Figure 3 -** Typical auto-power spectrum of HRV signals of normal subjects and epileptic patients in standing position. HRV - heart rate variability, R - respiration rate, B - blood pressure oscillation.

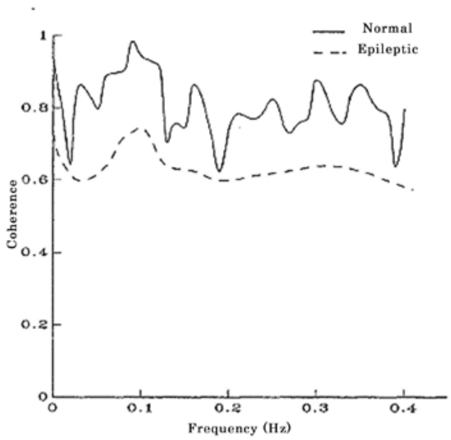


**Figure 4 -** Typical coherence spectrum between heart rate variability signal and peripheral blood signal for normal subjects and epileptic patients in supine position.

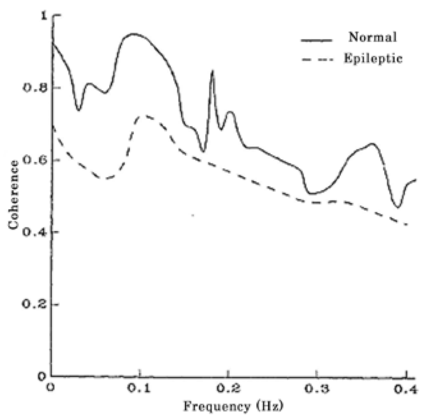


**Figure 5 -** Typical coherence spectrum between heart rate variability and peripheral blood signal for normal subjects and epileptic patients in standing position.

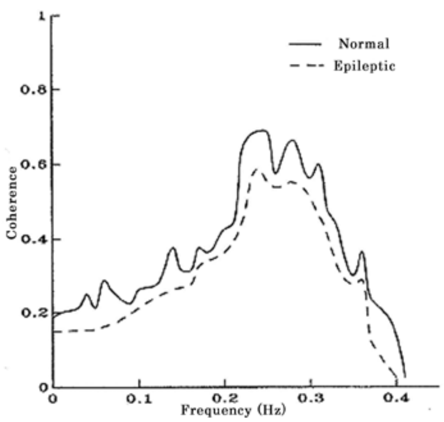


**Figure 6 -** Typical coherence spectrum between heart rate variability signal and respiration signal for normal subjects and epileptic patients in supine position.

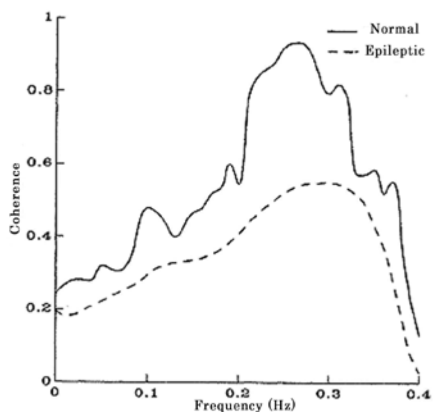


**Figure 7 -** Typical coherence spectrum between heart rate variability signal and respiration signal for normal subjects and epileptic patients in standing position.

0.25 Hz) as illustrated in **Figures 6 & Figure 7** in both the supine and standing position. This may be attributed to dysfunction of the autonomic nervous system of epileptic patients, especially the parasympathetic part, which normally conveys respiration signals to the heart and other body physiological signals.[11-16]

In fact, the introduction of coherence values in this study to assess the autonomic function of epileptics in an interictal state, and healthy control subjects may be helpful in using the coherence value as a diagnostic medical index for autonomic function assessment.[17-23] Power and coherence spectra combined with standing position as a stimulus seems promising in assessing the autonomic dysfunction in epileptic patients. Further studies may be needed to develop quantitative medical indices for possible screening and early diagnosis of autonomic dysfunction in epileptic patients using this methodology.

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## References


1. Annegers JF, Coan SP. SUDEP: overview of definitions and review of incidence data. ***Seizure*** 1999; 8: 347-352.
2. Mativo P, Anjum J, Pradhan C, Sathyaprabha TN, Raju TR, Satishchandra P. Study of cardiac autonomic function in drug-naïve, newly diagnosed epilepsy patients. ***Epileptic Disord*** 2010; 12: 212-216.
3. Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell W, Tarver B. Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death. ***Epilepsia*** 1998; 39: 206-212.
4. Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllylä VV, Isojärvi JI. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. ***J Neurol Neurosurg Psychiatry*** 2002; 72: 26-30.
5. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. ***Am J Cardiol*** 2004; 93: 381-385.
6. Baker GA, Nashef L, van Hout BA. Current issues in the management of epilepsy: the impact of frequent seizures on cost of illness, quality of life, and mortality. ***Epilepsia*** 1997; 38 Suppl 1: S1-S8.
7. Devinsky O, Perrine K, Theodore WH. Interictal autonomic nervous system function in patients with epilepsy. ***Epilepsia*** 1994; 35: 199-204.
8. Koseoglu E, Kucuk S, Arman F, Ersoy AO. Factors that affect interictal cardiovascular autonomic dysfunction in temporal lobe epilepsy: role of hippocampal sclerosis. ***Epilepsy Behav*** 2009; 16: 617-621.
9. Scorza FA, Arida RM, Cysneiros RM, Terra VC, Sonoda EY, de Albuquerque M, et al. The brain-heart connection: implications for understanding sudden unexpected death in epilepsy. ***Cardiol J*** 2009; 16: 394-399.
10. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. ***Int J Cardiol*** 2002; 84: 1-14.
11. Frysinger RC, Harper RM. Cardiac and respiratory correlations with unit discharge in epileptic human temporal lobe. ***Epilepsia*** 1990; 31: 162-171.
12. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. ***Epilepsia*** 2010; 51: 725-737.
13. Goodman JH, Homan RW, Crawford IL. Kindled seizures elevate blood pressure and induce cardiac arrhythmias. ***Epilepsia*** 1990; 31: 489-495.
14. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. ***Circulation*** 1991; 84: 482-492.
15. Baselli G, Cerutti S, Civardi S, Liberati D, Lombardi F, Malliani A, et al. Spectral and cross-spectral analysis of heart rate and arterial blood pressure variability signals. ***Comput Biomed Res*** 1986; 19: 520-534.
16. Kamal A. Assessment of autonomic function for healthy and diabetic patients using entrainment methods and spectral technique. Bioengineering Conference, 2006. Proceedings of the IEEE 32nd Annual Northeast; 2006 April 1-2; Easton, Pennsylvania (USA). IEEE; 2006.
17. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. ***Circ Res*** 1986; 59: 178-193.
18. De Ferrari GM, Sanzo A, Schwartz PJ. Chronic vagal stimulation in patients with congestive heart failure. ***Conf Proc IEEE Eng Med Biol Soc*** 2009; 2009: 2037-2039.
19. Jick SS, Cole TB, Mesher RA, Tennis P, Jick H. Idiopathic epilepsy and sudden unexplained death. ***Pharmacoepidemiology and Drug Safety*** 1992; 1: 59-64.
20. Dasheiff RM, Dickinson LJ. Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure. ***Arch Neurol*** 1986; 43: 194-196.
21. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. ***Eur J Neurol*** 2006; 13: 930-936.
22. Oppenheimer S. Forebrain lateralization and the cardiovascular correlates of epilepsy. ***Brain*** 2001; 124: 2345-2346.
23. Berilgen MS, Sari T, Bulut S, Mungen B. Effects of epilepsy on autonomic nervous system and respiratory function tests. ***Epilepsy Behav*** 2004; 5: 513-516.