# PD2i Heart Rate Complexity Measure can Detect Cardiac Autonomic Neuropathy: an Alternative Test to Ewing Battery

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## Abstract

*This study evaluates the usefulness of a new heart rate variability (HRV) complexity measure, the Point Correlation Dimension (PD2i), derived from short term ECG recordings, as a screening tool for Cardiac autonomic neuropathy (CAN). The PD2i was developed to measure complexity in nonstationary data with some tolerance for background noise. ECG recordings during supine rest were acquired from diabetic subjects with CAN (CAN+) [10 subjects] and without CAN (CAN-) [33 subjects] and analyzed. PD2i indices (mean, standard deviation, minimum and maximum) were used for analyzing HRV signals of all subjects. Significantly reduced ($p < 0.01$) PD2i indexes were found in CAN+ group, which could be a practical diagnostic and prognostic marker.*

## 1. Introduction

The prevalence of diabetes mellitus (DM) is currently estimated at 200 million people worldwide exceeding 360 million patients in 2030 [1]. For these patients, the incidence of cardiac autonomic neuropathy (CAN) increases with time and reaches 65% after 10 years. Cardiovascular autonomic neuropathy (CAN) may be the most clinically important form of diabetic autonomic neuropathy [2] because of its link to arrhythmic death. CAN has been frequently postulated to increase susceptibility to ventricular arrhythmias and sudden cardiac death in diabetic patients. This neuropathy has a negative impact on the survival and quality of life as it is associated with fatal and nonfatal cardiovascular events, ischemic cerebrovascular events and overall mortality [3]. Early detection of subclinical autonomic dysfunction in diabetic patients is, therefore, of vital importance for risk stratification and management for the prevention of serious adverse events [4].

### 1.1. Existing methods to detect CAN

Currently, the diagnosis of CAN relies on non-invasive Ewing test battery [5] that was specifically designed for the diagnostic of the CAN, and for assessing its development stage. The procedure consists of five tests i.e. the heart-rate responses induced by controlled breathing, the Valsalva maneuver, standing up, and the changes in blood pressure induced by standing and handgrip. Recent research studies focus on the noninvasive techniques for the detection and progression of the severity of CAN from heart rate variability analysis techniques using surface ECGs.

### 1.2. Detection of CAN from nonlinear HRV analysis methods

A study on young DM patients by Javorka and associates [6] indicated that new measures of heart rate variability (HRV) that assess its complexity, as opposed to its statistical parameters and power spectra, provide additional diagnostic information regarding early subclinical autonomic dysfunction. Nonstationarity and noise are problems for nonlinear algorithms, as any noise in the data becomes amplified and a nonstationarity in the data obscures the algorithmic result [7]. The Point Correlation Dimension (PD2i) [3] was developed to measure complexity in short term nonstationary data with some tolerance for background noise. In this study, we investigate whether PD2i indices (Minimum, Maximum, Mean and Standard deviation) of HRV are able to detect the presence of CAN in Diabetic patients as diagnosed by the Ewing maneuvers.

## 2. Methods

A total of 43 sets of 20 minute ECG recordings during supine rest were acquired from diabetic subjects with CAN (CAN+) [10 subjects] and without CAN (CAN-)

[33 subjects] and analyzed. Participants in the study were identified as CAN+ by the use of the lying to standing tests for heart rate and blood pressure changes, as was done and suggested by Ewing to be useful as an indicator of autonomic dysfunction in clinical testing. All patients in this study were individuals enrolled in the Diabetes Complications Research Initiative (DiScRi) at Charles Sturt University. The Vicor PD2i Analyzer (Vicor Technologies, Inc., Boca Raton, FL, USA) was used to calculate all PD2i values from the data-set of R–R interval provided to Vicor in a coded blinded manner. PD2i indices (mean, standard deviation, minimum and maximum) were used for analyzing HRV signals of all subjects.

## 2.1. Calculation of PD2i index

This nonlinear algorithm begins with pair wise sampling of i and j groups of heartbeats in the heart rate data series. The next step is comparison of the two samples, after each sample is first converted into an m-dimensional vector. The comparison is the vector difference length (VDL), scaled for all VDLij. The "i" and "j" represent values that are incremented throughout the data series and the VDLs are repetitively calculated until the end of the data stream is reached for both i and j. Values where i = j are omitted, as they will always be equal to zero; the end of the data stream is not Ni (number of data points), but Ni minus the number of data points needed to make the last of the m-dimensional vectors (m is called the "embedding dimension"). Once all of the VDLij values are made for each embedding dimension and collected together for each fixed value of i compared to all values of j, they are rank ordered by their absolute values. The mathematical model is $C = R^{PD2i}$. where C is the count of VDL's for each range or step-size, R. The "i" in "PD2i" is added to emphasize that PD2i is time-dependent and calculated for each fixed value of "i" in the data series, and the "D2" means that the mean PD2i approaches the correlation dimension (D2) as Ni goes to infinity.

PD2i is then calculated as the slope of the log-log plot of C vs. R, as shown in Figure 1. For large data length (i.e., as Ni approaches infinity) there will be a first long linear slope (1) followed by shorter ones that eventually disappears as Ni gets very large. For Ni = $10^{PD2i}$ there will be more than the first scaling region because of the finite data length, but this minimum-Ni is sufficient to capture all dimensions or degrees of freedom in the time-series. This minimum Ni should be adopted. not only for adequate sampling, but also to achieve clear convergence of slope vs. m (i.e., by the 9th embedding dimension for physiological data).

With finite data length, but following the rule that Ni > $10^{PD2i}$, a "floppy tail" appears initially in the logC vs. logR plot (FT, Figure 1E). The FT is unstable as m is increased, and is caused by the finite digitization rate for the data. The use of a "linearity" criterion in conjunction with the restrictive "plot length" parameter (that makes the PD2i unique) results in the observed slope lying just above the FT and within the first slope (1) region.

The running mean PD2i stays within 4% of its known value (D2) when used to analyze non-stationary data made from linking sub-epochs with known degrees of freedom [8]. The D2i algorithm, the only other time-dependent algorithm that measures degrees of freedom, shows spurious values with this data mainly because its slope is determined over the whole plot of logC/logR. The slope length of PD2i is restricted to lie between the FT and up to 15% of the total plot length, so that when the reference point i moves into a new sub-epoch, the slope changes accordingly, as new small logR values are obtained.

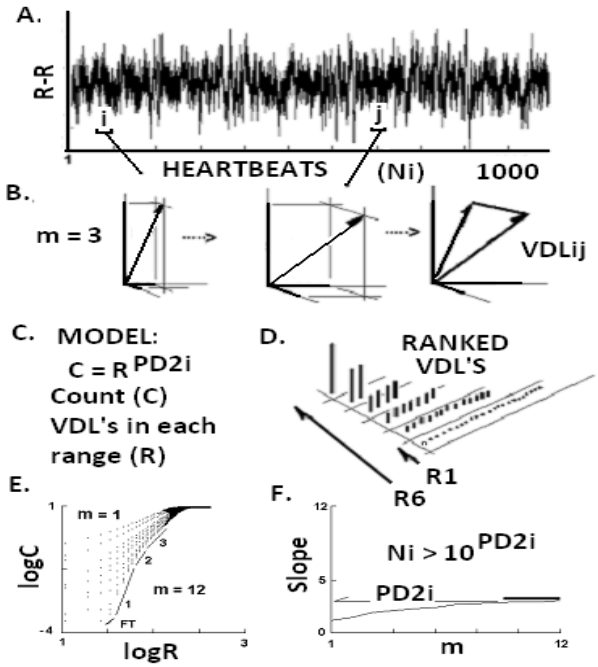


Figure 1. Calculation of the PD2i (degrees of freedom). A. The successive R-R intervals are sampled; the i-samples stay the same (fixed in time) while the j-samples travel through the entire data series. B. The sampled heartbeats are plotted in orthogonal axes and the resultant is determined (here 3 heartbeats are sampled and plotted in 3 dimensions); the two resultants are compared by taking their vector difference length (VDLij). C. The mathematical model is C scales as R raised to the PD2i power, where C is the count of VDL's for each range or step-size, R; this model is the same as PD2i = logC/logR, a slope value. D. Counts and Range size are plotted after rank ordering the absolute values of all VDLij's for a fixed (in time) value of i (and m). E. logC vs. logR plot where the slope increases as m is incremented (m is the embedding dimension or number of heartbeat coordinates

used to make the i- and j vectors). F. PD2i is defined as the convergent slope (horizontal bar and arrow), where convergence means that an increment in m no longer causes an increase in the slope; Ni, the total number of heartbeats, must be larger than $10^{PD2i}$ to enable adequate sampling and clear convergence; here PD2i is approximately 3, so 1000 heartbeats are required.

## 2.2. Results

Significantly reduced ($p < 0.01$) PD2i indexes were found in CAN+ group shown in Table 1, which could be a practical diagnostic and prognostic marker. The relative importance of PD2i features was determined by receiver-operating curve (ROC) analysis for CAN+/- discrimination [9]. The areas under the ROC curves were found to be 0.72, 0.79, 0.80 and 0.70 for minimum, maximum, mean and standard deviation of PD2i respectively as shown in Figure 2.

Table 1: Values of different PD2i indices classifying CAN- and CAN+ groups

| Features | CAN- group(33) | CAN+ group(10) | Area under ROC curve |
|---|---|---|---|
| **Maximum(PD2i)** | **3.58 ± 0.96** | **2.58 ± 0.76** | **0.79** |
| **Minimum(PD2i)** | **2.41 ± 0.88** | **1.65 ± 0.50** | **0.72** |
| **Mean(PD2i)** | **3.88 ± 0.96** | **2.83 ± 0.70** | **0.80** |
| **Std(PD2i)** | **0.82 ± 0.22** | **0.71 ± 0.26** | **0.70** |

All values are given as Mean ± Standard deviation

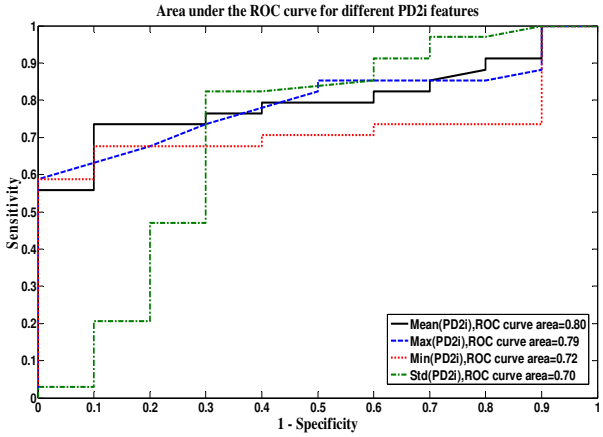


Figure 2. Area under the ROC curves for different PD2i features. The Mean (PD2i) index has the largest ROC area showing the best discriminatory power in classifying CAN- from CAN+ group.

## 3. Discussions

The non-invasive Ewing test battery [5] was specifically designed for identifying CAN, which consists of five tests. The Ewing battery however requires patient cooperation and for the disease to be present [10]. It is also less sensitive to changes associated with cardiac autonomic neuropathy compared to spectral methods [11]. More importantly it is often not able to be performed due to co-morbidities in the patients like existing heart or respiratory disease, which is a counter indication for the Valsalva manoeuvre. Use of antihypertensive medication influences the outcome of the lying to standing test that measures blood pressure changes on standing and identifies orthostatic hypotension. The hand grip test is hindered by lack of strength in the elderly and more often by arthritis in the hands. The lying to standing heart rate (HR) test is the easiest test to perform, although it may be difficult for some with a lack of mobility as is often found in the elderly [12].

The most common methods that are non-invasive and independent of patient cooperation used are heart rate variability analysis techniques. A change in HRV is regarded as one of the early signs of CAN [10]. The conventionally used time and frequency domain parameters of HRV are not always suitable for analysis because of the non-stationary characteristic of the ECG recordings, the influence of respiration and the presence of nonlinear phenomena in the physiological signal's parameter variability [12].

The nonlinear algorithm, the Point Correlation Dimension (PD2i), is preferred as it is not only accurately provides the degrees of freedom in the heartbeats, but it is also insensitive to data nonstationarity and small amounts of noise that invariably get into the data [8]. As a complexity measure it determines the degrees of freedom, or a number of independent variables operating at each point in time to produce the data and will track those changes with only a small (4%) error [8]. For this unique feature in comparison to other complexity and entropy algorithms developed to work on shorter data lengths, the minimum PD2i value was far more predictive of future lethal arrhythmogenesis in high-risk cardiac patients [14] In addition, in contrast to the other nonlinear methods that require long, relatively noise-free ECG data, the PD2i algorithm has been found to perform effectively on even relatively short, noisy data [16].

In this study, reduction of PD2i values in CAN+ groups could indicate that PD2i may be sensitive to cardiac risk in DM patients. In the previous studies, the PD2i was reduced in DM patients without signs of cardiac effects and in cardiac patients without signs of DM [15]. The reduced PD2i has been interpreted as the result of cooperation (phase coherency) among the various independent regulators of the heartbeats that lie in the brain [14].

## 4. Conclusions

The reduced PD2i index values show the presence of CAN. This study needs to be further extended to make sure whether CAN+ at the early stages could be detected by PD2i features which may not be possibly detected by Ewing tests.

## References


[1] Bax Jeroen J and Ernst E van der Wall. Assessment of coronary artery disease in patients with symptomatic diabetes. European Heart Journal 2006;27:631-632.

[2] Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553–79.

[3] Skinner JE et al. Nonlinear PD2i heart rate complexity algorithm detects autonomic neuropathy in patients with type 1 diabetes mellitus. Clin Neurophysiol 2011, doi:10.1016/j clinph 2010.12.046

[4] Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, et al. Diabetes, glucose, insulin, and heart rate variability: the atherosclerosis risk in communities (ARIC) study. Diabetes Care 2005;28:668–74.

[5] Ewing DJ, Martyn CM, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8:491–3.

[6] Javorka M, Trunkvalterova Z, Tonhajzerova I, Javorkova J, Javorka K, Baumert M. Short-term heart rate complexity is reduced in patients with type 1 diabetes mellitus. Clin Neurophysiol 2008;119:1071–81.

[7] Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N. Chaos and physiology. Physiol Rev 1994;74:1–47.

[8] Skinner, JE, Molnar, M, and Tomberg, C. The Point Correlation Dimension: Performance with Non-Stationary Surrogate Data and Noise. Integ. Physiol. Behav. Sci. 1994;29:217-234, 1994.

[9] Hanley JA, McNeil BJ. The meaning and use of the area under receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.

[10] Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J 1982;285:916–8.

[11] Pagani M. Heart rate variability and autonomic diabetic neuropathy. Diabetes Nutr Metab 2000;13:341–6.

[12] Ewing DJ, Campbell IW, Murray A, Neilson JM, Clarke BF. Immediate heart-rate response to standing: simple test for autonomic neuropathy in diabetes. Br Med J 1978;1:145–7.

[13] 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. Circulation 1996;93:1043–65.

[14] Skinner JE, Meyer M, Nester BA, Geary U, Taggart P, Mangione A, et al. Comparison of linear stochastic and nonlinear deterministic algorithms in the analysis of 15-minute clinical ECGs to predict risk of arrhythmic death. Therap Clin Risk Manag 2009;5:671–82.

[15] Skinner JE. Role of the brain in ventricular fibrillation and hypertension: from animal models to early human studies. Cleve Clin J Med 2007b;74:S73–8.

[16] Batchinsky A, Skinner J, Salinas J, Necsolu C, Nguyen R, Waker K, et al. Does heart rate-complexity analysis work on real-world data? The point correlation dimension of the heart rate and pre hospital life-saving interventions. Circulation 2009;120:S1441–2.



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