VIA MEDICA

NEW DRUGS AND TECHNOLOGIES IN CARDIOLOGY

Cardiology Journal
2010, Vol. 17, No. 3, pp. 316–318

ISSN 1897–5593

Characterizing the heart-brain connection using non-linear mathematics

Daniel N. Weiss

Vicor Technologies, Inc., Boca Raton, FL, USA

The existence of beat-to-beat changes in heart rate, known as 'heart rate variability' (HRV), has long been recognized by physiologists. However, over the past 20 years it has been determined that HRV is not a random phenomenon but can be influenced by the brain through the autonomic nervous system (ANS). Sympathetic and parasympathetic projections to the heart at nodal (sinoatrial and atrioventricular) and myocardial loci act together to control the heartbeats at characteristic frequencies that are found in HRV.

Not only do the brain and autonomic nerves control the heartbeats, they also control the vulnerability of the heart to fatal arrhythmogenesis. Ebert et al. [1] first showed that complete denervation of the heart would prevent ventricular fibrillation (VF) following coronary artery occlusion in an anesthetized dog. Backtracking from the cardiac nerves into the brain, it was found that blockade of descending projections from the frontal lobes [2] and amygdala [3] would prevent VF in a conscious pig following coronary artery occlusion. In the same animal model, the reduction of stress apparently stops the descending output over the autonomic nerves, as it also prevents the occurrence of VF [2].

The annual incidence of sudden cardiac death in the United States has recently been estimated at 350,000. Most of these patients die from ventricular tachyarrhythmias. Currently, there is a limited ability to predict reliably which patients are at risk of these events, based mostly upon left ventricular ejection fraction. Because HRV is primarily regulated by the ANS, it may not be coincidental that analysis of HRV has become an important clinical tool in predicting risk among cardiac patients. Significant decreases in HRV due to increases in sympathetic input to the heart, or decreases in parasympathetic input, have correlated with increased mortality in post-myocardial infarction patients [4]. The natural extension of this analysis would be to study whether HRV could predict future arrhythmic events in potentially vulnerable patients. Indeed, various mathematical analytical methods have been applied to the problem of risk stratification for sudden cardiac death (SCD), with varying degrees of success, including statistical correlations [5], Fourier analysis [6], and wavelet decomposition [7]. These methods, while always showing some efficacy, were nevertheless plagued by inadequate sensitivity, specificity, and predictive positive and negative values, most likely due to those models not taking into account such issues as data non-stationarity and intra-data correlations. In contrast, the aim of the chaos approach is to get beyond these limitations in an effort to understand the complex interactions that determine the vast variety of ways in which the human organism responds to experience. Chaos theory takes into account variables that are otherwise impossible to consider and thus provides one of the best opportunities for understanding the complexities of biologic systems.

The quantification of a chaotic system can occur by calculating its degrees of freedom, or 'correlation dimension' (D2). It can be made from relatively small samples of data that the system generates. The D2 algorithm is really a mathematical tool utilized to quantify the number of independent variables, including those that are fractional, necessary for explaining the system's total behavior or 'dynamics'.

By being inclusive to more variables, D2 calculations can provide greater sensitivity and specificity than stochastic (linear) measures. In addition, this improved resolution or definition to the data can provide deterministic (predictive) information. The D2 dimension is constructed by taking samples of a time series of data points and plotting the data points as co-ordinates in an m-dimension-

Address for correspondence: Daniel N. Weiss, MD, FACC, Chief Medical Officer, Vicor Technologies, Inc., Boca Raton, FL, USA, tel: +1 561-995-7313, x220 (office), +1 561 573 3784 (cell), e-mail: DWeiss@vicortech.com

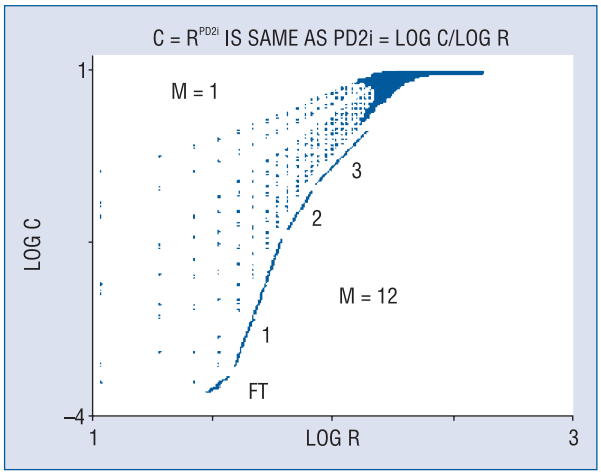

Figure 1. Calculation of PD2i. PD2i = convergent slope of a series of plots at different embedding dimensions (M) of log C *vs* log R, where C = cumulative count of the vector difference lengths and R = the cumulative range. Using M = 9 – 12 is sufficient to test for convergence. FT = 'floppy tail', the data due to noise in the system, that is skipped over. PD2i is the slope seen at section '1'. PD2i differs from D2 and D2i in that it is calculated at every possible data point, instead of only once over the whole data set.

al vector, and then finding pair-wise all vector difference lengths (VDRLs) from all samples. Once calculated, the VDRLs are rank-ordered and the cumulative count (C) is plotted against their cumulative range (R) on a log C *vs* log R plot (Fig. 1). The slope of the log-log plot is recognized as the system's correlation dimension. D2 calculations allow for information in the signal (e.g. variables or degrees of freedom) that would have previously been considered noise and therefore filtered out. Instead of being regarded as noise, this high frequency activity is recognized as low-dimensional chaos and is part of the deterministic signal. One potential limitation in standard D2 calculations is the presumption of stationarity of data. The point-D2i (PD2i) model for calculating the correlation dimension permits non-stationarity in the data and allows for the tracking of non-stationarities, such as the state changes that often occur in the physiological dynamics of the human organism (e.g. induced by seizure, myocardial infarction, and other overt events on the one hand, or simple and subtle influences associated with changes in behavioral state on the other). For HRV analysis, it requires as input only a resting ECG recording of approximately 2–15 minutes' duration, depending upon the clinical application. Whereas D2 looks at all VDRLs from all possible vectors together at once, PD2i takes each individual data point's vectors one at a time (the 'i' vector) and calculates the VDRLs from all the other possible data points' vectors (the 'j' vectors). Thus, rather than generating just one overall average dimension, PD2i generates the dimension of the system that existed at each individual data point in time.

Utilizing PD2i, Skinner et al. [9] compared Holter-monitor tracings from a high risk patient group (n = 11) who manifested VF to two control groups. One of the control groups included patients who presented with non-sustained ventricular tachycardia (VT, n = 14) and the second group presented with premature ventricular complexes (n = 13). Results showed that the VF group demonstrated low dimensional PD2i excursions which preceded the lethal dysrhythmias by several hours. In contrast, the matched controls did not show the same reductions in PD2i (sensitivity, 91% specificity, 85%) [9]. In a similar study, Vybiral et al. [10] and Skinner et al. [11] analyzed 61 ECG tracings of ambulatory high-risk cardiac patients and found that PD2i reduction was 100% sensitive and 83% specific in predicting VF. In addition, the PD2i reductions preceded lethal VF by a mean of 12 hours. In a larger study of 918 patients presenting to the emergency department with chest pain, a minimum PD2i value below 1.4 during the recording period had a sensitivity of 96%, specificity of 85%, and a relative risk of > 24 for SCD in the ensuing 12 months (see Fig. 2 for examples).

Following the paradigm of PD2i reflecting autonomic influence on HRV, in a study of 34 patients, PD2i accurately detected the presence of autonomic neuropathy (sensitivity 94%, specificity 71%, positive predictive value 71%, negative predictive value 92%) (manuscript in preparation). Additional applications being evaluated include detection of concussion and characterization of the severity of neurotrauma. Lastly, it has been developed as a tool for trauma triage, again with high sensitivity and specificity seen in several studies (e.g. [12]).

Conclusions

A novel non-linear measure of HRV, PD2i, has been developed. Studies show it to have utility in assessing the interplay between the ANS and disease, including SCD, trauma triage, and the detection of ANS dysfunction. Other clinical applications continue to be studied. Non-linear analyses of HRV, and PD2i in particular, may play a significant role in future diagnosis and risk assessment.

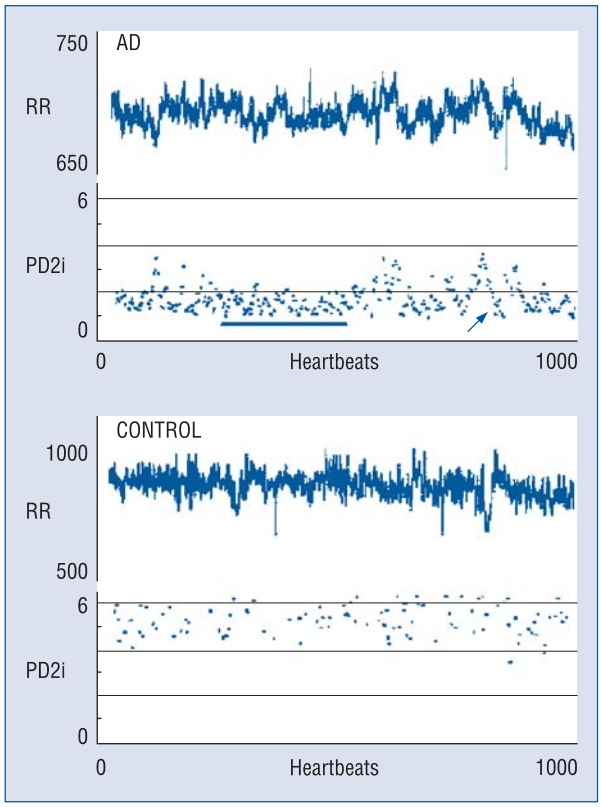

Figure 2. RR intervals and associated PD2is from two types of patient. The upper panel shows RR data and corresponding PD2i results from a patient who experienced documented arrhythmic death (AD) within 24 hours; note the two patterns of both a sustained low--dimension excursion (line) and periodic low-dimensional excursions (arrow). Either pattern is correlated with a high risk of sudden death. The lower panel shows data and results from a normal patient discharged after diagnosis of gastro-esophageal reflux disorder (CONTROL).

Acknowledgements

The author is the Chief Medical Officer of Vicor Technologies, Inc. which owns PD2i algorithm.

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