

TIME-DOMAIN ANALYSIS OF HEART RATE VARIABILITY IN DIABETIC PATIENTS WITH AND WITHOUT AUTONOMIC NEUROPATHY

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The normal heart rate is determined by dynamic interaction between the spontaneous cardiac impulse generated by the sinoatrial (SA) node and conflicting influences of the sympathetic and parasympathetic nervous systems on the conducting tissue of the heart. The rate of spontaneous depolarization of the SA node is itself affected by its metabolic milieu and in the longer term, by hormonal influences. Normal resting heart rate is maintained by the tonic influence of the parasympathetic vagus nerve, and acceleration of the heart rate is affected both by the inhibition of vagal influence and the stimulation of the sympathetic nervous system. The activity of the autonomic is also governed by moment-to-moment changes in blood pressure and respiration, which alter heart rate continuously. The resultant heart rate is the summation of all these influences and thus inherently unpredictable on a beat-to-beat basis.

Recent advances in technology have enabled accurate recordings and the automated analysis of 24-hour ECG to detect beat-to-beat variability, providing not only more detailed, but much more accurate and precise information than the earlier tests.¹ Heart rate variability (HRV) decreases with age,² and shows a circadian variation, being maximum during sleep.³ It is also rate dependent, the heart rate showing more variability at lower heart rates. The loss of this beat-to-beat variability is a sign of disease.

It has long been known that cardiovascular autonomic diabetic neuropathy (CADN) is associated with a loss of heart rate variability.^{4,5} These patients have a poor cardiovascular prognosis,^{6,7} with a 5-year mortality greater than 50%.⁸ Some of this may be attributed to micro- or macrovascular disease,⁹ however, a recent study has shown the relatively poor prognosis of patients with CADN in the absence of clinically detectable micro- or macrovascular conditions.¹⁰ Clinically detectable autonomic failure is usually evident many years or decades after the onset of

diabetes. It is likely that these patients develop subtle deficits in HRV much earlier, and these may include diminution in time-domain analysis. Detection of such changes may be used as markers of pathology, particularly to study the benefits of therapeutic interventions. Thus, the aim of this work was to study HRV in diabetic patients with clinical and sub-clinical autonomic neuropathy (AN), and to determine whether HRV in patients with sub-clinical AN is abnormal in comparison to normal controls.

Subjects and Method

Following Local Ethical Committee approval, we studied 10 consecutive, newly diagnosed non-insulin dependent diabetics mellitus (NIDDM), 10 with NIDDM with autonomic diabetic neuropathy (ADN), and 10 age-matched normal controls (Table 1). Informed consent was obtained from each subject. The patients were selected from King Abdulaziz University Hospital in Jeddah, Saudi Arabia, under supervision of a medical consultant. The analysis of HRV was done in the Department of Physiology. We found no gender differences in any measure of HRV (data not shown), which is consistent with previous published work.¹⁰ All subjects had no evidence of pre-existing cardiovascular disease, were normotensive, had no previous history of ill health, and were taking no regular medication except standard diabetic therapy.

24-Hour ECG Recording

The 24-hour electrocardiogram (ECG) recordings were carried out using a two-channel tracker (DEL MAR Holter System). One channel records the ECG signal and the second channel records a time signal generated by the recorder. The time signal is used to make correction for variations in tape speed. Individuals went about normal daily activities. A new cassette tape and battery were used for each recording.

The electrodes were positioned in standard positions over the precordium. Reply, QRS detention and measurement of the RR interval was performed using DEL MAR ECG Analyzer. After analogue to digital conversion, a digital computer stored the time intervals (ms) between successive R waves as the interval tachogram (time series).

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All intervals <200 ms, and >2000 ms were rejected as being artifacts. From the time series, using HRV analysis programs, time analysis was performed.

Time-Domain 24 Hours ECG Analysis

We measured several time domain variables (Table 2), which can be divided into three groups:

1. Measures of mean value and range, which includes mean RR and mean HR for the recording period;
2. Measures of variance, which include the standard deviation of all RR intervals around mean RR for the entire recording (SDRR), and St. George's index. The St. George's index was calculated from the frequency histogram of 24-h recordings. A triangle is fitted to the frequency histogram, the perpendicular height approximating to the model RR interval, and the area approximating to the total number of detected intervals. The index is calculated by dividing twice the area by height.¹¹ The 24-hour SDRR and St. George's index are dependent not only on short-term variability but also on long-term variability and diurnal changes in mean RR interval. They, therefore depend not only on vagal modulation but also on cardiac sympathetic tone, neurohumoral activity and other factors. Hence, SDRR and St. George's index may be considered as a broadband measure of autonomic balance.
3. Parameters that analyze the differences between adjacent intervals including the standard deviation of the differences between adjacent RR intervals (root mean square of successive RR interval differences or RMSSD) and the Edinburgh index which is the number of times that the difference between adjacent normal RR intervals greater than 50 ms (NN50) is computed over the entire 24-hr ECG recording.¹² NN50 and RMSSD quantitate short-term HRV and they reflect alterations that are almost wholly mediated by vagal tone. These parameters are considered as vagal indexes.¹³

Statistical Analysis

Comparisons between data were made using Student's *t*-test for unpaired normally distributed values. However, because distributions of power spectrum values were skewed towards high values, these data were log transformed and then analyzed using Analysis Of Variance (ANOVA) test (general factorial model). $P < 0.05$ was

TABLE 3. Time domain parameters of D without AN, D with AN, and normal subjects (n=10). Values are mean±SD (and range).

Time domain parameters	Normal control (n=10)	D without AN (n=10)	D with AN (n=10)	P-values* t-test	
MHR	79±3	80±2	83±5	D without AN vs N	P=0.6
(beats/min)	(76-86)	(78-86)	(79-90)	D with AN vs N	P=0.2
Mean RR	740±57	738±102	743±72	D without AN vs N	P=0.8
(ms)	(688-825)	(596-774)	(683-824)	D with AN vs N	p=0.8
SDRR	155±11	36±17	77±106	D without AN vs N	P=0.01
(ms)	(145-176)	(14-59)	(16-200)	D with AN vs N	p=0.01
SDRR index	60±8	37±6	29±4	D without AN vs N	P=0.001
	(48-74)	(31-48)	(24-32)	D with AN vs N	p=0.001
SNN 50	15813±8335	4217±2094	3120±3600	D without AN vs N	P=0.001
Count	(3784-25820)	(1285-6726)	(672-7252)	D with AN vs N	p=0.04

considered significant. Data were expressed as the mean ± SD and range.

Results

The first step in any time series analysis is to plot the time series, so a graph of x_t versus t was done. This was done to save us from rediscovering trivial aspects of the time series as well as suggest useful or interesting

TABLE 1. Age and sex of D without AN, D with AN and normal subjects (n=10). Values are mean±1 SD and range.

Group*	N	Sex	Age (years)
D without AN	10	6/4	34±10 (18-50)
D WITH AN	10	7/3	40±10 (35-62)
N	10	6/4	34±6 (22-40)

*D=diabetic; AN=autonomic neuropathy; n=normal control.

TABLE 2. Different time domain measures of heart rate variability.

Variable	Units	Definition
SDRR	ms	Standard deviation of normal RR intervals (1)
SDRR index	ms	Mean of the standard deviations of all normal RR intervals for all 5 minutes segments of a 24-hour ECG recording
SNN50 counts	beats	The number of time that the difference between adjacent normal RR intervals greater than 50 minutes, computed over the entire 24-hour recording (1)
PNN50	%	Percent of difference between adjacent RR intervals that are greater than 50 minutes computed over the entire 24-hour ECG recording
RMSSD	ms	Root mean square of successive RR intervals difference: the square root of the mean of the sum of the squares of the differences between adjacent normal RR intervals over the entire 24-hour ECG recording (1)
St. George's index	ms	The St. George's index is calculated from the frequency histogram of 24-hour ECG recordings

FIGURE 1. Example of RR interval series of 1000 RR intervals for: a) normal subject; b) diabetic patient with symptomatic autonomic neuropathy and; c) diabetic patient with clinical autonomic neuropathy.

hypotheses to test. It has been reported that time series of RR intervals from patients with autonomic damage were noticeably smoother than those from normal subjects with

PNN50%	15±8 (3-25)	3±1 (1-6)	2±3 (0.6-6)	D without AN vs N D with AN vs N	P=0.01 p=0.04
RMSSD (mes)	37±10 (21-49)	22±3 (18-2)	19±8 (14-29)	D without AN vs N D with AN vs N	P=0.01 p=0.03
St. George's index	40.7±6.2 (33.5-47.6)	27±5 (21-35)	20±5 (15-25)	D without AN vs N D with AN vs N	P=0.002 p=0.002

*D=diabetic; AN=autonomic neuropathy; N=normal control.

large abrupt changes in heart rate.¹ The beat-to-beat variation is represented as a time series (Figure 1A, B, C) in which the y axis is the time between beats (ms) and the x axis is the number of beats. The RR interval time series illustrates the normal pattern of fluctuations for the healthy adult (A) compared to the smooth pattern of beat-to-beat intervals for a diabetic patient with a symptomatic diabetic neuropathy (B) and a very smooth pattern of RR intervals for diabetic patient with clinical diabetic neuropathy (C). It was possible to observe a smaller RR variation in all diabetic subjects when compared to normal controls, and calculation confirmed this impression.

Table 3. summarizes the result of time-domain analyses for normal controls, diabetic patients without autonomic neuropathy and patients with autonomic neuropathy. There was no significant difference in mean heart rate in diabetic patients compared to normal subjects [normal controls 79±3 beats/min, D with AN 83±5 (P=0.2) and D without AN 80±2 (P=0.6)]. All time-domain parameters (SDRR, SDRR index, SNN50, pNN50%, RMSSD and George index) were significantly decreased in patients with and without diabetic neuropathy compared to normal controls.

There was no significant correlation between fasting blood sugar level and different HRV parameters in patients with and without diabetic autonomic neuropathy (results not shown).

Discussion

Diabetes is known to be complicated by a dreadful disease, autonomic neuropathy, which affects about 40% of all diabetic patients and, in its severe form, offers a very poor prognosis. As HRV reflects the degree of autonomic control of the heart, it is widely used for the diagnosis of autonomic dysfunctions in noncardiological diseases on the assumption that if such a dysfunction in the heart is identified, it is a sign of a more widespread autonomic neuropathy affecting all organs. In the case of a systemic disease such as diabetes, this assumption is usually justified. Another reason why we used tests based on HRV as marker for cardiac autonomic diabetic neuropathy is because they are very accurate, noninvasive and generally reproducible.

In Saudi Arabia, the clinical importance of HRV tests is easy to appreciate if one considers the high incidence of diabetes in the Saudi population and the high incidence of diabetic neuropathy among diabetics. However, despite this high incidence of diabetes, a review of the literature revealed that our work is the first study that used tests based

on HRV as markers for diabetic neuropathy in Saudi patients. Using time domain analysis of HRV, our study showed that despite the normal mean resting heart rate (as measured by RR interval) in diabetic subjects, there was a striking reduction in HRV when compared with normal controls. This reduction in HRV can be present even in patients without any clinical features of autonomic neuropathy. It has been reported¹ that the measurement of risk RR interval changes, such as SDRR index, pNN50% and RMSSD aim to evaluate parasympathetic activity, which, of course, is directly responsible for rapid HR fluctuation. From the results that have been obtained in this study, it appears that vagal indices are decreased in diabetic patients compared to normal. However, the reduction is more pronounced in patients with autonomic neuropathy. Decreased parasympathetic activity is, of course, responsible for high heart rate usually reported in patients with diabetic autonomic neuropathy.

Although this method is very interesting, and has met with success in cardiological applications,¹ it is not yet widely used by diabetologists, perhaps because it is not easy to carry out due to the large number of patients affected by diabetes mellitus.

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