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ORIGINAL ARTICLE

Paper Electrocardiograph Strips May Contain Overlooked Clinical Information in Screen-Detected Type 2 Diabetes Patients

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Abstract

Background:

A large number of nondigitized electrocardiograph (ECG) strips are routinely collected in larger cohort studies such as the ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care). These ECG strips are routinely read manually but may contain overlooked information revealing cardiac autonomic dysfunction. The aim of this study was to investigate whether clinical information may be lost using manual R wave to R wave (RR) interval measurements in the calculation of heart rate variability (HRV) in patients with type 2 diabetes mellitus (T2DM).

Method:

From the Danish part of the ADDITION study, we randomly selected 120 T2DM patients at baseline of the ADDITION study. Analysis of the ECG strips was performed using two different methods: (1) by experienced technicians using rulers and (2) by experienced technicians using a high-resolution computer-assisted method. Calculation of heart rate and time domain HRV [standard deviation of normal-to-normal RR intervals (SDNN) and root mean square of successive differences (RMSSD)] were performed with the same software.

Results:

When comparing results from the two methods, the following values of Pearson's r are obtained: 0.98 for heart rate, 0.76 for SDNN, and 0.68 for RMSSD. These results indicate that heart rate and HRV measurements by the computer-assisted and manually based methods correlate. However, Bland-Altman plots and Pitman's test of difference in variance revealed poor agreements ($p < .01$) for both HRV measurements (SDNN and RMSSD); only heart rate showed substantiated agreement ($p = .54$) between the two methods. Low HRV was statistically significantly associated to high heart rate, systolic blood pressure, and diastolic blood pressure in these screen-detected T2DM patients.

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Abbreviations: (bpm) beats per minute, (CAN) cardiac autonomic neuropathy, (CV) coefficient of variation, (ECG) electrocardiograph, (HbA1c) hemoglobin A1c, (HRV) heart rate variability, (ln) natural logarithm, (QTc) QT interval corrected for heart rate, (RC) reproducibility coefficient, (RMSSD) root mean square of successive differences, (RR) R wave to R wave, (SD) standard deviation, (SDNN) standard deviation of normal-to-normal RR intervals, (T2DM) type 2 diabetes mellitus

Keywords: autonomic dysfunction, complications, diabetes, neuropathy, risk stratification, ultra short-term HRV

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Abstract cont.

Conclusions:

Paper ECG strips may contain overlooked clinical information on the status of autonomic function in patients with T2DM. In our study, manual measurements of RR intervals were inferior to the computer-assisted method. Based on this study, we recommend cautiousness in the clinical use and interpretation of HRV based on manual or low resolution measurements of RR intervals from ECG strips. High resolution measurements of RR intervals reveal significant associations between low HRV and high heart rate, systolic blood pressure, and diastolic blood pressure among patients with screen-detected T2DM. It is feasible to use a computer-assisted method to determine RR intervals in patients with T2DM.

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Introduction

Heart rate variability (HRV) is defined as the variation in heart rate from beat to beat caused by changes in breathing, blood pressure, hormones, mental/physical state, and certain pathological conditions. HRV has received much attention over the years as an indicator of autonomic nervous dysfunction,[1–3] and associations between abnormal HRV and several pathological conditions or events are well established.[2,4–7] Autonomic dysfunction is highly prevalent, especially in the diabetes population, and may progress to autonomic neuropathy affecting various organs.[8] HRV is most often evaluated by means of electrocardiographic (ECG) recordings and R wave to R wave (RR) interval measurements during sessions ranging from a few seconds to several hours.[2,5–7,9] Ultra short-term HRV analysis from ECG strips is cheap and fast compared to longer measurements. However, ultra short-term HRV measurements are also more sensitive to artifacts, e.g., extra beats, missed beats, or body movements, and therefore require visual inspection. The quality of both short and long HRV analyses relies on the resolution of a given interbeat interval, i.e., the sampling rate (digitalization) of the raw ECG signal or the paper speed of older ECG devices. In order to resolve interbeat intervals with a resolution of at least 1–2 ms, a sampling frequency of 500–1000 Hz is necessary and recommended.[1] But, this resolution is difficult or even impossible to obtain with nondigitized ECG strips and the traditional manual method. The aims of this study were to compare manual RR interval measurement with a high-resolution computer-assisted method, and to assess a computer-assisted method to determine RR intervals in patients with type 2 diabetes mellitus (T2DM).

Methods

The ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) study is a multicenter study on early detection and multifactorial treatment of T2DM in primary care. From the Danish arm of the ADDITION study, we randomly selected 133 T2DM patients of the 1533 participants from the baseline examination. All patients previously underwent standard 10 s, resting, 12-lead ECG recordings. In 13 patients, the manual method was not able to measure any RR interval difference because of distorted and poor quality paper ECG. After exclusion of the 13 patients, the remaining 120 subjects were included in this study. All analyses of the ECG strips were performed using two different methods: (1) by experienced technicians using rulers and (2) by experienced technicians (not the same as former) using a high-resolution computer-assisted method.

Computer-Assisted RR Interval Detection

The 10 s ECG strips were scanned and digitized by the program IrfanView 4.25 (Irfan Skiljan, Wiener Neustadt, Austria)[10] with a sampling frequency of 500 Hz (500 pixels/s), which gives a temporal resolution of 2 ms. If necessary, contrast and other image adjustments were performed in ImageJ (National Institutes of Health, Bethesda, MD)[11] (the ink of some ECG strips was very faded during storage). Each RR peak was marked and the results (coordinates) were stored in a file. A custom-developed MATLAB (Version 7.0.0.19920, MathWorks, Natick, MA) program calculated the heart rate and time domain HRV parameters: standard deviation of normal-to-normal RR intervals (SDNN) and root mean square of successive differences (RMSSD) from the image coordinates.[1]

Manual RR Interval Detection

Manual RR interval determination was performed by experienced technicians. The resolution of the 10 s ECG strips used in this study was 100 ms/mm, and the technician used a standard ruler with a resolution of 1 mm. The obtainable resolution with this technique was approximately 50 ms. A ruler with a resolution of 0.5 mm was tested but it did not improve the results because it seemed to blur the identification of the R peaks. After manual measurements, RR intervals were keyed in by hand, and calculations of heart rate, SDNN, and RMSSD were performed in Microsoft® Office Excel® 2007 (Microsoft Corporation, Seattle, Washington).

Intra- and Interoperator Variation

In a substudy of 10 patients, intra- and interoperator reproducibility was examined, both for the manual method and the computer-assisted method. The RR intervals were measured three times by three operators.

Statistical Analysis

Patient characteristics are presented as unadjusted means. The Bland-Altman analysis with Pitman's test of difference in variance was used to test the agreement between computer-assisted and manual methods. Intra- and interoperator reproducibility were assessed by calculating coefficient of variation ($CV = SD_{within}/mean * 100$) (where SD = standard deviation), and the reproducibility coefficient ($RC = SD^2_{between}/(SD^2_{between} + SD^2_{within}) * 100$) was calculated by analysis of variance to obtain test-retest reliability. Two sample *t*-tests and Chi-square tests were used to compare patients with and without low HRV; *p* values of less than .05 were considered statistically significant. Calculation of natural logarithms (ln) of SDNN and RMSSD was performed to obtain a normal distribution.

Results

The persons, all screen-detected T2DM patients, were predominantly males approximately 68 years old, and most had elevated blood pressure. Demographic and clinical characteristics are presented in **Table 1**.

Computer-Assisted vs Manual Method

The correlation between the methods, expressed as Pearson's *r*, was 0.93 for HR, 0.77 for SDNN, and 0.63 for RMSSD. The correlation between the two devices indicates that heart rate and HRV measurements by the computer-assisted and the manually based methods are highly correlated but not necessarily in agreement.[12,13]

Table 1.
Clinical Differences in the Calculation of Heart Rate Variability[a]

Baseline characteristics	Screen-detected T2DM patients		
	All patients	Computer-assisted (Bottom 10% of SDNN values)	Manual (Bottom 10% of SDNN values)
n	120	12	12
Age (years)	67 ± 7	70 ± 6	66 ± 76
Sex ratio (male/female)	67/53	3/7	4/6
Heart rate (bpm)	69 ± 11	81 ± 12[b]	70.3 ± 10.6
QTc (ms)	409 ± 15	412 ± 12	403 ± 12
HRV; SDNN (ms)	27 ± 18	10 ± 2[b]	15 ± 2[b]
HRV; RMSSD (ms)	28 ± 22	12 ± 3[b]	15 ± 2[b]
Body mass index (kg/m^2)	31 ± 5	32 ± 7	31 ± 5
Waist (cm)	104 ± 13	105 ± 21	104 ± 13
SBP (mm Hg)	151/24	162 ± 28[c]	153 ± 17
DBP (mm Hg)	86/13	94 ± 12[b]	88 ± 13
HbA1c (%)	6.91 ± 1.74	7.75 ± 1.87	6.69 ± 1.33

[a] Continuous measures are shown as mean ± SD and dichotomous variables are shown in percentages.
[b] $p < .01$
[c] $p < .05$

Bland-Altman Plot

Comparing Heart Rate Measured by Computer-Assisted and Manual Methods

Figure 1 shows a minimal difference and a high agreement between the two methods. The result of Pitman's test showed that there is no significant (p = .54) difference between the measuring errors of the two methods.

Comparing SDNN Measured by Computer-Assisted and Manual Methods

Figure 2 shows a large difference between the two methods and poor agreement. For SDNN, 95% limits of agreement converted to linear scale (±1.96 SD) are ±16.7 ms. As indicated in **Figure 2** and shown in **Table 2**, the manual method was higher in the low range of SDNN than the computer-assisted method. The test of difference in variance, Pitman's test, showed significant (p < .01) variability in the measurements of the two methods.

Comparing RMSSD Measured by Computer and Based on Manual Method

Figure 3 compares manual and computer-based analysis of RMSSD and shows poor agreement and high variation between the two methods indicated by 95% limits of agreement of ±27.7 ms (converted to a linear scale). As indicated in **Figure 3** and shown in **Table 2**, RMSSD was higher in the low range of RMSSD when performed by the manual method compared to the computer-assisted method. The test of difference in variance, Pitman's test, showed significant (p < .01) variability in the measurements of the two methods.

Table 1 shows that patients with low HRV identified through the computer-assisted method had higher hemoglobin A1c (HbA1c), higher age, higher QT interval corrected for heart rate (QTc), and significantly higher heart rate, systolic blood pressure, and diastolic blood pressure when compared to the full cohort. This was not the case using the manual method.

Table 2 shows the comparison of the two methods in the low range of HRV. Low HRV was defined as SDNN and RMSSD values below 20 ms,[2] and in this case, 35 out of 46 patients were misclassified with normal HRV using the manual method.

Intra- and Interoperator Variation

Reproducibility was high in both methods, with RC ranging from 99–99.7% and CV ranging from 0.03–0.7%. RC higher than 75% represents good reproducibility. Low values, less than 10%, of CV represent good reproducibility.[14–17]

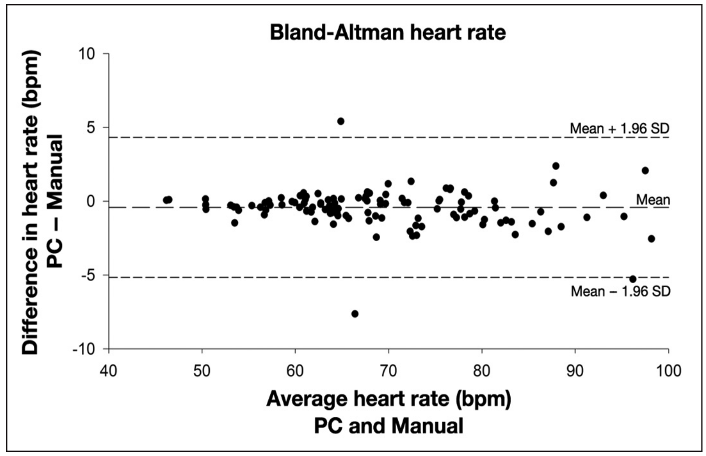

Figure 1. Difference plotted against average heart rate, with mean and 95% limits of agreement. The 95% limits of agreement (±1.96 SD) are ±4.7 beats per minute (bpm). PC, computer-assisted.

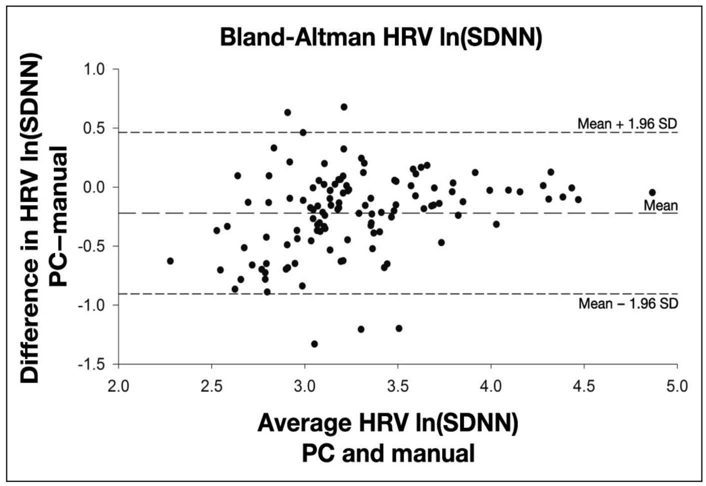

Figure 2. Difference plotted against average of ln(SDNN), with mean and 95% limits of agreement. The 95% limits of agreement converted to linear scale (±1.96 SD) are ±16.7 ms. PC, computer-assisted.

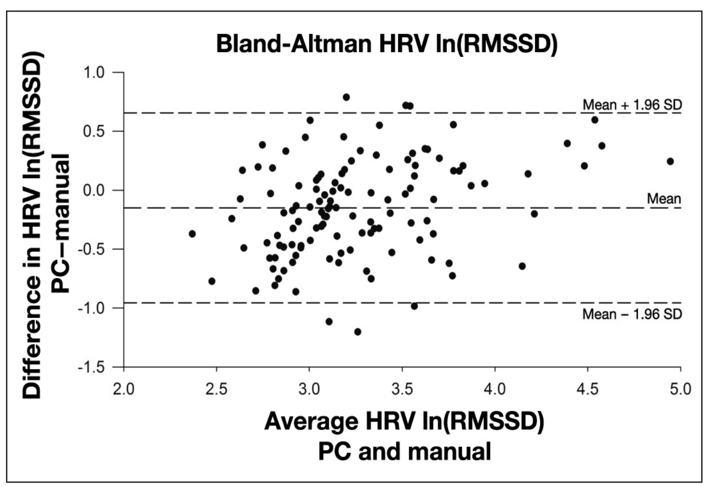

Figure 3. Difference plotted against average of ln(RMSSD), with mean and 95% limits of agreement. The 95% limits of agreement converted to linear scale (±1.96 SD) are ±27.7 ms. PC, computer-assisted.

Table 2.
Comparison of the Two Methods in the Low Range of HRV (SDNN and RMSSD)[a]

	n[b]	Computer-assisted	Manual	*p*[c]
HRV; SDNN	46	14.89 ± 3.63	24.75 ± 8.52	<.001
HRV; RMSSD	46	15.56 ± 3.75	23.59 ± 8.12	<.001
Number of patients misclassified		0%	76% (35/46)[d]	

[a] Continuous measures are shown as mean ± SD.
[b] Number of patients with SDNN or RMSSD below 20 ms found with the computer-assisted method.
[c] RMSSD and SDNN values were log transformed before calculation of *p* values.
[d] 35 out of 46 patients were misclassified with normal HRV using the manual method.

Discussion

When comparing manual methods to computer-assisted methods, we found that there was a significant disagreement between the calculations of the HRV metrics SDNN and RMSSD. There was a statistically significant difference in the low range of both HRV metrics (SDNN and RMSSD), which in our study led to a misclassification of patients when using the manual method. We found that low HRV assessed with the computer-assisted method was associated with higher heart rate, blood pressure, HbA1c, age, and QTc. This association between low HRV and higher values in heart rate, blood pressure, HbA1c, age, and QTc was not apparent when using the manual method. The results from the computer-assisted method are in agreement with other papers[18,19] that support testing of HRV since it may be the earliest clinical indicator of cardiac autonomic neuropathy (CAN), i.e., timely intervention and treatment for this condition can thereby be ensured.

Ultra-short HRV analysis performed on a standard 10 s ECG has been shown to be as reliable as short-term HRV from a 5 min ECG.[20–22] In this study, we present a computer-assisted method for measuring the RR interval based on 10 s paper strips. The measuring accuracy of the computer-assisted method corresponds to guidelines of HRV analysis equal to a resolution of 1–2 ms[1] as opposed to the well-established and clinically used manual method that varies from 20–100 ms depending on the paper speed of the ECG device. In our study, the resolution of the manual technique was approximately 50 ms. To avoid erroneous or misleading conclusions based purely on correlation coefficients and scatter plots, we analyzed the agreement between our computer-assisted RR interval detection and the well-established manual method.[12,13] The evaluation showed, in spite of correlation, a poor agreement between the two methods in the calculations of the time domain HRV parameters SDNN and RMSSD. Pitman's test showed significant variability between the two methods for both HRV measurements. The manual ruler method tended to produce higher values than the computer-assisted method in the low range of SDNN and RMSSD. Approximate spreads of 33 ms for SDNN and 55 ms for RMSSD within the limits of agreement are too large to defend the use of the manual method as opposed to the computer-assisted method. Only measurements of heart rate showed suitable agreement between the manual and the computer-assisted method. These results show how important high resolution measuring is when analyzing HRV based on ultra-short ECG strips.

Low HRV has been shown to be associated with compromised health in the general population and predictive of mortality from all causes.[2] In the diabetes population, low HRV is associated with hypertension,[23] ischemic stroke,[24] and glycemic variability,[25] and may by important in detection and prevention of hypoglycemia.[26,27] Furthermore, low HRV is a marker of the development of CAN.[28–32] However, little is known regarding the onset and progression of the changes in the balance of the autonomic nervous system in patients with diabetes. Autonomic function impairment may develop in the prediabetes stage. A large number of nondigitized ECG strips are routinely collected in larger studies such as the ADDITION study.[33,34] These ECG strips may contain important information revealing cardiac autonomic dysfunction and the progression to autonomic neuropathy. In the absence of cardiovascular reflex test,[32,35,36] autonomic dysfunction was estimated by short-term HRV analysis. Only 10 s ECGs were recorded[37] at baseline of the ADDITION study, which necessitated the use of accurate and standardized data acquisition and calculations methods of HRV as described in this study.

Precision of the ECG strips used in this study was 100 ms/mm, and the technician used a standard ruler with a resolution of 1 mm to measure RR intervals. A higher resolution for the ECG strips will improve the manual method. However, this should be compared with the computer-assisted method with a precision of 2 ms. The challenge in relation to the use of the computer-assisted method in larger studies is time consumption. On average, 15 min was used with the computer-assisted method compared to 5 min with the manual ruler method. However, a more automatized version of the computer-assisted method is under development, and results will be published accordingly.

Conclusions

In patients with diabetes, paper ECG strips may contain overlooked clinical information on the status of autonomic function. In our study, manual measurements of the RR interval were inferior to the computer-assisted method. Based on this study, we recommend cautiousness in the clinical use and interpretation of HRV based on manual or low resolution measurements of RR intervals from paper ECG strips. High resolution measurements of RR intervals reveal significant association between low HRV and high heart rate, systolic blood pressure, and diastolic blood pressure in screen-detected T2DM patients. It is feasible to use a computer-assisted method to determine RR intervals in patients with T2DM.

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