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A Pocket-size Device to Detect Autonomic Neuropathy

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Abstract

Background:

Diabetic autonomic neuropathy (DAN) is a very frequent complication in the diabetic population (type 1 and type 2 diabetes), and patients may suffer debilitating symptoms from various organ systems. In the less symptomatic and even in the asymptomatic condition it severely impacts health. Testing for DAN is currently time-consuming and costly due to the technical setups available today, therefore the examination may not be offered regularly. The purpose of this study was to evaluate the clinical performance of a pocket-size device for detecting DAN by measuring heart rate variability (HRV).

Method:

Ten healthy young males and eight type 1 diabetes patients suffering symptomatic DAN were selected. The standardized spectral analysis equipment VariaPulse TF3® (Sima Media, Olumouc, Czechoslovakia) was used as a reference method for evaluating a prototype of the pocket-size device according to a specified protocol. HRV, inhalation/exhalation ratio (E:I) (deep breathing test), and 30:15 ratio (response going from lying to standing) were measured using both methods. Statistical calculations were performed.

Results:

The correlation between the two devices was $R^2 = 0.98$ and $R^2 = 0.81$ when 30:15 ratio and E:I were measured, respectively. Bland-Altman plots showed suitable agreement between the two devices, substantiated by 95% limits of agreement of the differences of ±0.014 and ±0.033 when 30:15 ratio and E:I were measured, respectively.

Conclusions:

The pocket-size device was fully interchangeable with the hitherto-used, research-based setup. It proved highly suitable for ambulatory testing of autonomic nervous function and may facilitate screening for DAN according to Danish and international recommendations.

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Abbreviations: (DAN) diabetic autonomic neuropathy, (DSP) digital signal processor, (E:I) inhalation/exhalation ratio, (ECG) electrocardiogram, (HRV) heart rate variability, (SD) standard deviation

Keywords: autonomic neuropathy, cardiac, complications, diabetes, neuropathy, risk stratification

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Heart rate variability (HRV) measures are an important means of determining cardiac autonomic function.[1] Detecting and measuring autonomic dysfunction in the diabetic population is of particular interest and importance. First of all, it may identify patients at risk of developing late complications of diabetes, some of which may be threatening to quality of life and general health. This may in turn enable earlier intervention and treatment for the individual patient.[2] Diminished HRV is associated with an increased risk of coronary heart disease and death, and it is hypothesized that low HRV is indicative of poor general health.[3] Of particular clinic interest within the diabetic population has been "the sudden death in bed syndrome" which has been connected to diabetic autonomic neuropathy (DAN).[4] It has been shown that low heart rate variability is a risk factor for sudden cardiac death in type 2 diabetes.[5] HRV measures are important diagnostic tools for the physician in reaching a correct diagnosis and determining whether autonomic dysfunction plays a role in the patient's symptoms.

In spite of the importance of determining DAN, testing has rarely been available in hospitals and outpatient settings, and then primarily for research use. Possible explanations for this may be that the apparatus available has been both very time- and cost-consuming to use and of dimensions not allowing bedside testing. These are major obstacles to general testing of the diabetic populations, as is recommended,[2,3] and the introduction of the pocket-size device described in this article may offer solutions to overcome these barriers.

Therefore, the purpose of this study was to evaluate the clinical performance of a pocket-size prototype device for detecting DAN by measuring HRV.

Materials and Methods

The clinical evaluation of the new device was performed on 10 healthy volunteers and 8 type 1 diabetes patients suffering symptomatic DAN, using recordings from VariaPulse TF3® (Sima Media, Olumouc, Czechoslovakia) as reference (**Table 1**). All type 1 diabetes patients were recruited from the neuropathy clinic in the department of medicine. All demonstrated two or more of the following symptoms of autonomic dysfunction: gustatory sweating, postural hypotension, diabetic gastroparesis, diabetic diarrhea, or neurogenic bladder.

The pocket-size prototype device and clinical setup is shown in **Figure 1a**. The volunteer places his left and right hands on the two separate metal electrodes, and the device records an electrocardiogram (ECG) signal from which the heart rate and heart rate variability are calculated and shown in the display. An onboard graphical user interface guides the user through the standard tests to assess autonomic function. The patients were instructed to follow the graphical elements on the display. In the deep breathing [inhalation/exhalation ratio (E:I)] test, the graphical user interface visualizes the breathing pattern with a continuously moving bar and a short text message. When the bar moves up, the text "Breathe in" appears, and when the bar moves down the display shows the text "Breathe out."

Table 1.
Subject Characteristics

Parameters	Control	DAN patients
Number of subjects	10	8
Age (years)*	34 ± 4	43 ± 12
Systolic/diastolic (mm Hg)*	129/79 ± 12/10	141/91 ± 20/17
Heart Rate (beats/min)*	56 ± 9	82 ± 11
* Mean ± standard deviation		

A bedside screening device warrants a user-friendly instrument that does not require substantial time for preparation and data analysis. The present prototype device was optimized for easy ad-hoc bedside examination requiring no preparation before use. For example, the integrated metal electrodes were specially designed for dry operation, and therefore need no gel. The device is based on two-electrode ECG recordings measured by two hand electrodes, and is powered by two 1.5-v AAA batteries to secure mobility and patient safety.

The signal processing was performed automatically by a digital signal processor (DSP), where the discrete heartbeats were detected using a correlation algorithm adapting to individual *R* wave shapes to account for biological variation. Ectopic heart beats were removed automatically by digital filtering. The correlation algorithm is an optimized version of an earlier clinically tested device showing no significant systematic error of the detecting software compared with standard ECG devices. Correlation between the methods was $R^2 = 1.00$ and $R^2 = 0.99$ when measuring heart rate and the time domain HRV parameter, root mean square successive difference, respectively.[6] A Preliminary test on the MIT-BIH Database indicates a high precision.

For logistical and practical reasons, measurements with the two setups were not performed simultaneously. It was not possible to synchronize the two devices, which of course may lead to differences in the recorded data caused by the time difference between measurements. However, testing was performed under identical circumstances by the same personnel, with one measurement followed immediately by the next.

To show that the recorded differences were not a systematic error of the prototype device, we made a control measurement with the VariaPulse TF3 immediately after each recording with the prototype device.

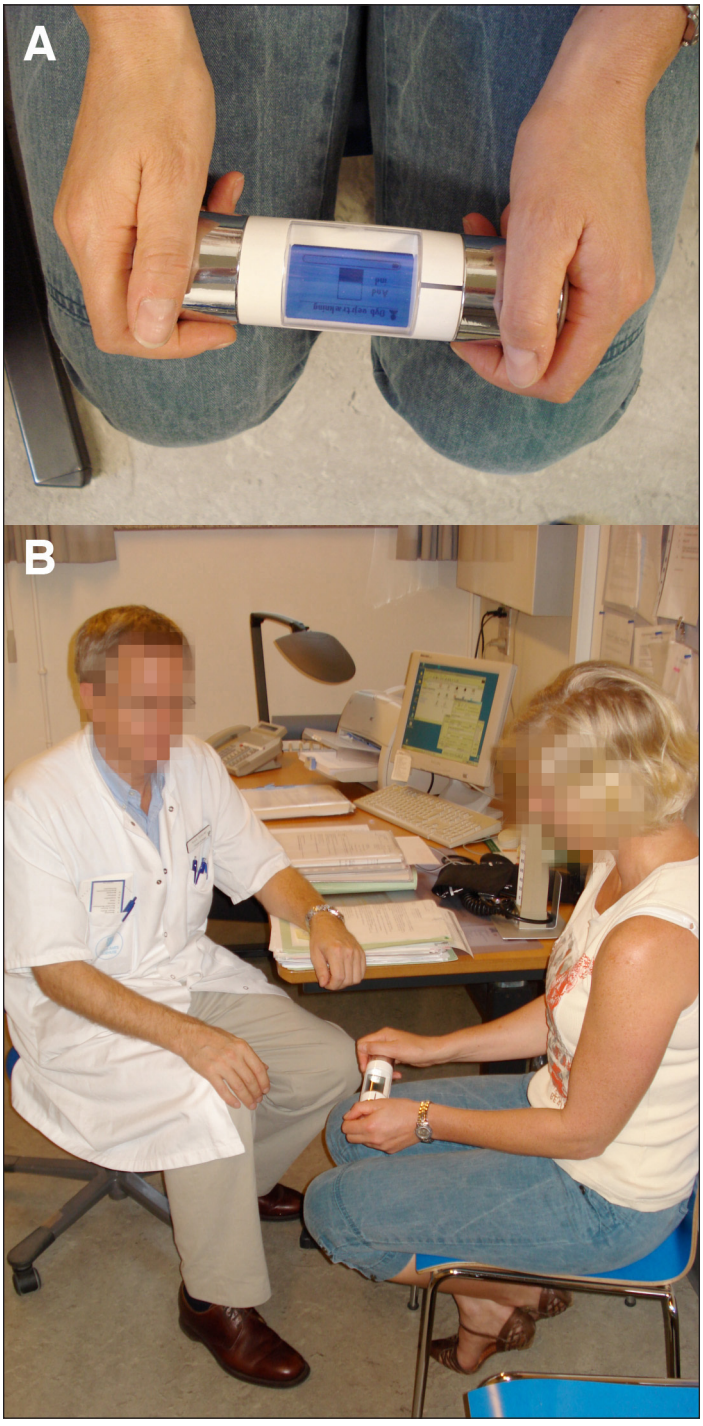

Figure 1. The prototype device. **(a)** The user places her hands on the two electrodes, and heart rate and heart rate variability are measured and shown in the display. The onboard user interface guides the user through the tests, in this case, the deep breathing test. **(b)** Shows ambulatory testing.

Results

The correlations were first visualized in a scatter plot (**Figure 2**) and then calculated using the Pearson R^2 test and the mean difference between the methods. A high degree of correlation between the two methods is evident, with Pearson R^2 and mean difference values shown in **Table 2**.

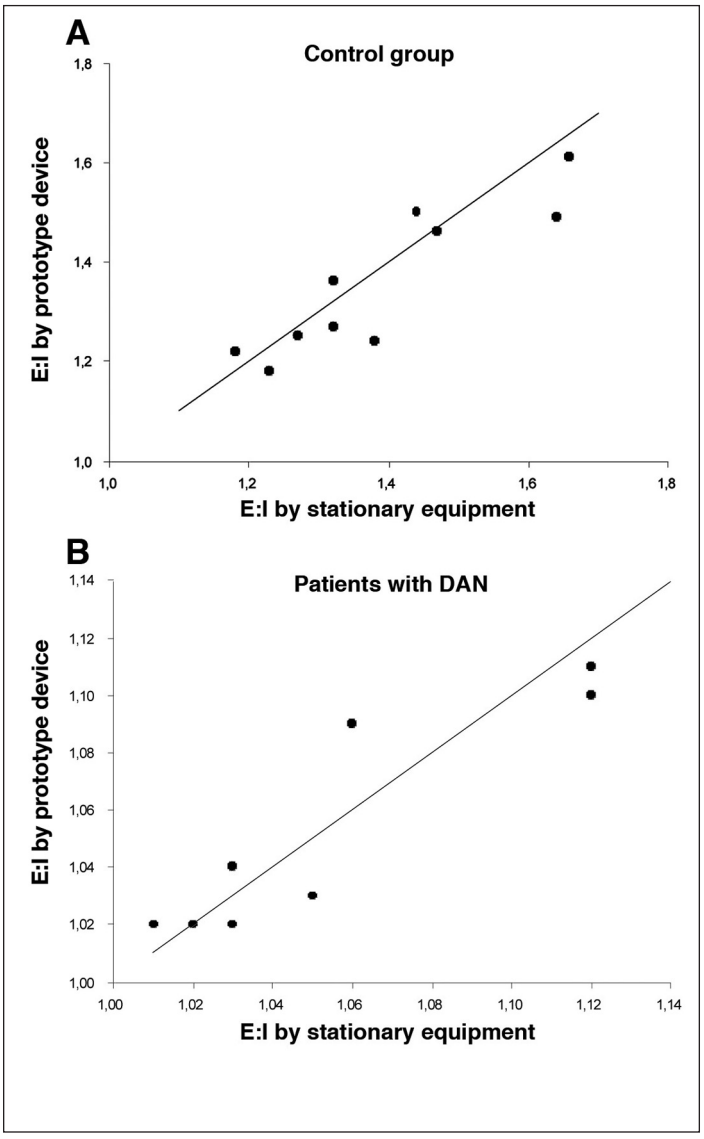

Figure 2. Prototype device and stationary equipment, with line of equality.

Note that **Figures 2–4** have different scales for the **A** plot compared to the **B** plot because of the great difference in the recorded data between the control group and the diabetic group.

The high correlation between the two devices indicates that HRV measurements by the pocket-size device and the stationary VariaPulse TF3 device are highly correlated, but not necessarily in agreement.[7,8] Bland-Altman plots were applied to examine the agreement between the two methods. **Figure 3** and **Figure 4** depict a high level of agreement between the novel device and VariaPulse TF3. This is substantiated by 95% limits of agreement [±1.96 standard deviation (SD)] of the difference showed in **Table 3**.

The limits of agreement between the two devices are ±0.14, indicating that 95% of the difference in E:I was

Table 2.
Pearson R^2 and Mean Difference

	Control Group		Patients With DAN	
	R^2	Mean difference	R^2	Mean difference
30:15 ratio	0.92	-0.031	0.98	0.003
E:I	0.81	-0.033	0.81	0.001

Table 3.
Limit of agreement

	Control Group	Patients With DAN
	±1.96·SD	±1.96·SD
30:15 ratio	±0.17	±0.014
E:I	±0.14	±0.033

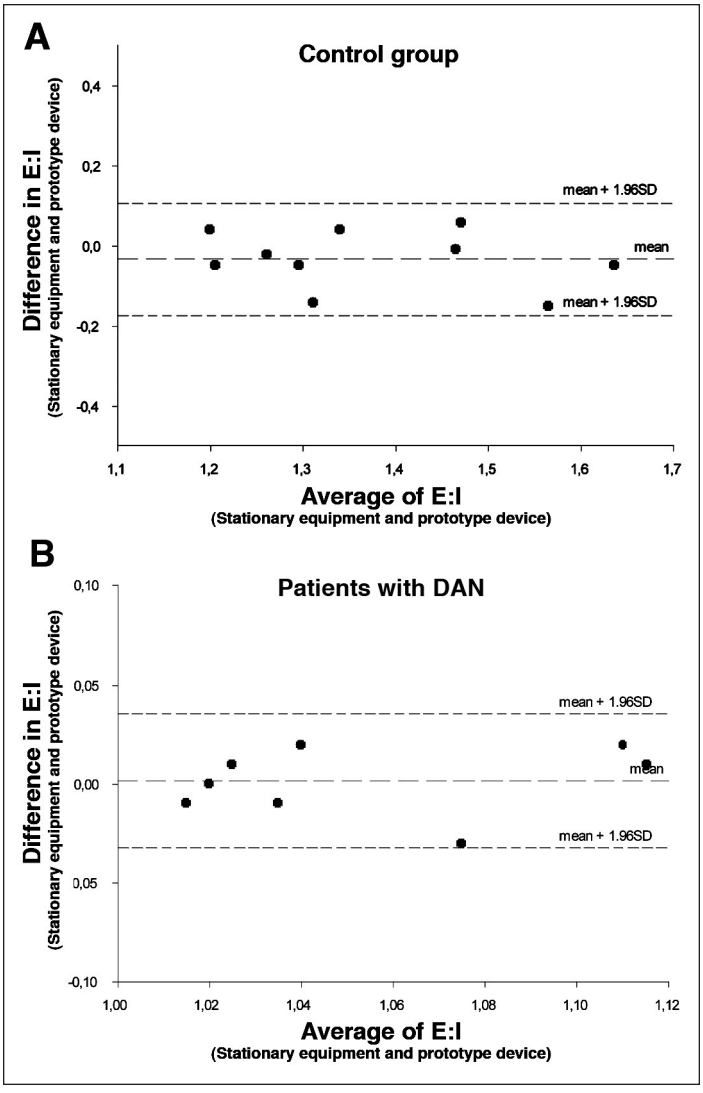

Figure 3. E:I test: difference of average of prototype device and stationary equipment, with mean and 95% limits of agreement.

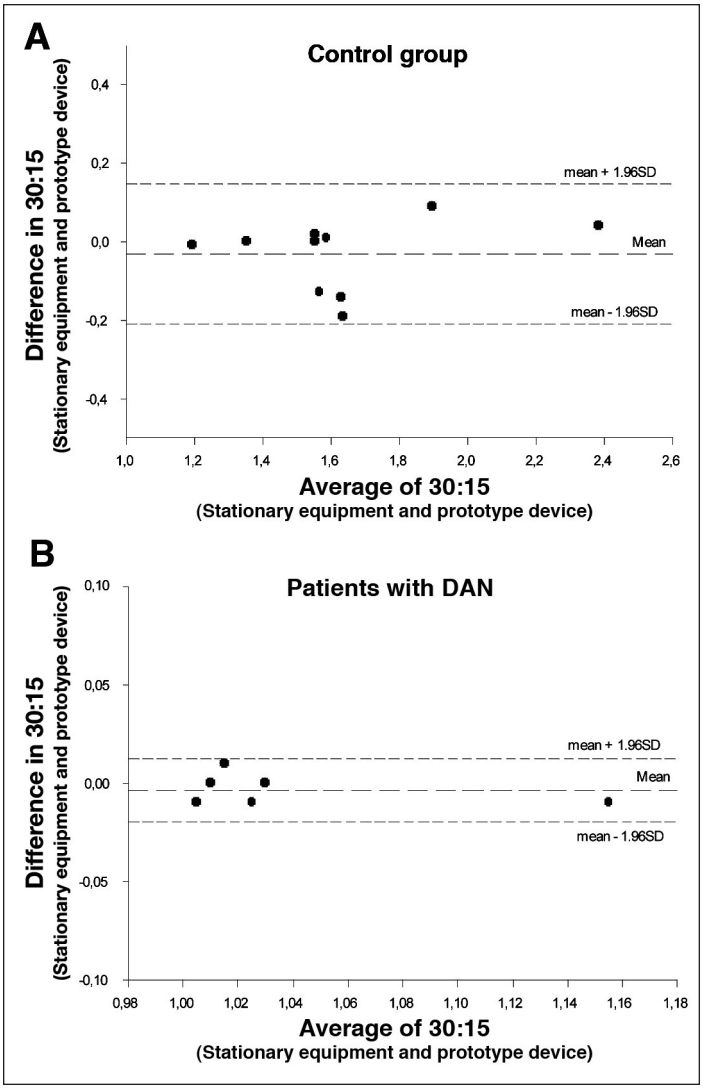

Figure 4. 30:15 test: difference of average of prototype device and stationary equipment, with mean and 95% limits of agreement (6 patients only; 2 failed due to amputation/poor health).

between 0.107 and -0.173 for the healthy control group with a mean and standard deviation of 1.37 ± 0.15. When measuring E:I two times in a row with the VariaPulse TF3 (with a 1-minute break between the measurements), the limits of agreement were ±0.2, indicating a difference in E:I between -0.14 and 0.27 for the same healthy control group.

The limits of agreement between the two devices in the group of DAN patients with a response going from lying to standing (30:15 ratio) measured in the range of 1.05 ± 0.04 were ±0.014, indicating that 95% of the difference in the 30:15 ratio was between 0.01 and -0.017 for this group. These results indicate a good agreement between the two methods.

Discussion

Traditionally, DAN screening devices require manual data analysis and attachment of electrodes or chest belt to the patient beforehand and removal afterward, which prolongs the examination unnecessarily, resulting in increased time consumption and cost. To overcome these obstacles to regular testing, we have examined a new pocket-size device. With only a short introduction to the device, and especially the graphical and textual information on the display, the patients were able to perform the tests correctly.

We admit that only two measures of HRV (E:I and 30:15 ratio) have been tested and not the Valsalva maneuver. Ideally, all three tests should be performed in a much broader investigation in the diabetic population. The new version of the device is able to measure the Valsalva maneuver, and results will be published accordingly.

In statistical terms, we have shown that the minor time lapse between testing one apparatus and the other is of no significance. Furthermore, we have shown that the tested pocket-size device is fully interchangeable with the well-known stationary setups when used for clinical examinations, both in practical and statistical terms.

Conclusion

A pocket-size prototype device for estimating cardiac autonomic function by measuring HRV was compared to stationary equipment used for diabetic autonomic function testing in a pilot investigation with a limited number of patients in our department. A statistically significant degree of correlation and agreement between measurements using the two setups was found, suggesting that this new pocket-size device is suitable for point-of-care screening for diabetic autonomic dysfunction and may facilitate screening according to Danish and international recommendations.

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Disclosure:

Jesper Fleischer is co-founder of Medicus Engineering Ltd, Aarhus, Denmark.

References:

1. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8(5):491-8.
2. Vinik AI, Erbas T. Recognizing and treating diabetic autonomic neuropathy. Cleve Clin J Med. 2001;68(11):928-30, 932, 934-44.
3. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities. Circulation. 2000;102(11):1239-44.
4. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553-79.
5. Kataoka M, Ito C, Sasaki H, Yamane K, Kohno N. Low heart rate variability is a risk factor for sudden cardiac death in type 2 diabetes. Diabetes Res Clin Pract. 2004;64(1):51-8.
6. Kristiansen NK, Fleischer J, Jensen MS, Andersen KS, Nygaard H. Design and evaluation of a handheld impedance plethysmograph for measuring heart rate variability. Med Biol Eng Comput. 2005;43(4):516-21.
7. Bland J.M, Altman, DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-10.
8. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. Lancet 1995;346(8982):1085-7.