An automated human–machine interaction system enhances standardization, accuracy and efficiency in cardiovascular autonomic evaluation: A multicenter, open-label, paired design study

Xiaoying Fu[1#], Qunzhi Liu[2#], Qi Pan[3], Rong Peng[1], Zeshan Huang[4], Xingyuan Guo[1], Mingkai Tan[5], Qiang Li[6], Lijing Jia[7], Yanbing Li[8], Liehua Liu[8], Jian Kuang[1], Wen Wu[9], Lixin Guo[3]

[1]Department of Endocrinology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong Province, China;
[2]Department of Cardiology, Shenzhen University General Hospital, Shenzhen, Guangdong Province, China;
[3]Department of Endocrinology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China;
[4]Department of Gastroenterology, The People's Hospital of Xiangzhou, Zhuhai, Guangdong Province, China;
[5]Research & Development Department, REEM (Shenzhen) Healthcare Co., Ltd, Shenzhen, Guangdong Province, China;
[6]Department of Endocrinology, Shenzhen University General Hospital, Shenzhen, Guangdong Province, China;
[7]Department of General Practice, Shenzhen People's Hospital, Shenzhen, Guangdong Province, China;
[8]Department of Endocrinology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong Province, China;
[9]Department of Endocrinology, Guangdong Geriatrics Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong Province, China

ABSTRACT

Background and Objectives: The conventional diagnostic process for cardiovascular autonomic neuropathy (CAN) is often time-consuming and lacks standardization. The Cardiovascular Autonomic Nervous Function Multi-Parameter Evaluation System is the first intelligent device designed for CAN diagnosis, featuring wireless wearable modules and human–computer interaction. This study aims to evaluate the accuracy and efficiency of the novel device. **Methods:** A two-part, paired-design multicenter study involving a total of 200 subjects (122 with diabetes) from three centers was conducted. Cardiovascular autonomic reflex tests (CARTs) and 5-min heart rate variability (HRV) analyses were performed via the study device. Concurrent manual measurements with physician diagnoses and nonstandardized conventional methods served as controls in Part I and Part II, respectively. **Results:** In Part I, the study device diagnosed 19.3% (29/150) of the subjects with CAN, demonstrating 96.6% sensitivity and 100% specificity. There was excellent agreement with the physician's CAN diagnosis for CARTs (Cohen's kappa of 0.979, $P < 0.001$) and with the control device for HRV parameters (intraclass correlations [ICCs] > 0.9). Part II showed weak to moderate intermethod correlations with the nonstandardized conventional method (ICCs = 0.193–0.632). Repeated tests revealed high reproducibility (coefficients of variation = 3%–20%). The investigational device required only one examiner to perform a standardized assessment and saved 33 minutes compared with manual methods. **Conclusions:** The proposed system provides efficient and standardized testing with excellent accuracy and reproducibility for CAN assessment. This novel device will facilitate the evaluation of therapeutic efficacy and promote streamlined clinical workflows.

Key words: diabetes, cardiovascular autonomic neuropathy, human–machine interaction, wireless, cardiovascular autonomic reflex tests, heart rate variability

#These authors contributed equally to this work.

Address for Correspondence:
Lixin Guo, Department of Endocrinology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China.
Email: glx1218@163.com;
https://orcid.org/0000-0001-6863-1798

Wen Wu, Department of Endocrinology, Guangdong Geriatrics Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510080, Guangdong Province, China.
Email: wuwen@gdph.org.cn;
https://orcid.org/0000-0002-2144-8491

Access this article online

Website:
www.intern-med.com

DOI:
10.1515/jtim-2025-0013

INTRODUCTION

Cardiovascular autonomic neuropathy (CAN) is a common and serious complication of diabetes. [1–3] The reported prevalence of CAN in patients with diabetes varies widely, ranging from 20% to 60%, which can be attributed to the absence of standardized diagnostic tools, inconsistent diagnostic criteria and variation in study designs. [4–8] Early detection of CAN is challenging because it typically has an occult onset and is often asymptomatic in the early stages.[9] Furthermore, pathogenetically oriented therapies are limited, underscoring the importance of advancing diagnostic and screening methods.

Cardiovascular autonomic reflex tests (CARTs) have been recommended as the gold standard for the screening and diagnosis of CAN by clinical guidelines and expert consensus.[10–13] However, existing methodologies present notable limitations. In the absence of specialized equipment, the accuracy of maneuvers relies heavily on physician's inspection and the use of basic, unverified devices. Moreover, the interpretation of results often requires manual measurements and calculations, which are time-consuming, labor-intensive and prone to error.[13] Although computerized systems have been developed to address some of these issues by reducing errors in the manual reading of paper-based electrocardiograms (ECGs), they fail to offer real-time feedback on whether a subject's maneuvers comply with the standards.[14–17] Additionally, these devices lack integrated solutions for automating the workflow, restricting the widespread clinical application of CARTs. Efforts are needed to achieve truly "standardized" stimuli and streamline the clinical workflow.

To bridge these gaps, we developed the Cardiovascular Autonomic Nervous Function Multi-Parameter Evaluation System, a first-of-its-kind intelligent device for CAN diagnosis. This novel system incorporates wireless wearable modules and human–computer interaction capabilities, delivering maneuver-specific instructions and real-time feedback to ensure compliance with diagnostic standards. The aim of this study was to assess the accuracy and efficiency of this innovative device, offering insights into its potential to enhance the standardization and efficiency of the diagnostic process of CAN.

METHODS

Participants

Patients with diabetes and healthy volunteers were recruited from three research centers. Individuals who were 18 years of age or older were eligible. Participants were excluded if they had proliferative retinopathy, retinal detachment, fundus hemorrhage, glaucoma, poorly controlled blood pressure (defined as a systolic blood pressure not less than 160 mmHg or a diastolic blood pressure of 100 mmHg or higher), documented arrhythmias except occasional premature beats, heart failure, pregnancy, acute stress or acute illnesses. Those who had experienced acute coronary syndrome within 3 months or were taking medication known to affect heart rate were also excluded.[13]

Study design

This was a multicenter, open-label, pair-designed study comparing a novel medical device with reference methods for assessing cardiovascular autonomic function. Given that both maneuvers and the data analysis process can influence assessment outcomes, the study was divided into two parts to identify their respective impacts. Part I of the study compared the diagnostic outcomes of the study device with physician diagnosis, whereas Part II assessed the overall systemic differences between the standardized, automated processes of the study device and the nonstandardized, conventional manual methods. The details of the methods used for the CARTs in both Part I and Part II are illustrated in Supplementary Table S1.

Part I was conducted as a component of the CARTS study registered with the identifier NCT06447896. Each participant underwent simultaneous diagnostic assessments using both the study device and the reference method, with the maneuvers guided and standardized through real-time feedback from the device under study. The subjects performed a series of maneuvers under voice and visual guidance from the investigational device, including a 5-min supine rest and CARTs maneuvers (lying to standing, deep breathing, the Valsalva maneuver, and sustained hand grip). Concurrently, a physician recorded the ECG using the electrocardiograph model ECG-5503B (Sanrui, Guangzhou, China) during the same CARTs sessions. Upon completion, the device being investigated automatically calculated the assessment results, whereas the reference method relied on the physician's manual interpretation of the data. Comparisons were made between the study device's diagnoses and those of the physician. Additionally, the 5-min resting ECGs were exported and processed using algorithms from the ECG Workstation Model i12 plus (Rencare, Shenzhen, China) to calculate the heart rate variability (HRV) parameters, which served as a reference for comparison.

Part II employed a randomized, crossover design to evaluate the overall systemic differences between the device being investigated and the traditional method. The participants were randomized into two groups to minimize the potential influence of testing order on the results. One group first underwent automatic evaluation with the proposed system, followed by assessment with the conventional method,

whereas the other group completed the procedures in reverse order. In this part, the study device independently guided participants' maneuvers with real-time feedback, automatically processed the data, and generated diagnostic results. In contrast, the conventional method involved maneuvers performed without quality control guidance, ECG measurements taken manually, and diagnostic results determined by a physician. Specifically, conventional CARTs were performed by two trained physicians using common equipment, including a syringe connected to a manometer, a dynamometer, a double-headed stethoscope, a mercury sphygmomanometer, and an ECG machine. ECG data and blood pressure values obtained *via* the conventional method were manually recorded on paper. After the examinations, two physicians, blinded to the results, reviewed the ECG traces and blood pressure values recorded in both Part I and Part II, calculated the CARTs indices, and rendered a diagnosis.

The evaluation of the blood pressure measurement module was verified according to the international standard ISO 81060-2: 2018 (Supplementary Table S2). To assess reproducibility, we conducted a separate exploratory study in which the tests described in Part I were performed four times within three days on an additional six subjects.

This study was approved by the ethics committees of all medical institutions involved in the research and adheres to the principles of the Declaration of Helsinki. All patients signed written informed consent forms.

Outcome measurements

The primary outcome of the study was the agreement between the two methods in diagnosing CAN in Part I, as assessed by Cohen's kappa. The secondary outcomes include the following: the intermethod agreement and correlation of the CARTs indices; the correlation of the HRV parameters between the two devices; the reproducibility of the CARTs indices; and the time required to complete the CARTs.

Prior to the examinations, the participants were instructed to abstain from vigorous physical activity for at least 24 hours, and to refrain from smoking, alcohol, coffee, and tea for 2 hours. Additionally, they were required to either fast or consume a light meal for at least 2 hours prior to the examinations.[10,18] During the tests, the participants were instructed to keep quiet and stay awake.

The CARTs were conducted with four standardized maneuvers, which generated five indices. During the tests, heart rate was continuously monitored, while blood pressure was measured at 1-min intervals. The indices included the ratio of the longest R-R interval at the 30th heartbeat to the shortest interval at the 15th heartbeat upon standing (R30: 15), the ratio of the longest R-R interval during relaxation to the shortest R-R interval during the Valsalva maneuver (VR), the difference between the maximum heart rate during inhalation and the minimum heart rate during exhalation during deep breathing paced at 6 breaths per minute (I-E), the difference between the supine systolic blood pressure and the minimum systolic blood pressure upon standing (systolic blood pressure changes from lying-to-standing, LS-SBP), and the difference between the maximum diastolic blood pressure during sustained handgrip and the baseline diastolic blood pressure (SHG-DBP).

The battery of tests enabled the classification of participants into normal, early, definite, severe, and atypical categories.[19] CAN was defined as the presence of at least two abnormal heart rate tests, where definite and severe involvement indicated CAN, and all other cases were classified as non-CAN. The cutoffs proposed by Ewing were used to define abnormal results.[20] The maneuvers and calculations of indices were performed according to established protocols.[13,21–23]

HRV was assessed using the ECG recorded during 5 minutes of supine rest, incorporating a range of indices. These indices encompassed the standard deviation of the normal-to-normal (NN) intervals (SDNN), the root mean square of the successive differences of NN intervals (RMSSD), the number of pairs of NN intervals that differ by more than 50 milliseconds (NN50), the proportion of NN50 divided by the total number of NN intervals (pNN50), the triangular index of HRV (TI), the mean of the RR intervals (mean RR), the deceleration capacity of heart rate (DC), the deceleration capacity series of heart rate (DCs), the very low frequency component (VLF), the low frequency component (LF), the high frequency component (HF), the ratio of LF to HF (LF/HF), and the total power (TP) of the HRV spectrum.

Study device

The Cardiovascular Autonomic Nervous Function Multi-Parameter Evaluation System Model R6000, manufactured by REEM (Shenzhen) Healthcare Co., Ltd. (Shenzhen, China), is a novel device developed for the diagnosis and screening of CAN. The device features a wireless respiratory flow sensor and a digital dynamometer (Supplementary Figure S1), which transmit parameters during maneuvers, including deep breathing, the Valsalva maneuver, and sustained hand grip, thereby facilitating human–machine interaction.

During the examination, a wireless ECG patch continuously collects ECG signals, whereas the blood pressure module

intermittently measures blood pressure at prespecified intervals. The device can automatically mark key time points associated with maneuvers, identify and process ECG artifacts, and generate a diagnosis upon completion of the examination. Additionally, the software provides HRV analysis for different stages, such as supine rest and the Valsalva maneuver.

As standardized stimuli are essential for achieving reliable results, the design philosophy of the novel device emphasized ensuring accurate performance during the assessment. During the Valsalva maneuver, participants are required to maintain an intraoral pressure of 40 mmHg for 15 seconds. During this period, the examiner must observe the participants closely to ensure the correctness of the maneuver.[13] Controlling the breathing rhythm in the deep breathing test also presents a challenge, as this test requires a 1: 1 inhalation-to-expiration ratio, which differs from that in the normal physiological state. Therefore, an interactive design composed of wireless sensors, verbal instructions, and animations was implemented to promptly recognize substandard maneuvers, provide reminders, and terminate nonstandard stimuli. Specifically, a respiratory flow sensor was designed to transmit real-time data to the screen, displaying the intraoral pressure during the Valsalva maneuver and the respiratory curve during the deep breathing test. This represents one of the features that provides objective indicators during the tests, thereby assisting in the standardization of the maneuvers.

Statistical analysis

The data were analyzed *via* R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were computed for continuous variables (means ± standard deviations) and categorical variables (frequency and percentage). Paired data were analyzed using the paired *t* test or Wilcoxon signed-rank test for continuous variables and the McNemar test for categorical variables. Agreement measurements included Cohen's kappa coefficient for categorical scales and the intraclass correlation coefficient (ICC) for continuous variables such as five indices in CARTs and the HRV parameters. The sensitivity and specificity were calculated to evaluate the diagnostic performance. The significance level was set at 0.05 (two-tailed). The coefficients of variation (CVs) were calculated to evaluate reproducibility.

For the primary outcome, the agreement of CAN diagnoses between the two methods in Part I was assessed by Cohen's kappa, which is commonly used for categorical data, and a target agreement level of 75% was set. The sample size was calculated using PASS 15 software with a significance level α of 0.05 and a power of 0.8. On the basis of a pilot study indicating a 16% positive rate, the minimum sample size was 146 participants, adjusting for a 20% dropout rate.

Table 1: Participant characteristics

	Part I (*n* = 150)	Part II (*n* = 44)
Age, years (Mean ± SD)	50.25 ± 13.65	34.86 ± 8.80
Sex, *n* (%)		
Male	84 (56.0%)	21 (47.7%)
Female	66 (44.0%)	23 (52.3%)
Waist circumference, cm (Mean ± SD)	84.41 ± 25.37	80.98 ± 10.22
BMI, kg/m^2 (Mean ± SD)	25.18 ± 4.52	23.40 ± 3.68
Diabetes type, *n* (%)		
T1D	14 (9.3%)	0
T2D	122 (81.3%)	0
Unclassified diabetes	2 (1.4%)	0
Nondiabetes	12 (8.0%)	44 (100%)

SD, standard deviation; BMI, body mass index; T1D, type 1 diabetes; T2D, type 2 diabetes.

RESULTS

Baseline characteristics of the study participants

In the first part of the study, 151 subjects were screened, 150 of whom completed the CARTs and a 5-min HRV examination, while one subject was excluded due to retinal hemorrhage. The average age of the subjects was 50.25 years, 56% were male, and 81.3% had been diagnosed with type 2 diabetes. In the second part, 44 healthy subjects were included, with an average age of 34.86 years, and 47.7% were male. The clinical characteristics of all the subjects are summarized in Table 1.

Part I

The investigational device recorded parameters related to the maneuvers performed during the CARTs. The actual recorded time for the Valsalva maneuver was 15 seconds, and deep breathing was paced at 6 breaths per min, adhering to the protocol. The average grip strength recorded was 7.86 ± 1.76 kgf, closely matching the standard value of 7.88 ± 1.97 kgf, which corresponds to 30% of the subjects' maximum grip strength. Additionally, the intraoral pressure measured during the Valsalva maneuver was 38.30 ± 3.04 mmHg, which aligns with the recommended standard of 40 mmHg.

The agreement between the investigational device and the physician in measuring the R30: 15, VR, and I-E was high, with ICCs of 0.969 (95% confidence interval [CI]: 0.957–0.977), 0.991 (95% CI: 0.972–0.996), and 0.995 (95% CI: 0.991–0.997), respectively. All heart rate indices measured by the study device were strongly correlated with those

Table 2: Diagnosis of cardiovascular autonomic neuropathy

Study device	Physician's diagnosis					
	Normal	Early	Definitive	Severe	Atypical	Overall
Normal	39	0	0	0	0	39
Early	0	43	1	0	0	44
Definite	0	0	16	0	0	16
Severe	0	0	0	13	0	13
Atypical	0	2	0	0	36	38
Overall	39	45	17	13	36	150

The classification criteria were defined according to Ewing and colleagues (1985).

calculated by the physicians, with correlation coefficients (r) above 0.9. Bland–Altman plots are presented to further characterize the consistency between methods (Figure 1).

The five-category classification of CAN showed an overall agreement of 98% between the study device and the physician's diagnosis, with a weighted kappa value of 0.972 ($P < 0.001$). For CAN defined by the presence of at least two abnormal heart rate tests, Cohen's kappa for the diagnosis was 0.979 ($P < 0.001$). Using the physician's diagnosis as the "gold standard", the proposed system demonstrated a sensitivity of 96.6% and a specificity of 100% for CAN diagnosis. Table 2 compares the diagnostic outcomes of the study device with those of the physician's diagnosis.

All the HRV indices generated by the study device were strongly correlated with those calculated by the reference device, with excellent agreement (ICC > 0.9) (Supplementary Table S3).

Part II

The indices measured by the study device demonstrated the following ICCs in correlation with the reference method: 0.598 for R30: 15 ($P < 0.001$), 0.632 for VR ($P < 0.001$), and 0.466 for I-E ($P = 0.0065$). The LS-SBP had an ICC of 0.193 ($P = 0.0714$), whereas the SHG-DBP had an ICC of 0.368 ($P = 0.0078$). Moderate correlations were observed between the research device and the conventional method for R30: 15, VR, and I-E ($r = 0.572$–0.691). In contrast, LS-SBP and SHG-DBP exhibited weak correlations ($r = 0.268$–0.379). A comparison of two sets of measurements is illustrated using Bland–Altman plots (Figure 2).

Reproducibility

The reproducibility study involved two healthy female and four healthy male subjects with an average age of 24 years. The reproducibility of the indices R30: 15, VR, and I-E were high. Their CVs obtained from both the device and reference methods are presented in Table 3. Notably,

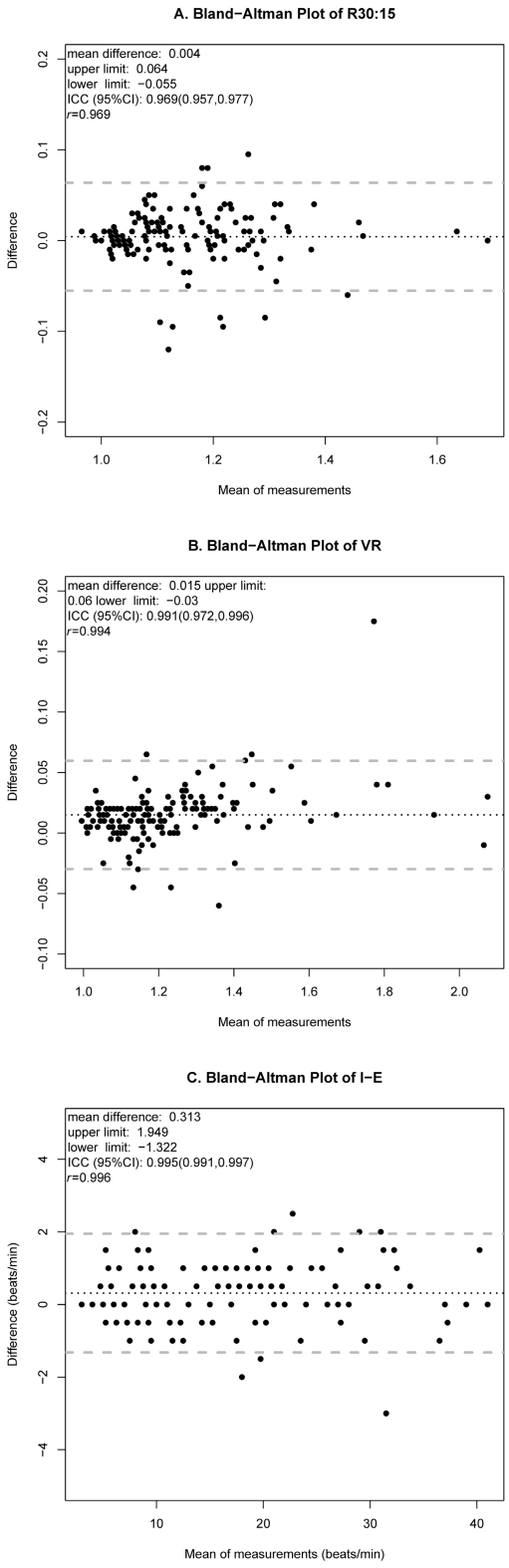

Figure 1: Bland–Altman plots of each heart rate index in Part I. The plots show differences in the heart rate indices measured with the study device and the reference method in Part I, with the mean difference (dotted black line) and the limits of agreement (dashed gray lines). (A) R30: 15, heart rate response to standing; (B) VR, heart rate response to the Valsalva maneuver; (C) I-E, heart rate response to deep breathing.

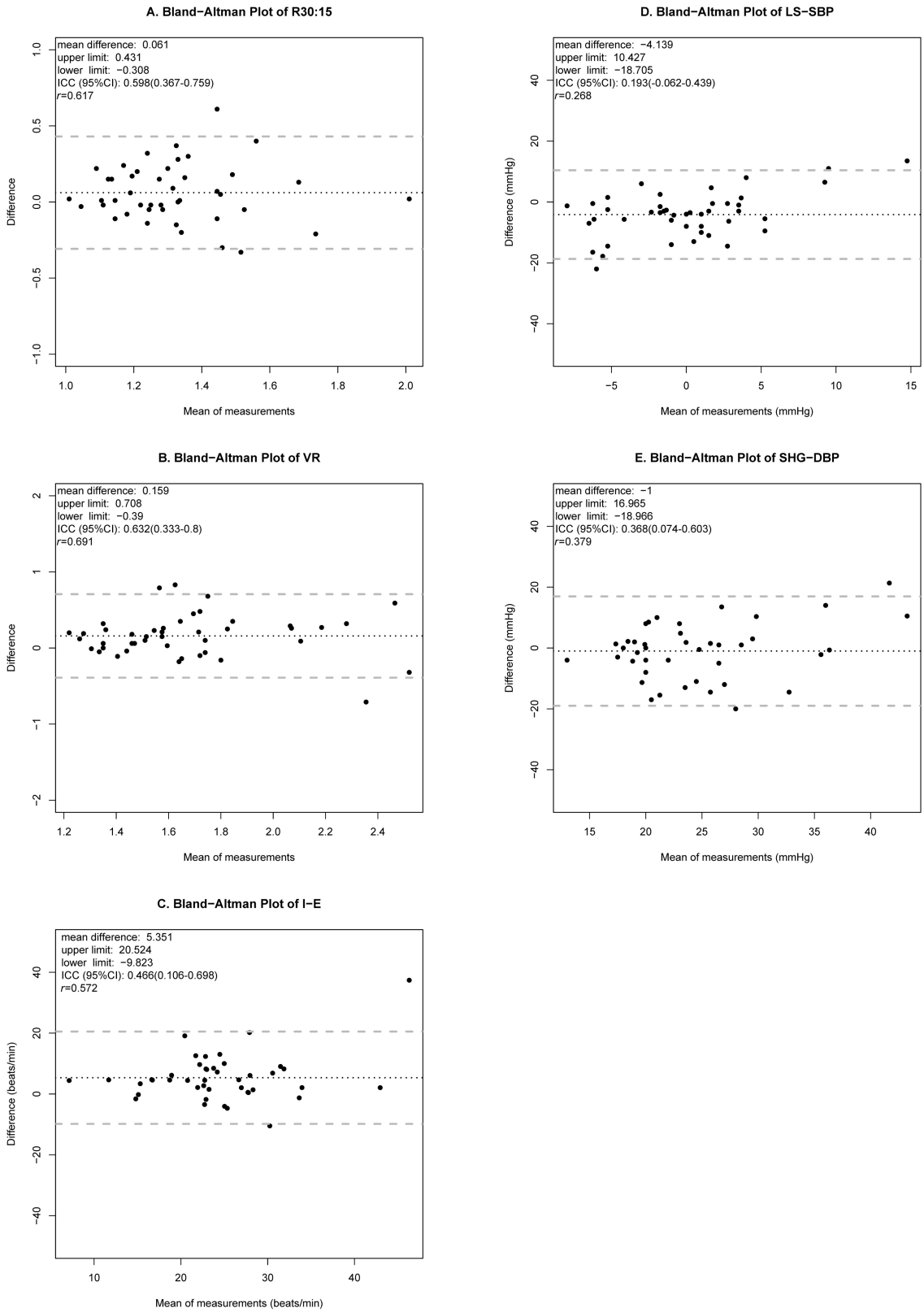

Figure 2: Bland–Altman plots of each index in Part II. The plots show differences in the indices from the cardiovascular autonomic reflex tests measured with the study device and the reference method in Part II, with the mean difference (dotted black line) and the limits of agreement (dashed gray lines). (A-C) R30:15, VR and I-E stand for heart rate response to standing, the Valsalva maneuver and deep breathing, respectively. (D) LS-SBP, change in systolic blood pressure during lying-to-standing; (E) SHG-DBP, diastolic blood pressure changes during sustained handgrip.

Table 3: Reproducibility of heart rate tests

	CV of the study device		CV of manual reference method*		*P*
Indices	Mean ± SD	Range	Mean ± SD	Range	
R30:15	11% ± 6%	3%–19%	12% ± 4%	6%–15%	0.8856
VR	9% ± 3%	3%–11%	9% ± 3%	4%–12%	0.9168
I-E	14% ± 6%	4%–20%	23% ± 8%	11%–35%	0.0449

*, The reference method is described in Part I. CV, coefficient of variation; SD, standard deviation; R30:15, heart rate response to standing; VR, heart rate response to the Valsalva maneuver; I-E, heart rate response to deep breathing.

the reproducibility of the I-E measured manually was significantly greater than that of the device measurements (CV: 14% *vs.* 23%, $P = 0.0449$).

Efficiency

Using the study device, a single examiner was able to complete a battery of CARTs within an average of 34.8 minutes, and the study device automatically presented the final diagnosis immediately upon completion. In comparison, the reference methods outlined in Part I and Part II required two examiners and took 67.8 minutes for ECG reading and manual calculations to make a diagnosis.

DISCUSSION

This study demonstrated that the investigational device provides a reliable and efficient method for assessing cardiovascular autonomic function. In particular, CAN diagnosis by the study device has high sensitivity, specificity and reproducibility.

In Part I, the physician's diagnosis was used as a reference. The results showed that the study device can accurately measure and calculate heart rate indices of CARTs (Cohen's kappa of 0.979, $P < 0.001$) and has a high degree of accuracy in diagnosing CAN (96.6% sensitivity and 100% specificity). Additionally, the HRV analysis algorithm of the investigational device has been proven to be highly consistent with the control device approved by the Center of Medical Device Evaluation of China's National Medical Products Administration (intraclass correlation > 0.9).

In Part II, maneuvers were strictly standardized by the device under investigation, whereas the conventional method utilized basic devices in clinical practice without monitoring functions. Forty-four subjects underwent CARTs *via* both methods in a randomized order. The correlations (*r*: 0.268–0.691) and consistencies (ICC: 0.193–0.632) between the indices measured by the study device and the control method were found to be weaker than those observed in Part I. This discrepancy can be attributed to several reasons. First, the standardization of maneuvers in Part II was not as stringent as that in Part I, potentially leading to erroneous indices due to substandard stimuli. Second, physiological variations could play a significant role, as the data were not recorded synchronously between the two methods. Among the five indices, the poorest correlation was found for the two blood pressure indicators ($r = 0.268$ and 0.379). The difference in the time taken for cuff inflation and blood pressure readings could further explain the greater discrepancy observed in these indices.

On the basis of the combined findings from both parts of the study, it is evident that the measurement consistency between the study device and the conventional method was inadequate owing to differences in the standardization of maneuvers. However, once this factor was controlled, measurements of the investigational device strongly agreed with the physician's diagnosis, highlighting the significant impacts of maneuver standardization on examination outcomes. Overall, these findings emphasize the critical role of real-time monitoring and standardization in ensuring the accuracy of CARTs.

The reproducibility data from published articles indicate that in normal subjects, the CVs are 16.0%–16.6% for I-E, 8.0%–15.4% for the Valsalva ratio, and 5.3%–9.0% for R30: 15.[24,25] In our research, the CVs for heart rate indices measured by the study device ranged from 3%–20%, suggesting high reproducibility. In contrast, the control method showed poorer reproducibility, with CVs ranging from 4%–35%. Notably, the CV for the I-E measured by the device under investigation was significantly greater than that of the control (14% *vs.* 23%, $P = 0.0449$). Since maneuvers in the CARTs were identically standardized in both groups, the observed differences may be attributed to variations in the timing of marking the switch between inhalation and exhalation, as well as the method used for measuring RR intervals of ECG. Although data on the reproducibility of blood pressure measurements were not collected in our study, previous studies reported that blood pressure tests, especially the sustained handgrip test, have relatively poor reproducibility.[13] The proposed system standardizes procedures by providing real-time feedback on grip force, ensuring consistent effort within the target range across trials. Additionally, the device minimizes observer-related variability by automating blood pressure measurements at predefined intervals, reducing potential timing discrepancies. These improvements might contribute to more reliable and reproducible assessments of sympathetic function and should be explored in future studies.

Given that our device enables real-time monitoring of dynamic grip force changes, it offers a potential avenue for further investigation into the factors contributing to this variability. We have clarified this point in the discussion section.

The study device has shown superiority in terms of time efficiency and reduced personnel requirements. A single examiner using R6000 was able to complete the tests in an average of 34.8 minutes, which is much shorter than the 67.8 minutes required by the conventional method, which necessitated two examiners. In contrast to the study device, which automatically presented the final diagnosis immediately upon completion, the reference method required an extra 33 minutes for ECG reading and manual calculations. This finding emphasizes the potential of the tested device to streamline the testing process while requiring fewer personnel.

Efforts have been made to develop an automated system for CARTs and HRV in the last century. O'Brien *et al.*[16] described an early automated system using a microcomputer, a cardiac ratemeter and an interface unit. While this system demonstrated the feasibility of automated R-R interval measurement and HRV analysis, it was limited in its scope, focusing primarily on hardware integration without addressing a systematic diagnostic solution. Gerritsen *et al.*[17] introduced a PC-based system that uses a hardware QRS detector and an arterial pressure monitoring device. Their system applied offline data processing and verification through visual inspection. In contrast, our device offers comprehensive automation, which integrates standardized real-time feedback for maneuver execution and simultaneous data processing into a unified framework.

One of the reasons that CAN remains underdiagnosed is the limited availability of trained experts for cardiovascular tests.[13,26] The wireless sensors and interactive design of the study device enable continuous monitoring during the tests and provide real-time feedback and instant instructions to correct the maneuvers. By utilizing this device, medical staff with basic training can conduct highly standardized tests, thereby promoting early and wider screening of CAN in high-risk populations. This is significant for increasing medical accessibility and optimizing resource allocation. Currently, effective therapies for CAN are limited. Challenges in drug development arise in part from the time-consuming examination process and the absence of standardized tools. The enhanced efficiency offered by the study device not only streamlines the clinical workflow but also facilitates quicker and more accurate evaluation of therapeutic efficacy.

Currently, research on automated CARTs devices has not systematically explored their impact on diagnostic efficacy or clinical resource optimization. Our study is among the first to provide practical evidence of how such a device can improve diagnostic efficiency and facilitate the early screening and management of CAN. This not only introduces new possibilities for clinical application but also provides a valuable reference for future research in this field.

This research has several limitations. First, the study focused mainly on a specific population—patients with type 2 diabetes and healthy subjects. However, CAN is also common in other conditions, such as panautonomic failure, Parkinson's disease and systemic amyloidosis. As a result, the findings are specific to the study population included in this study, and future research is needed to verify the accuracy and reliability of the device in a broader range of populations. Second, Part II of the study included only healthy subjects, necessitating further research in patients with pathological conditions. Third, the reproducibility study did not involve blood pressure indices. One reason why the sustained handgrip test has not been considered an essential part of the cardiovascular test battery in recent years is its limited reproducibility.[27,28] The real-time monitoring of dynamic grip force changes offers a potential avenue for further investigation into the factors contributing to this variability. Furthermore, whether the reproducibility of blood pressure tests can be improved by standardizing maneuvers and ensuring consistency across trials warrants further investigation.

CONCLUSION

In conclusion, this study introduces a novel diagnostic tool, the Cardiovascular Autonomic Nervous Function Multi-Parameter Evaluation System, Model R6000, for CAN evaluation. The device shows excellent accuracy and reproducibility for CAN assessment. The integration of wearable monitoring modules with wireless transmission significantly enhances efficiency by standardizing maneuvers and eliminating the need for time-consuming manual measurements. This novel device will facilitate the evaluation of therapeutic efficacy and promote streamlined clinical workflows.

Supplementary Information

Supplementary materials are only available at the official site of the journal (www.intern-med.com).

Acknowledgements

We would like to thank REEM (Shenzhen) Healthcare Co., Ltd., for providing the study device free of charge.

Author Contributions

Fu X and Kuang J designed the study. Fu X, Liu Q, Pan Q and Wu W developed the methodology. Fu X conducted

the literature research and drafted the initial version. Liu Q, Pan Q, Huang Z, Liu L and Peng R handled data curation, analysis, and validation. Jia L and Wu W provided supervision. Tan M developed and maintained the software. Guo X managed project administration. Li Y and Wu W was responsible for resources. Li Q, Wu W, Guo L and Kuang J reviewed and edited the manuscript. All authors contributed and approved the final version for submission.

Source of Funding

This work was supported by the National Key R&D Program of China (2018YFC1314100) and the Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences) Special Project-Applied Basic to Clinical Translational Research Fund (Y012015335).

Ethical Approval

This research was approved by the ethics committees of Guangdong Provincial People's Hospital, Shenzhen University General Hospital and Shenzhen People's Hospital.

Informed Consent

All participants in this study provided written informed consent.

Conflict of Interest

Guo X was working at Guangdong Provincial People's Hospital during the research and subsequently joined REEM (Shenzhen) Healthcare Co., Ltd., the manufacturer of the study device. This employment change occurred after the data collection and analysis were completed. The authors declare that this transition has not influenced the objectivity of the research. Tan M is an employee of REEM (Shenzhen) Healthcare Co., Ltd. All the other authors declare that they have no competing interests.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

Data available upon reasonable request to the corresponding author.

REFERENCES

1. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care 2003;26:1895–1901.
2. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, *et al.* Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004;27:1954–1961.
3. Lee KH, Jang HJ, Kim YH, Lee EJ, Choe YS, Choi Y, *et al.* Prognostic value of cardiac autonomic neuropathy independent and incremental to perfusion defects in patients with diabetes and suspected coronary artery disease. Am J Cardiol 2003;92:1458–1461.
4. Valensi P, Pariès J, Attali JR; French Group for Research and Study of Diabetic Neuropathy. Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications--the French multicenter study. Metabolism 2003;52:815–820.
5. Ziegler D, Gries FA, Mühlen H, Rathmann W, Spüler M, Lessmann F. Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes centers. The Diacan Multicenter Study Group. Diabetes Metab 1993;19:143–151.
6. Pan Q, Li Q, Deng W, Zhao D, Qi L, Huang W, *et al.* Prevalence and Diagnosis of Diabetic Cardiovascular Autonomic Neuropathy in Beijing, China: A Retrospective Multicenter Clinical Study. Front Neurosci 2019;13:1144.
7. Chung JO, Cho DH, Chung DJ, Chung MY. Physiological serum bilirubin concentrations are inversely associated with the prevalence of cardiovascular autonomic neuropathy in patients with Type 2 diabetes. Diabet Med 2014;31:185–191.
8. Tang ZH, Zeng F, Ye K, Yu X, Zhou L. The analysis of a reference value for baroreflex sensitivity and cardiovascular autonomic neuropathy prevalence in a Chinese population. Eur J Med Res 2014;19:8.
9. American Diabetes Association Professional Practice Committee. Introduction and Methodology: Standards of Care in Diabetes-2024. Diabetes Care 2024;47:S1–S4.
10. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, *et al.* Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011;27:639–653.
11. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, *et al.* Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017;40:136–154.
12. Vinik AI, Camacho PM, Davidson JA, Handelsman Y, Lando HM, Leddy AL, *et al.* American association of clinical endocrinologists and american college of endocrinology position statement on testing for autonomic and somatic nerve dysfunction. Endocr Pract 2017;23:1472–1478.
13. Spallone V, Bellavere F, Scionti L, Maule S, Quadri R, Bax G, *et al.* Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis 2011;21:69–78.
14. Ejskjaer N, Fleischer J, Fleischer J, Jacobsen PE, Poulsen PL, Nygaard H. A Pocket-size Device to Detect Autonomic Neuropathy. J Diabetes Sci Technol 2008;2:692–696.
15. Park SB, Lee BC, Jeong KS. Standardized tests of heart rate variability for autonomic function tests in healthy Koreans. Int J Neurosci 2007;117:1707–1717.
16. O'Brien IA, Corrall RJ. Cardiovascular autonomic function testing: an automated method for measuring heart rate variation. Diabet Med 1985;2:143–144.
17. Gerritsen J, TenVoorde BJ, Dekker JM, Kingma R, Kostense PJ, Bouter LM, *et al.* Measures of cardiovascular autonomic nervous function: agreement, reproducibility, and reference values in middle age and elderly subjects. Diabetologia 2003;46:330–338.
18. Andersen ST, Witte DR, Fleischer J, Andersen H, Lauritzen T, Jørgensen ME, *et al.* Risk Factors for the Presence and Progression of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes: ADDITION-Denmark. Diabetes Care 2018;41:2586–2594.
19. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care

1985;8:491–498.
20. Charles M, Fleischer J, Witte DR, Ejskjaer N, Borch-Johnsen K, Lauritzen T, *et al*. Impact of early detection and treatment of diabetes on the 6-year prevalence of cardiac autonomic neuropathy in people with screen-detected diabetes: ADDITION-Denmark, a cluster-randomised study. Diabetologia 2013;56:101–108.
21. Wieling W, Karemaker JM. Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. 5 ed. Mathias CJ, Bannister SR, editors: Oxford University Press; 01 Jul 2013.
22. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. Muscle Nerve 1997;20:1561–1568.
23. Gehrking JA, Hines SM, Benrud-Larson LM, Opher-Gehrking TL, Low PA. What is the minimum duration of head-up tilt necessary to detect orthostatic hypotension?Clin Auton Res 2005;15:71–75.
24. Lawrence GP, Home PD, Murray A. Autonomic function testing in diabetic subjects using sequential measurements. Diabet Med 1992;9:799–805.
25. O'Brien IA, O'Hare P, Corrall RJ. Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function. Br Heart J 1986;55:348–354.
26. Eleftheriadou A, Spallone V, Tahrani AA, Alam U. Cardiovascular autonomic neuropathy in diabetes: an update with a focus on management. Diabetologia 2024;67:2611–2625.
27. Ziegler D, Laux G, Dannehl K, Spüler M, Mühlen H, Mayer P, *et al*. Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. Diabet Med 1992;9:166–175.
28. Cheshire WP, Freeman R, Gibbons CH, Cortelli P, Wenning GK, Hilz MJ, *et al*. Electrodiagnostic assessment of the autonomic nervous system: A consensus statement endorsed by the American Autonomic Society, American Academy of Neurology, and the International Federation of Clinical Neurophysiology. Clin Neurophysiol 2021;132:666–682.

How to cite this article: Fu X, Liu Q, Pan Q, Peng R, Huang Z, Guo X, *et al*. An automated human–machine interaction system enhances standardization, accuracy and efficiency in cardiovascular autonomic evaluation: A multicenter, open-label, paired design study. J Transl Intern Med 2025; 13: 170-179.