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Screening for Diabetic Cardiac Autonomic Neuropathy Using a New Handheld Device

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Abstract

Background:

Cardiac autonomic neuropathy (CAN) is a serious complication of longstanding diabetes and is associated with an increased morbidity and reduced quality of life in patients with diabetes. The present study evaluated the prevalence of CAN diagnosed by reduced heart rate variability (HRV) using a newly developed device in a large, unselected, hospital-based population of patients with diabetes.

Methods:

The study examined 323 patients consisting of 206 type 1 diabetes (T1DM) patients and 117 type 2 diabetes (T2DM) patients. The new handheld prototype Vagus™ was used to screen for CAN. Three different standardized cardiac reflex tests were performed to calculate HRV: 30:15 ratio, E:I ratio, and the Valsalva maneuver. An abnormal HRV in one test is indicative of early CAN, and if two or more tests show abnormal HRV, the diagnosis of CAN is established.

Results:

In total, 86% of examined patients completed all three tests. Each test was completed by more than 90% of the patients. The prevalence of established CAN was 23%, whereas 33% of the patients had early signs of CAN. The prevalence was higher in T2DM patients (27.8%) than in T1DM patients (20.6 %), $p = .02$. Patients with CAN were older and had a longer duration of diabetes, higher systolic blood pressure, more nephropathy and retinopathy, and a higher vibration threshold.

Conclusions:

Cardiac autonomic neuropathy is frequent in both T2DM and T1DM patients, especially in those with other late diabetes complications. Screening for CAN with the new device is feasible.

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Abbreviations: (ADA) American Diabetes Association, (BMI) body mass index, (CAN) cardiac autonomic neuropathy, (HbA1c) hemoglobin A1c, (HRV) heart rate variability, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

Keywords: cardiovascular autonomic neuropathy, cardiovascular reflex tests, diabetes mellitus, diagnostic tests, heart rate variability

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Introduction

Cardiac autonomic neuropathy (CAN) is a serious complication of longstanding diabetes, resulting in abnormalities in heart rate control.[1] Cardiac autonomic neuropathy increases morbidity and reduces quality of life and activities of daily living in patients with diabetes.[1,2] Studies have found an increased mortality rate for diabetic CAN patients of up to five times higher than for individuals without cardiovascular autonomic involvement.[1–5] Reduced heart rate variability (HRV) is the earliest indicator of CAN[3,6,7] and is associated with increased risk of coronary heart disease and death.[1–3,8]

Currently, no specific therapeutic strategies can be recommended for established CAN.[1,9] However, intensive glycemic control has been shown to prevent the onset and progression of CAN.[1,3,10,11] The response to improved glycemic control is dependent on the degree of CAN in the patient.[1] Reversibility of early CAN has been demonstrated in type 1 diabetes patients as early as 1 year after initiation of strict glycemic control.[1] It seems relevant to screen for CAN in diabetes patients since early intervention can improve development and progression of CAN.

The diagnosis of CAN is divided into two categories: a clinical diagnosis based on clinical signs or symptoms of CAN or a subclinical diagnosis established by simple bedside reflex tests based on HRV.[12,13] Testing for CAN is, however, currently time-consuming and costly due to the technical setups available, and therefore the examination may not be offered regularly.[14]

Furthermore, the reported prevalence of CAN varies depending on the clinical setting, type and number of tests performed, different diagnostic methods applied, and selection criteria for patients.[1,3,7] Fifteen studies using different end points have reported prevalence estimates ranging from 1% to 90%.[3,9]

The present study was therefore undertaken to evaluate the prevalence of CAN diagnosed by reduced HRV measured by a new handheld device in a large, unselected hospital-based cohort of patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Methods

Patients

All patients attending the outpatient clinic at Steno Diabetes Center (a tertiary referral center) scheduled for a yearly status visit from December 1, 2009, to February 28, 2010, were invited to participate in the study. Inclusion criteria were age above 18 years and T1DM or T2DM. As shown in **Figure 1**, a total of 901 patients fulfilled the inclusion criteria and were invited by regular mail to participate in the study at their next scheduled visit. Due to time restriction of either the patient or the investigator, 578 patients were not examined. Eleven patients were not included because of immobility, difficulty in holding the device, pacemaker (not implantable cardioverter defibrillator), arterial fibrillation, Parkinson's disease, or severe dementia. No additional selection criteria were applied. At their next scheduled visit to the clinic, 323 (36%) of the invited patients were approached and investigated, consisting of 206 T1DM patients and 117 T2DM patients. Patients who participated in the study did not differ significantly from nonparticipants with respect to sex, duration of diabetes, hemoglobin A1c (HbA1c), or complication status, but nonparticipants were, on average, four years younger. All patients gave their informed consent. The study was conducted in accordance with the Helsinki Declaration and approved by the research ethics committee.

Research Methods

All patients were examined by a single investigator (Elisabeth Gulichsen). Patients did not consume caffeine-containing liquids 30 min prior to examination, and no restrictions in intake of medication were applied. Baseline data were collected from the clinical status visit performed on the same day as the CAN examination.

The CAN examination started with the patient resting in lying position for 5 min. A 12-lead ECG (electrocardiogram) was performed with a standard device. Thereafter, the handheld prototype Vagus™ from Medicus Engineering (Århus, Denmark) was used to screen for CAN. The device is based on two-electrode ECG recordings obtained by two handheld electrodes and is powered by batteries.[14] Heart rate variability is calculated automatically and shown in the display for each single test. The patient held the device as shown in **Figure 2** and was instructed to follow the graphical elements on the display.

To evaluate CAN, the device measures resting heart rate and performs three different standardized cardiac reflex tests to calculate HRV: 30:15 ratio, E:I ratio, and the Valsalva maneuver. These three tests reflect the overall condition of the parasympathetic nerve fibers.

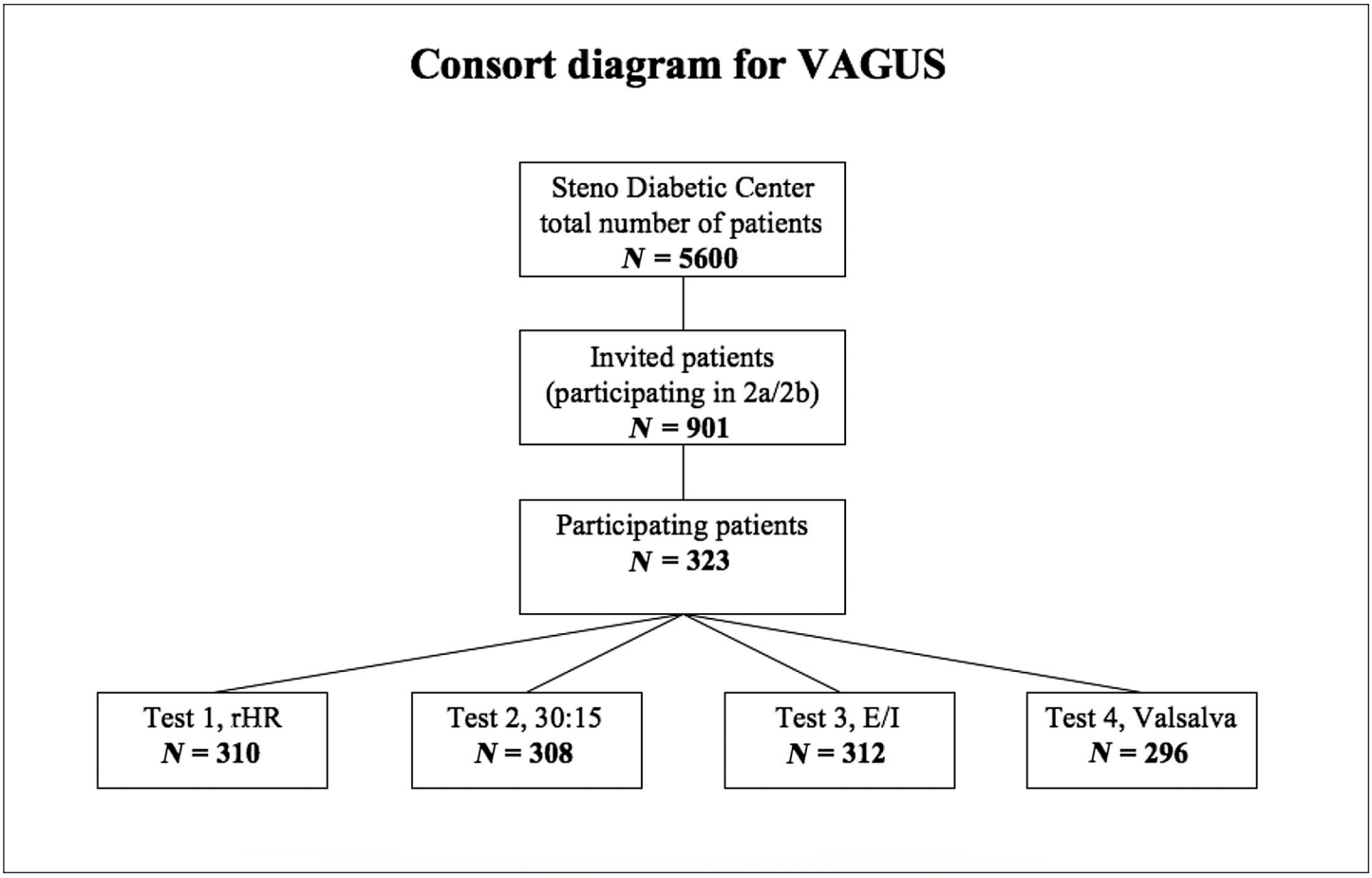

Figure 1. The consort diagram for this study. At Steno Diabetes Center, 901 (16%) patients fulfilled the inclusion criteria and were invited by mail to participate in the study at their next scheduled visit. Out of the invited amount, 323 patients (36%) were included in the study. The four individual tests in the examination were each completed by more than 90% of the patients. rHR, resting heart rate.

Figure 2. Picture of handheld prototype Vagus.

The cardiac reflex tests were performed by the device as indicated in **Table 1**. The graphics on the display instructed the patient on how to perform each test and helped the patient keep rhythm during the breathing tests. The whole examination lasted 15–20 min per patient, and no time for preparation was needed. Results were recorded in a manual scheme for each patient, entered into the computer, and double-checked.

Interpretation of Results

An abnormal result for each test is defined as HRV below that of the fifth percentile of a normal age-matched population.[3,16] The normal ranges for the ratios are age dependent,[17,18] but the variation in range is small, and certain approaches can be used. Boulton and colleagues[15] have presented some limits for tests to be considered as abnormal; these values are listed in **Table 1** and applied in the present study. An abnormal HRV in one test (not resting heart rate) is indicative of early signs of CAN, here referred to as borderline CAN. If two or more tests show abnormal HRV, the diagnosis of CAN is established.[3]

Statistical Analysis

Nominal values are presented as number of cases with percentages. Continuous data are presented as mean ± standard deviation for normally distributed variables and as median (range) for non-normal distributions. A Chi-square test was used to compare noncontinuous variables. Analysis of variance was used to compare normally distributed clinical variables and Kruskal–Wallis test for non-normal distributed parameters. A two-tailed p value ≤ 0.05 was considered statistically significant. All calculations were performed with a commercially available program (SPSS for Windows, version 14.0).

Results

Clinical Characteristics

Baseline characteristics are shown in **Table 2**. The prevalence of CAN was higher in T2DM patients (27.8%) than in T1DM patients (20.6%), p = .02. Furthermore, patients with CAN were older, had a longer duration of diabetes, had higher systolic blood pressure, had higher vibration threshold, had more nephropathy, had more proliferative retinopathy, and used more antihypertensive drugs than patients without CAN. No significant differences were found for gender, HbA1c, lipids, or body mass index (BMI) between patients with and without CAN.

Cardiac Reflex Tests

In total, 86% of patients completed all tests. The three individual tests were each completed by 95%, 97%, and 92% for 30:15, E:I, and Valsalva, respectively (shown in **Figure 1**). Only 4 patients (1%) could not complete any test, and 41 patients (13%) completed one or two tests. When patients did not complete all three tests, it was either due to hand tremor, chronic pulmonary disease, or arthritis or because of device failure (28 out of 969 tests, 3%). Results of most tests were correlated with each other.

Established CAN (two or three abnormal tests) was diagnosed in 74 patients (23%), and 105 patients (33%)

Table 1.
Cardiac Reflex Tests Performed by Prototype Vagus[a]

	Cardiac reflex test	Parameter	Examination activity	Nerve affection	Abnormal test result
1	RHR	HR response during rest	Patient lies down resting for 5 min	Increased RHR indicates parasympathetic dysfunction[1,12]	RHR > 100 bpm[15]
2	30:15	HR response 15 and 30 s after changing position	Patient rise from lying position and stand up in full upright position for 1 min	Reflects the overall condition of the parasympathetic fibers[1,3,12]	30:15 ratio < 1.03[15]
3	E:I	HR response during deep expiration and inspiration	Patient sits down and breathes deeply in a rhythm of six breaths per minute for 1 min	Predominantly a function of parasympathetic activity[1,3,12]	E:I ratio < 1.17[15]
4	Valsalva	HR response during Valsalva maneuver	Patient maintains an expiratory pressure of 40 mm Hg for 15 s by means of forced expiration into a mouthpiece connected to the Vagus device; thereafter, the patient remains seated and HR is recorded for further 45 s	Indicative of overall condition of the parasympathetic and sympathetic fibers[1,3,13]	Valsalva < 1.20[15]

[a] HR, heart rate; RHR, resting heart rate

Table 2.
Clinical Characteristics of 319 Diabetes Patients Who Completed the Exam for Cardiac Autonomic Neuropathy[a]

	Normal	Borderline CAN	CAN	*P* values
n	140 (44%)	105 (33%)	74 (23%)	
Abnormal reflex tests	0	1	≥2	
Men (%)	55%	51%	58%	0.7
Type 1 diabetes	101 (50%)	61 (30%)	42 (21%)	0.02
Type 2 diabetes	39 (34%)	44 (38%)	32 (28%)	
Age (years)	51 ± 14	61 ± 10	62 ± 9	<0.001
Duration of diabetes (years)	19 ± 13	22 ± 13	26 ± 13	<0.001
BMI (kg/m^2)	27.1 ± 4.7	28.1 ± 5.6	28.9 ± 5.7	0.07
HbA1c (%)	8.0 ± 1.2	8.1 ± 1.3	8.2 ± 1.3	0.6
Total cholesterol	4.5 ±1.0	4.4 ± 1.0	4.3 ± 1.2	0.4
High-density lipoprotein cholesterol	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.6	0.5
Systolic blood pressure (mm Hg)	133 ± 14	141 ± 17	139 ± 17	<0.001
Diastolic blood pressure (mm Hg)	78 ± 9	78 ± 9	74 ± 10	0.014
Plasma creatinine (µmol/liter)	69 (40;197)	73 (37;196)	80 (54;491)	<0.001
Urinary albumin excretion rate (mg/24 h)	9 (2;538)	13 (3;4403)	20 (4;3271)	<0.001
Retinopathy[b]				<0.001
- Nil	65 (46%)	27 (26%)	12 (16%)	
- Simplex	63 (45%)	61 (58%)	34 (46%)	
- Proliferative	11 (8%)	11 (10%)	21 (28%)	
Vibration threshold	15 (3;50)	21 (8;50)	30 (11;49)	<0.001
Smokers (%)	26%	31%	26%	0.7
Angiotensin converting enzyme inhibitors	37 (26%)	47 (45%)	41 (55%)	<0.001
Angiotensin II receptor antagonists	28 (20%)	31 (30%)	27 (36%)	0.03
Beta blockers	5 (4%)	14 (13%)	22 (30%)	<0.001
Calcium channel blockers	22 (16%)	41 (39%)	29 (39%)	<0.001

[a] Data are given as *n* (%), mean ± standard deviation, median (range).
[b] *n* = 305.

had one abnormal test and were considered as borderline CAN. Six patients (2%) had a resting heart rate above 100 bpm, 3 with CAN and 3 with borderline CAN. The E:I ratio had the largest number of abnormal tests results (52%), followed by Valsalva (23%) and 30:15 ratio (13%), shown in **Figure 3**. Applying a lower cutoff value (<1.10) increased the number of abnormal E:I ratio tests to 64%.

To investigate the association between duration of diabetes and development of CAN, variables were divided into quintiles. The results showed no major difference in prevalence of abnormal cardiac reflexes after 10 years of duration and up to 33 years of duration of diabetes.

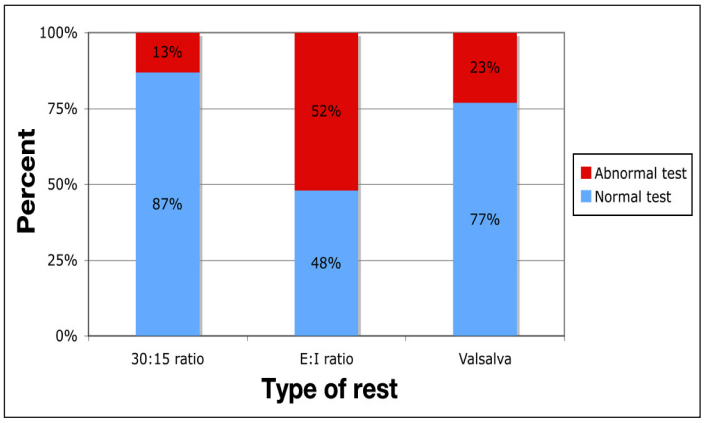

Figure 3. Results of cardiac reflex tests and overall outcome.

The results were furthermore divided into duration of T1DM and T2DM and the prevalence of CAN, shown in **Figure 4**.

Discussion

Prevalence of Cardiac Autonomic Neuropathy

In the present study, we found that the prevalence of CAN in an unselected cohort of diabetes patients is 23%. In addition, borderline CAN was present in 33% of the patients. The prevalence was highest in T2DM.

The reported prevalence of CAN has varied considerably in some studies, depending on the clinical setting, type of tests performed, and selection criteria for patients. Valensi and associates[19] examined 396 patients with T1DM or T2DM by using the same three standardized tests as in the present study. They found a total CAN prevalence of 51% (borderline + manifest CAN) and a prevalence of 20% for manifest CAN. This is in accordance with our findings, where the values are 56% and 23%, respectively. However, in this French study, the prevalence of CAN was found to be higher in T1DM patients (18.2%) than in T2DM patients (12.3%). Lacigová and coworkers[20] found borderline CAN in 36% and asymptomatic CAN in 18% in a study with 107 T1DM patients. Finally, in the Diacan multicenter study, Ziegler and colleagues[17] found a prevalence for CAN of 16.8% in T1DM patients and 22.1% in T2DM patients—data comparable to our findings.

We found no major difference in prevalence of abnormal cardiac reflexes in either type of diabetes after 10 years of duration and up to 33 years of duration, suggesting that the majority of patients at risk of developing CAN already have developed CAN after 10 years duration of diabetes. In this way, duration of diabetes may have little influence on occurrence of CAN after 10 years of diabetes. **Figure 4** also shows that a greater number of T2DM patients developed CAN during the first 10 years of duration compared with T1DM patients. The EURODIAB study concluded that duration of diabetes was no longer related to incidence of CAN when adjusted for age and sex.[11]

In the French multicenter study, CAN was found in 47% of T2DM patients with a duration of diabetes shorter than 18 months.[19] The fact that CAN seems to be more prevalent, appears earlier, and causes higher mortality rates in T2DM is likely due to the longer duration of the metabolic abnormalities, which occur even prior to the diagnosis of T2DM, in the prediabetic and metabolic syndrome stages.[3]

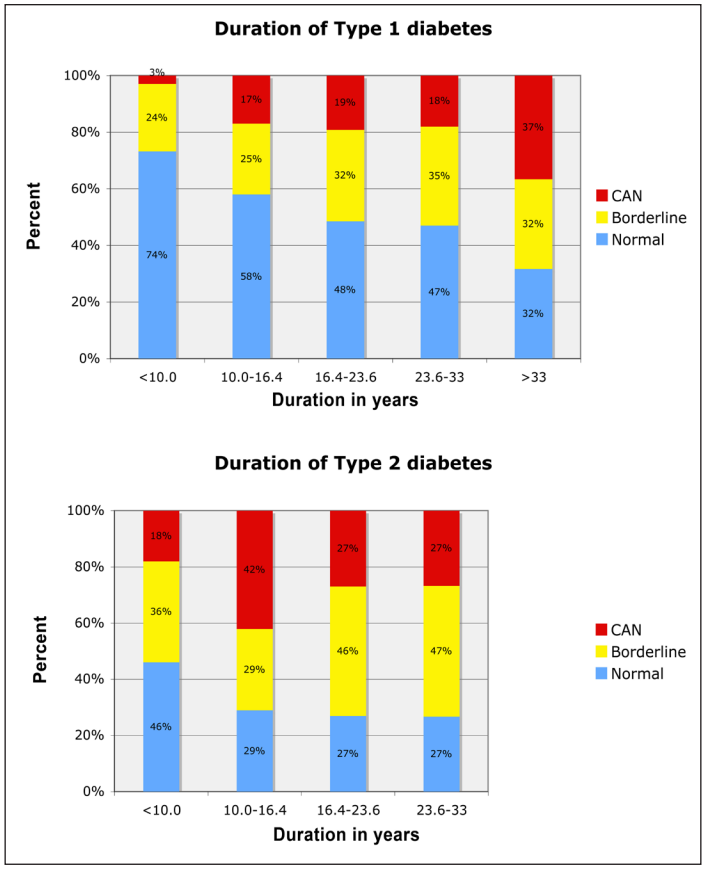

Figure 4. Duration of diabetes and development of CAN.

Clinical Implications

The significant differences found between patients with and without CAN for age, duration of diabetes, systolic blood pressure, nephropathy, vibration threshold, and retinopathy in the present study confirms many other studies. In the EURODIAB study, age, HbA1c, systolic blood pressure, distal symmetrical polyneuropathy, and retinopathy were all found to be independent risk factors of CAN.[11]

Several other studies[9,20] have found significant relations between CAN and peripheral neuropathy, systolic blood pressure, retinopathy, and nephropathy, whereas no relationships with HbA1c, hyperlipidemia, or BMI were found. This is consistent with our findings. In agreement, Urbancic-Rovan and associates[16] concluded that the results of standard autonomic tests did not differ between those with good and poor glycemic control or in diabetes patients with or without autonomic neuropathy.

Clinical Intervention

The role of intensive glycemic control in preventing and slowing the progression of CAN in T1DM patients is well-known; in the Diabetes Control and Complications

Trial, the prevalence of CAN was reduced by 53%.[10] The Steno 2 study demonstrated that intensified multifactorial intervention against hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in T2DM patients reduced the risk of CAN progression by up to 63%.[21] In parallel, reduction of cardiovascular risk factors like hypertension, obesity, cholesterol, smoking, and diabetic microangiopathy might all benefit from the aim of limiting the risk of CAN development.[5,8,9]

Clinical symptoms of CAN generally do not occur until a long time after the onset of diabetes, and CAN may be asymptomatic even in patients with HRV changes.[15] On the other hand, neither age nor type of diabetes are limiting factors in emergence of CAN since it occurs in young individuals with newly diagnosed T1DM and in older individuals newly diagnosed with T2DM.[3]

Since clinical history and physical examination are ineffective for early detection of CAN and late stages of CAN are indicators of poor prognosis,[3] related to cardiac complications[6,7] and increased mortality,[5,11] it is of crucial importance to perform quantitative tests in order to diagnose CAN in its initial and still reversible stages.[22] In general, the recommendations for adults are that HRV measurements are initiated at the time of T2DM diagnosis and 5 years after T1DM diagnosis, with annual examinations thereafter to follow the progression.[1,3,9,15] Younger individuals with T1DM should be screened for CAN beginning at the first stage of puberty.[23]

Cardiac Reflex Tests

The earliest indicator of CAN is a decreased HRV during deep breathing,[2,3] and in the present study, the E:I ratio showed greatest number (52%) of abnormal values, see **Figure 3**. Parasympathetic nerves are first affected in CAN.[3,7] The Valsalva maneuver is later affected because it is more of a generalized test of autonomic function, and therefore, a greater degree of autonomic impairment is required before abnormalities are demonstrated.[15]

Out of the five tests for outpatients classically described by Ewing and coworkers,[24] three tests of HRV—deep breathing test (E:I), orthostatic test (30:15), and Valsalva maneuver—are currently recommended by the American Diabetes Association (ADA), the American Academy of Neurology, and the consensus from the San Antonio conference in 1992.[1,3,13,15,18] These three cardiac reflex tests are considered as reliable and reproducible and generally correlate with each other and with tests of peripheral somatic nerve function and have well-established normal values and demonstrated prognostic value.[1,3,13,15] However, diagnosis of CAN cannot be based on a single abnormal test; a battery of quantitative measures of autonomic reflexes should be used.[3,13] If the patient does not complete all tests, there is a risk of underestimations or overestimations of the prevalence of CAN.

Although the importance of the assessment of HRV is evident, it is rarely used routinely for baseline evaluation of CAN in patients with diabetes. The main problem is that the examination is expensive and time-consuming.[14] Development of new handheld devices for diagnosis of CAN may be helpful in increasing the number of patients screened for this important diabetic complication.

Screening for Cardiac Autonomic Neuropathy with the New Device

The new handheld prototype device is based on the tests recommended by the ADA. It has been tested and compared to gold standard stationary equipment with good agreement between measurements using the two setups. The limits of agreement between the two devices in the group of CAN 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.[14] In one study, the reproducibility of the prototype device was evaluated, and a high degree of correlation between repeated measurements in hospital and between self-monitoring testing and hospital testing in all cardiovascular reflex tests was found.[25]

We experienced that the device was easy to use as a screening tool for CAN and experienced no problems with patient cooperation in the use of the device. The instruction on the display was easily followed, and no time for preparation was needed.

Conclusion

In conclusion, CAN is a frequent complication of both type 1 and type 2 diabetes that can be asymptomatic for a long period. Cardiovascular risk factors and diabetic microangiopathy coexists in individuals diagnosed with CAN. An early detection of CAN may be important to further motivate patients to multifactorial risk factor intervention and thereby reduce further development of complications. Screening for CAN with the new prototype device is effective and feasible.

Disclosures:

Jesper Fleischer and Niels Ejskjaer hold stock in Medicus Engineering Ltd.

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