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Original article

Screening of cardiovascular autonomic neuropathy in patients with diabetes using non-invasive quick and simple assessment of sudomotor function

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Abstract

Aim. – Cardiovascular autonomic neuropathy (CAN) is a common but often overlooked complication of diabetes. Sympathetic C-fibers innervating sweat glands can be impaired early on in patients with diabetes. In this study, SUDOSCAN, a new non-invasive device that assesses sudomotor function was compared to methods generally used for the investigation of CAN.

Patients. – A total of 232 patients with diabetes were measured for heart rate variability (HRV) at rest and during moderate activity. Time and frequency domain analysis techniques, including measurement of the low-frequency (LF) domain component, were assessed during HRV testing. Ewing tests, as recommended by the French Health Authority, were also done. Electrochemical sweat conductance (ESC) was measured on the hands and feet, and a risk-score was calculated.

Results. – Using two abnormal Ewing tests as a reference for the area under the curve (AUC) of the receiver operating characteristics (ROC) curve for SUDOSCAN, the risk-score was 0.74, with a sensitivity of 92% and specificity of 49% for a risk-score cut-off value of 35%. For the ROC curve analysis using the LF power component during moderate activity at a threshold of 90 ms^2 (first quartile) as reference, the AUC was higher for the SUDOSCAN risk-score (0.77) compared with the standard Ewing tests [E:I ratio (0.62), 30:15 ratio (0.76) and blood pressure change on standing (0.55)]. Using a cut-off value of 35%, risk-score sensitivity and specificity were 88 and 54%, respectively.

Conclusion. – SUDOSCAN, which allows quick quantitative assessment of sudomotor function, may be used for early screening of CAN in everyday clinical practice before resorting to the more sophisticated and specific, but ultimately more time-consuming, Ewing tests.

Keywords: Diabetes mellitus; Neuropathy; Sudomotor function; Heart rate variability; Ewing tests; Cardiovascular autonomic neuropathy; SUDOSCAN

Résumé

Dépistage de la neuropathie autonome cardiaque chez des patients diabétiques par mesure rapide et non invasive de la fonction sudomotrice.

Objectif. – La neuropathie autonome cardiaque (NAC) est une complication fréquente mais souvent ignorée du diabète. Les petites fibres C qui innervent les glandes sudoripares peuvent être lésées très précocement chez le patient diabétique. SUDOSCAN, méthode récemment développée pour explorer la fonction sudomotrice, a été comparé aux méthodes habituellement utilisées pour explorer la NAC.

Patients. – La variabilité sinusale a été évaluée au repos et lors d'une activité modérée chez 232 patients diabétiques. L'analyse fréquentielle dans les domaines temporels et fréquentiels a été effectuée avec notamment la mesure des fluctuations de basse fréquence. Les tests d'Ewing tels que recommandés par la Haute Autorité de santé (HAS) ont également été réalisés. Les conductances électrochimiques ont été mesurées au niveau des mains et des pieds et un score de risque a été calculé.

Résultats. – En prenant deux tests d'Ewing anormaux comme référence, l'aire sous la courbe (AUC) de la courbe ROC pour le score de risque de SUDOSCAN était de 0,74 avec une sensibilité de 92 % et une spécificité de 49 % en prenant comme seuil pour le score de risque de 35 %. En choisissant la mesure des fluctuations de basse fréquence durant une faible activité avec un seuil de 90 ms^2 comme référence (correspondant au premier quartile), l'AUC était de 0,77 pour le score de risque SUDOSCAN, de 0,62 pour le rapport expiration/inspiration, de 0,76 pour le rapport 30/15 et de 0,55 pour l'hypotension orthostatique. Avec un seuil de 35 % pour le score de risque, la sensibilité était de 88 % et la spécificité de 54 %.

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Conclusion. – SUDOSCAN qui permet une mesure rapide et quantitative de la fonction sudomotrice pourrait être utilisé pour le dépistage précoce de la NAC en pratique courante avant la réalisation des tests d'Ewing qui sont plus spécifiques mais nécessitent plus de temps.

Mots clés : Diabète sucré ; Neuropathie diabétique ; Fonction sudomotrice ; Variabilité sinusale ; Test d'Ewing ; Neuropathie autonome cardiaque ; SUDOSCAN

1. Introduction

Autonomic neuropathy is probably the most overlooked area in the field of neuropathy [1,2]. Cardiovascular autonomic neuropathy (CAN) has been shown to be the most important risk factor for silent ischemia in patients with diabetes [3]. Heart rate variability (HRV) with time and frequency domain analysis is a non-invasive and objective way to assess sympathetic and parasympathetic modulation of heart rate. It is generally accepted that the sympathetic nervous system modulates the low-frequency (LF) component whereas the parasympathetic nervous system controls the high-frequency (HF) component [4]. Exercise has been shown to increase the accuracy of HRV analysis [5]. A joint consensus statement by the American Diabetes Association (ADA) and American Academy of Neurology has recommended that a battery of cardiovascular autonomic reflex tests (CARTs) to assess HRV during deep breathing and on standing and to monitor postural systolic blood pressure (BP) fall (usually described as "Ewing tests") should be performed to assess CAN [6,7].

Sweat glands are innervated by thin, non-myelinated sympathetic C-fibers, which may be impaired by peripheral neuropathy depending on their length. Sudomotor dysfunction has been observed in both prediabetes and diabetes, and a consensus statement by the ADA has suggested that sudomotor function be included in diagnostic tests for early detection of neuropathies in diabetes [8]. Several methods have been developed, but the lack of easy and quick tests to diagnose sudomotor dysfunction has restricted their widespread use in everyday clinical practice [9,10]. However, SUDOSCAN is a new device that allows quick, non-invasive, quantitative assessment of sudomotor function [11]. Several studies have shown that SUDOSCAN may be used to screen sympathetic nervous system dysfunction in patients with impaired glucose tolerance (IGT) or diabetes [12–14].

The aim of the present study was to compare SUDOSCAN findings with the results of standard Ewing tests in patients with type 2 diabetes.

2. Patients and methods

Type 2 diabetes patients from India aged 21 to 75 years, with or without peripheral or cardiac neuropathy and attending a diabetes clinic, were enrolled in the study after giving their informed consent to participate.

Exclusion criteria were: patients taking drugs that have an effect on the sympathetic system such as beta-blockers and antiarrhythmic drugs; those with amputated arms or legs; patients with either seizures or epilepsy; and patients who had suffered myocardial infarction (MI) and/or stroke within the past 6 months. No additional inclusion criteria were used.

2.1. Heart rate variability

Cardiac autonomic function was evaluated by HRV analysis on a three-lead electrocardiography (ECG) recording of patients at rest (15 min) and during moderate activity (stair-climbing at moderate speed for 45 min). Holter ECG recordings were analyzed by a commercially available Holter analysis system at a sampling rate of 200 Hz, using a certified programme (SyneScope, ELA Medical, Paris, France). Only the R–R intervals between successive normal beats (normal to normal R–R) were included in the calculation of HRV. Recordings with more than 1% ectopy or excess artifacts were excluded from the analysis. Time domain analysis was performed with calculation of the standard deviation of normal to normal (SDNN) R–R intervals correlated with total autonomic activity, and the root mean square of successive differences (RMSSD) correlated with parasympathetic activity. Frequency domain analysis was based on a fast Fourier transform (FFT) algorithm with total power (TP), very low-frequency (VLF; < 0.040 Hz), LF (0.04–0.15 Hz), mainly mediated by the sympathetic system, and HF (0.15–0.40 Hz), mainly mediated by the parasympathetic system. Power components were expressed as absolute units (ms^2). The LF:HF ratio, considered an index of cardiovascular sympathetic/parasympathetic tone balance, was also calculated.

2.2. Cardiac autonomic reflex tests (CARTs) or Ewing tests

The International Diabetes Foundation (IDF) has recommended the use of resting heart rate and heart rate response to provocation tests (lying/standing, Valsalva manoeuvre, deep breathing) in addition to lying/standing BP differences for the diagnosis of CAN [4]. As recommended by the French National Health Authority (*Haute Autorité de santé*, HAS), two tests were performed first: ECG during deep breathing (E:I ratio); and the standing test. These tests were considered abnormal if at least one of the two tests was abnormal (either the ECG or the BP response on standing). Each test was carried out according to the standard procedure described by Ewing et al. [7], using a commercial ECG system (CANS, Chennai, India).

The CART procedures were as follows:

- ECG during deep breathing (E:I ratio) was calculated by measuring the longest R–R interval during inhalation and the shortest R–R interval during exhalation, and calculating the ratio (normal values ≥ 1.21) and;

- ECG on standing (30:15 ratio) was calculated by measuring the shortest and longest (at around the 15th and 30th beats, respectively) R–R intervals upon standing and calculating the ratio (normal values ≥ 1.03), with the BP response also measured on standing (orthostatic BP response; normal fall for systolic BP ≤ 20 mmHg).

2.3. Measurement of sweat function

SUDOSCAN is a patented device designed to perform a precise evaluation of sweat gland function based on the electrochemical reaction between sweat chloride and nickel electrodes to which a low direct current (DC) has been applied as described elsewhere [11–14]. The device consists of two sets of electrodes for the feet and hands, respectively, that are connected to a computer for recording and data management. This non-invasive test lasts 2 min, during this time four combinations of 15 different low DC voltages are applied. No subject preparation is required for the test. The subject places the palms of both hands and soles of both feet on the electrodes. The device then measures the ESC of both hands and feet (right and left) using the ratio of the measured current over the constant power applied expressed as microSiemens (μS). A risk-score for CAN is calculated from these conductances and additional biometric data, and classified as low risk (≤ 25%), moderate risk (25–50%) and high risk (> 50%).

Results for quantitative variables were expressed as means ± SD. Log transformation was undertaken for outcome variables not normally distributed (RMSSD, TP, VLF, LF and HF). Quantitative variables were globally compared using Student's *t* test. Percentages were compared using Fisher's exact test. Analysis of variance (Anova) and logistic regression were also performed to compare quantitative variables and percentages. Adjustments were made according to significant and relevant variables, including diabetes duration, body mass index (BMI) and gender for SUDOSCAN risk-score stratification, but only diabetes duration for Ewing test abnormality stratification. Receiver operating curve (ROC) analysis was performed with calculations of area under the curve (AUC). Sensitivity, specificity and the Youden index (Se + Sp1) were also calculated. As a rule, a P value < 0.05 was regarded as statistically significant. Spearman's rank correlation coefficient was calculated. Data management and statistical analyses were done using SAS version 9.3 and R version 2.13.1 software [15].

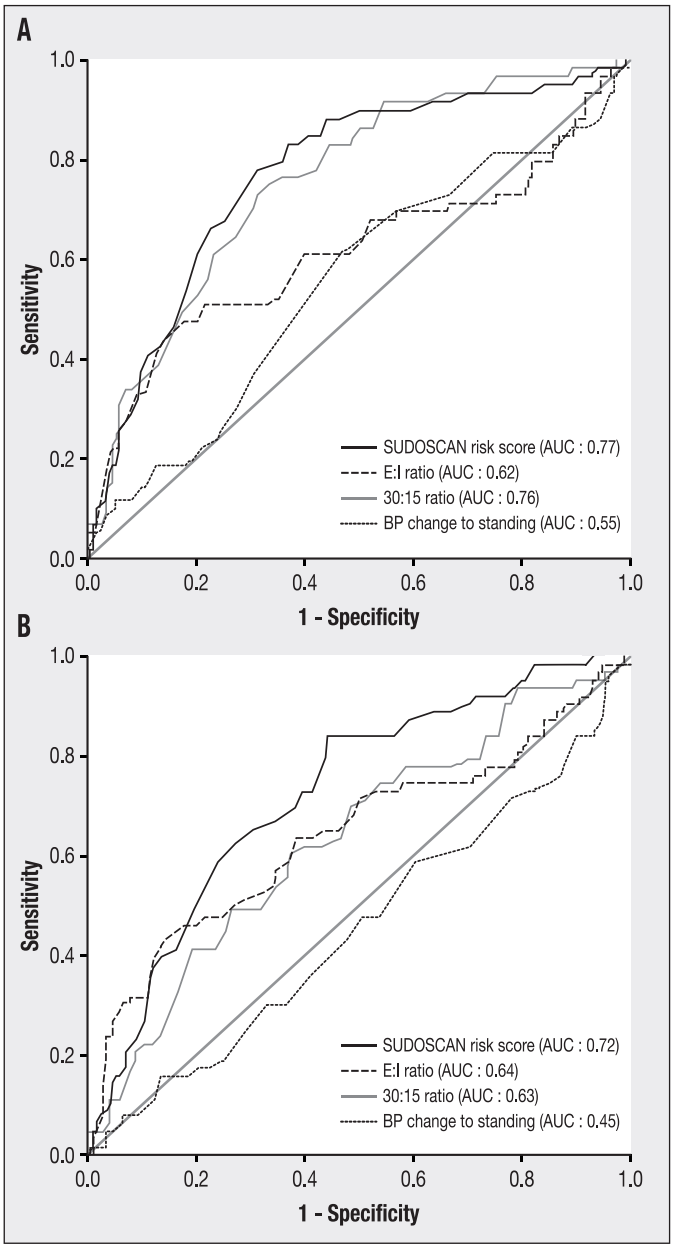

Fig. 1. Graphic representation of the diagnostic performance of the SUDOSCAN risk-score, E:I ratio, 30:15 ratio and blood pressure (BP) change on standing by receiver operating curve (ROC) analysis, using (a) the low-frequency power component during moderate activity at a threshold of 90 ms^2 (first quartile) and (b) the high-frequency power component during moderate activity at a threshold of 20 ms^2 (first quartile).

3. Results

Using two abnormal Ewing tests as reference (E:I ratio during deep breathing and the standing test for BP changes or 30:15 ratio in response to standing) for the ROC curve analysis, the AUC for the SUDOSCAN risk-score was 0.74. The optimal Youden index was 0.41 for a SUDOSCAN risk-score cut-off point of 35%, with sensitivity of 92% and specificity of 49%. Table 1 shows the patients' main characteristics, results for HRV during moderate activity and SUDOSCAN data according to Ewing test results. Patients were classified as having: no abnormal test; one abnormal test (E:I ratio during deep breathing or one of the two responses on standing); and two abnormal tests (E:I ratio during deep breathing and one of the two responses on standing). Table 2 presents the patients' main characteristics, HRV parameters and results of Ewing tests according to SUDOSCAN risk-score, with patients classified as low risk (≤ 25%), moderate risk (25–50%) and high risk (> 50%) according to their scores. Correlations between the SUDOSCAN risk-score and HF and LF power components during moderate activity were 0.47 and 0.40, respectively. Fig. 1 (A, B) shows graphic representations of the diagnostic performance of the SUDOSCAN risk-score, E:I ratio, 30:15 ratio and BP changes on standing

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Table 1
Demographic, heart rate variability (HRV) and SUDOSCAN characteristics according to Ewing test results.

		Ewing tests: E:I ratio during deep breathing and stand tests[a]			*P*-value	*P*-value adjusted[b]
		No abnormal test	1 abnormal test	2 abnormal tests		
n	232	134	74	24		
Men participants	140 (60%)	83 (62%)	40 (54%)	17 (71%)	NS	–
Diabetes duration (years)	9 ± 7	7 ± 6	10 ± 6	13 ± 9	< 0.001	–
BMI (kg/m^2)	26 ± 4	26 ± 4	26 ± 4	27 ± 4	NS	NS
Age (years)	52 ± 9	50 ± 9	56 ± 8	57 ± 7	< 0.001	NS
HbA_{1c} (%)	8.5 ± 1.8	8.4 ± 1.7	8.5 ± 1.9	9.2 ± 1.9	NS	NS
SBP (mm Hg)	120 ± 16	117 ± 16	124 ± 16	125 ± 18	0.003	0.024
DBP (mm Hg)	76 ± 8	75 ± 8	78 ± 7	78 ± 10	< 0.001	0.027
HR at rest	78 ± 11	75 ± 10	80 ± 10	85 ± 13	< 0.001	< 0.001
HR during moderate activity	93 ± 11	90 ± 11	95 ± 11	100 ± 13	< 0.001	< 0.001
LF during moderate activity	295 ± 299	376 ± 322	210 ± 245	105 ± 100	< 0.001	< 0.001
HF during moderate activity	107 ± 228	144 ± 285.9	66 ± 95	26 ± 39	< 0.001	< 0.001
ESC hands (μS)	59 ± 20	61 ± 20	57 ± 21	51 ± 21	0.051	NS
ESC feet (μS)	59 ± 21	63 ± 19	56 ± 22	48 ± 24	0.002	0.035
SUDOSCAN risk-score	37 ± 15	34 ± 14	40 ± 14	47 ± 12	< 0.001	0.006

SBP: systolic blood pressure; DBP: dialostic blood pressure; HR: heart rate; LF: low-frequency; HF: high-frequency; ESC: electrochemical sweat conductance; NS: non significant. Data are means ± SD.

[a] Heart rate and blood pressure response during active standing.

[b] *P*-value adjusted on diabetes duration.

according to ROC analysis, using as reference the LF power component during moderate activity at a threshold of 90 ms^2 (first quartile, threshold for the lowest 25% of data; Fig. 1A) and the HF power component during moderate activity at a threshold of 20 ms^2 (first quartile, threshold for the lowest 25% of data; Fig. 1B). As regards the LF component during moderate activity, the sensitivity and specificity were 88 and 54%, respectively, for the SUDOSCAN risk-score with a cut-off of 35%, and the Youden index was 0.42. Using the HAS recommended cut-off for E:I ratio (1.21; Youden index: 0.30), BP change in response to standing (20 mmHg; Youden index: 0.04) and 30:15 ratio (1.03; Youden index: 0.38), sensitivity was 44, 12 and 61%, respectively, and specificity was 86%, 92% and 77%, respectively, for the LF component during moderate activity. As for the HF component during moderate activity, the sensitivity and specificity were 84 and 53%, respectively, for the SUDOSCAN risk-score with a cut-off of 35%, and the Youden index was 0.37. Using the HAS-recommended cut-off for E:I ratio (1.21; Youden index: 0.29), BP change in response to standing (20 mmHg; Youden index: 0.00) and 30:15 ratio (1.03; Youden index: 0.23), sensitivity was 43, 8 and 49%, respectively, and specificity was 86, 91 and 73%, respectively, for the HF component during moderate activity.

No adverse events or discomfort during or after measurement were reported.

4. Discussion

The present study shows that the sensitivity of the SUDOSCAN risk-scores at a cut-off value of 35% was 92% for the diagnosis of two abnormal Ewing tests. In the same way, the highest AUC was observed for SUDOSCAN risk-scores compared with the standard Ewing tests (E:I ratio during deep breathing, 30:15 ratio and BP change on standing) and when using the first quartile (threshold for the lowest 25% of data) of the HF or LF power component during moderate activity as reference.

The highest correlation of SUDOSCAN risk-scores was observed with the LF power component during moderate activity, which is linked to the sympathetic nervous system component [5]. A lower correlation was observed with the HF power component during moderate activity (0.40 vs. 0.47), which is more closely linked to the parasympathetic component. Similarly, a significant difference was observed for the LF power component during moderate activity when patients were classified according to SUDOSCAN risk-score, whereas no significant difference was observed for LF at rest when adjusted for BMI, diabetes duration and gender (Table 2). This could be explained by the fact that moderate activity increases sympathetic activity and, thus, the LF power component [5]. Values selected as references for the LF and HF power components were in the same range as the values observed in previous studies of diabetic patients with peripheral neuropathy [16].

CARTs or Ewing tests have been proposed for the diagnosis of CAN, but they are very time-consuming and consequently rarely performed in everyday clinical practice [6,7]. In addition, one type of CART is based on the Valsalva manoeuvre and cannot be performed on some patients for safety reasons. Thus, to ensure that the same tests were performed on all patients, this test was excluded from our study.

Thin, non-myelinated, small nerve fibers can be damaged very early on in the development of diabetes, depending on their length, and small-fiber neuropathy has been proposed as a marker of peripheral neuropathy in diabetes [8]. Also, as sweat glands are innervated by small sympathetic C-fibers, the assessment of sudomotor function has been suggested for evaluation of peripheral autonomic neuropathy and especially in patients with diabetes [9]. The gold standard for sudomotor

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Table 2
Demographic, heart rate variability (HRV) and cardiovascular autonomic reflex test (CART) characteristics according to SUDOSCAN risk-scores.

	All	SUDOSCAN risk-score			*P*-value	*P*-value adjusted[a]
		Risk-score ≤ 25	Risk score]25–50]	Risk score > 50		
n	232	44	149	39		
Men participants	140 (60%)	31 (70%)	90 (60%)	19 (49%)	0.130	–
Diabetes duration (years)	9 ± 7	4 ± 4	9 ± 6	15 ± 7	< 0.001	–
BMI (kg/m^2)	26 ± 4	24 ± 3	26 ± 3	29 ± 4	< 0.001	–
Age (years)	52 ± 9	44 ± 8	53 ± 8	59 ± 7	< 0.001	< 0.001
HbA_{1c} (%)	8.5 ± 1. 8	7.4 ± 1. 8	8.3 ± 1.5	10.3 ± 1.7	< 0.001	< 0.001
SBP (mmHg)	120 ± 16	117 ± 16	119 ± 16	127 ± 16	0.011	NS
DBP (mmHg)	76 ± 8	77 ± 10	76 ± 8	77 ± 7	NS	NS
ESC hands (μS)	59 ± 20	72 ± 18	58 ± 19	46 ± 18	< 0.001	< 0.001
ESC feet (μS)	59 ± 21	77 ± 10	58 ± 19	43 ± 20	< 0.001	< 0.001
HR variability at rest						
Heart rate (bpm)	78 ± 11	77 ± 11	77 ± 11	81 ± 11	NS	NS
SDNN (ms)	35 ± 18	39 ± 18	36 ± 18	28 ± 18	0.001	NS
RMSSD (ms)	24 ± 20	28 ± 26	24 ± 18	20 ± 21	0.044	NS
TP (ms^2)	1353 ± 1410	1688 ± 1447	1385 ± 1428	851 ± 1168	< 0.001	0.036
VLF (ms^2)	699 ± 752	915 ± 849	701 ± 751	442 ± 549	< 0.001	0.098
LF (ms^2)	355 ± 423	392 ± 317	384 ± 470	200.0 ± 285	< 0.001	0.079
HF (ms^2)	221 ± 371	260 ± 442	228 ± 359	148 ± 322	0.002	0.047
LF/HF	2.8 ± 2.3	3.1 ± 2.3	2.7 ± 2.2	2.9 ± 2.4	NS	NS
HR variability during moderate activity						
Heart rate (bpm)	93 ± 11	92 ± 12	92 ± 11	97 ± 10	0.017	NS
SDNN (ms)	70 ± 27	76 ± 27	69 ± 27	66 ± 24	NS	NS
RMSSD (ms)	20 ± 16	24 ± 18	19 ± 12	19 ± 25	0.020	NS
TP (ms^2)	1477 ± 1373	2059 ± 1591	1444 ± 1336	942 ± 975	< 0.001	NS
VLF (ms^2)	964 ± 932	1300 ± 997	957 ± 943	611 ± 657	< 0.001	NS
LF (ms^2)	295 ± 299	449 ± 325	289 ± 299	142 ± 162	< 0.001	0.019
HF (ms^2)	107 ± 228	172 ± 415	104 ±	45 ± 74	< 0.001	0.034
LF/HF	4.8 ± 3.1	5.2 ± 3.1	4.6 ± 3.1	4.9 ± 3.2	NS	NS
CARTs						
Abnormal E:I ratio (< 1.21)	46 (20%)	6 (14%)	26 (17%)	14 (36%)	0.027	0.028
Abnormal 30:15 ratio (< 1.03)	71 (31%)	5 (11%)	44 (30%)	22 (56%)	< 0.001	< 0.001
Orthostatic hypotension (> 20 mmHg)	17 (7%)	3 (7%)	10 (7%)	4 (10%)	NS	NS

SBP: systolic blood pressure; DBP: dialostic blood pressure; HR: heart rate; LF: low-frequency; HF: high-frequency; ESC: electrochemical sweat conductance; SDNN: standard deviation of normal to normal; RMSSD: root mean square of successive differences; TP: total power; VLF: very low-frequency; CARTs: cardiovascular autonomic reflex tests. Data are means ± SD.

[a] *P*-value adjusted on gender, diabetes duration and BMI.

function assessment is the quantitative sudomotor axon reflex test (QSART) [9,17]. However, as this method lacks a simple, quick, non-invasive approach, it has not been used on a large scale. Lesions of the peripheral and cardiac autonomic nervous systems theoretically progress in parallel, and the QSART has been proposed for the peripheral item in the Composite Autonomic Scoring Scale (CASS) [18]. Another method proposed for sweat function assessment is Neuropad, a patch test for assessing plantar sweat production by means of a chemical reaction. However, this also is time-consuming, and its performance has yet to be confirmed as, so far, no study has been performed to compare Neuropad results and the presence of CAN [10,19].

The present study has several limitations:

- it was performed in a specific population;
- the Valsalva manoeuvre, which cannot be performed on all patients for safety reasons, was excluded to ensure that all patients underwent the same tests;
- and, the threshold values used as references for the LF and HF power components were based on the study population (first quartile).

Nevertheless, according to the results of this study (which need to be confirmed in a larger population), SUDOSCAN — a simple, non-invasive, quick and quantitative method — may be used as a screening test for CAN before resorting to Ewing tests that, while more specific and specialized, are very time-consuming and, for this reason, little used in everyday clinical practice. Thus, SUDOSCAN appears to offer better management of patients with type 2 diabetes by helping to avoid the development and progression of its life-threatening complications.

Disclosure of interest

C.S. Yajnik, V. Kantikar, A. Pande, and B. Bauduceau have no potential conflict of interest to disclose.

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