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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

C.S. Yajnik [a], V. Kantikar [a], A. Pande [a], J.-P. Deslypere [b], J. Dupin [b], J.-H. Calvet [c], B. Bauduceau [d,*]

[a] *Diabetes Unit, King Edward Memorial Hospital Research Centre, Pune, India*
[b] *Aesculape, Singapore*
[c] *Impeto Medical, Paris, France*
[d] *Begin Hospital, France*

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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 %.

* Corresponding author. Tel.: +33 (0) 85 38 27 51; fax: +33 (0) 43 98 59 71.
E-mail address: bernard.bauduceau@wanadoo.fr (B. Bauduceau).

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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;