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Sudomotor dysfunction as a measure of small fiber neuropathy in type 1 diabetes

Lynn Ang [a], Mamta Jaiswal [a], Brian Callaghan [b], David Raffel [c], Morton B. Brown [d], Rodica Pop-Busui [a,*]

[a] Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI 48109, United States
[b] Department of Neurology, University of Michigan, Ann Arbor, MI 48109, United States
[c] Department of Radiology, University of Michigan, Ann Arbor, MI 48109, United States
[d] Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, United States

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ABSTRACT

Background: This study evaluated whether measuring the electrochemical skin conductance (ESC), as an indirect measure of sudomotor function, may be also a reliable surrogate for early cardiovascular autonomic neuropathy (CAN).
Methods: Longitudinal study included 37 type 1 diabetes (T1D) subjects (mean age 38 ± 13 years, duration 15 ± 7 years, HbA1c 7.9 ± 1.1%, no known complications at baseline), and 40 age-matched healthy control (HC) subjects. Mean hands ESC (ESChands) and feet (ESCfeet) were measured with the SUDOSCAN (Impeto Medical, France). CAN was assessed with heart rate variability (HRV) studies (ANSAR Inc., PA), cardiovascular autonomic reflex tests (deep-breathing, Valsalva, postural test), and positron emission tomography with sympathetic analogue [11C]meta-hydroxyephedrine. Associations between measures of CAN and ESC were estimated using Spearman correlations. Longitudinal changes were analyzed using paired *t*-test.
Results: At baseline, there were no differences between T1D and HC in ESChands (69 ± 14 vs. 69 ± 13 μS; P = 0.84) or ESCfeet (82 ± 8 vs. 78 ± 9 μS; P = 0.12), while some indices of HRV and Valsalva ratio were significantly lower in T1D vs. HC. T1D subjects experienced a significant decline in both ESChands and ESCfeet at 12 months (mean change −7.2 ± 11.6 μS, P = 0.0006; −2.8 ± 7.3 μS, P = 0.023 respectively). No significant correlations were consistently found between ESC and measures of CAN at baseline or at 12 months.
Conclusion: Comparing patients with T1D to controls, no differences in ESC were observed at baseline. The associations between ESC and established measures of CAN were inconsistent, which does not support ESC as a reliable surrogate for CAN. While both hands and feet ESC declined over time, the significance of this finding is unclear and warrants further reliability testing.

1. Introduction

The continuous increase in the prevalence of diabetes mellitus and related complications worldwide is associated with significant burdens on patient's morbidity and quality of life, and with staggering health care costs (International Diabetes Federation, 2015). Diabetic neuropathy (DN) is one of the most prevalent diabetic complications affecting up to 60% of patients over their lifetime (Eastman, 1995; Pop-Busui, 2012). Although DN is rare in early stages of type 1 diabetes (T1D), its prevalence increases with disease duration and poor glycemic control (Eastman, 1995; Ang et al., 2014; Callaghan et al., 2012; Vinik et al., 2000–2015).

Besides glucose control, pathogenic therapies to treat DN are still missing, possibly because there are limited tools to detect DN in its earlier stages (Pop-Busui, 2012; Ang et al., 2014; Vinik et al., 2000–2015) that are most susceptible to therapeutic interventions. Therefore, developing sensitive, specific, non-invasive, and affordable tests to detect the earliest stages of autonomic dysfunction and of DN in general, which are most susceptible to therapeutic interventions, are important in the development of viable therapies to prevent or reverse the progression of this complication.

Abbreviations: DN, diabetic neuropathy; CAN, cardiovascular autonomic neuropathy; HC, healthy control; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; RI, retention index; ESC, electrochemical skin conductance; T1D, type 1 diabetes; sdNN, standard deviation of normal R–R intervals; rmsSD, root-mean square of the difference of successive R–R intervals; Lfa, low frequency power; Rfa, high frequency power; CARTs, cardiovascular autonomic reflex tests; HRV, heart rate variability; HDLc, calculated high-density lipoprotein cholesterol; LDLc, calculated low-density lipoprotein cholesterol; BP, blood pressure; LV, left ventricle; PET, positron emission tomography; HED, meta-hydroxyephedrine; DPN, diabetic peripheral neuropathy.

* Corresponding author at: Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, 5329 Brehm Tower, 1000 Wall Street, Ann Arbor, MI 48105, United States.
E-mail address: rpbusui@med.umich.edu (R. Pop-Busui).

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DN has a broad spectrum of manifestations, but the most common forms are distal symmetrical polyneuropathy and cardiovascular autonomic neuropathy (CAN) (Pop-Busui, 2012; Vinik et al., 2000–2015; Albert & Pop-Busui, 2014). One of the earliest signs of CAN is reduced heart rate variability (HRV) (Pop-Busui, 2012) and changes in several cardiovascular reflex tests (CARTs) (Pop-Busui, 2012; Tesfaye et al., 2010; Spallone et al., 2011; Vinik & Ziegler, 2007; Pop-Busui, 2010). Although these measures have been shown to be sensitive, non-invasive and reproducible, they are time-consuming and require trained personnel (Pop-Busui, 2012; Tesfaye et al., 2010; Spallone et al., 2011; Vinik & Ziegler, 2007; Pop-Busui, 2010).

Sudomotor function, which is largely regulated by the same small, postganglionic, unmyelinated cholinergic sympathetic C-fibers that also regulate cardiovascular autonomic function, may be impaired earlier in patients with DN (Tesfaye et al., 2010). The methods currently used to assess sudomotor function are expensive, time consuming, and require specialized trained personnel (Provitera et al., 2010; Illigens & Gibbons, 2009; Low, 2004). The recently developed SUDOSCAN device (Impeto Medical; Paris, France) provides a simple and non-invasive method that indirectly assesses sudomotor function by measuring the electrochemical skin conductance (ESC) (Yajnik et al., 2012; Mayaudon et al., 2010; Gin et al., 2011; Hubert et al., 2011; Vinik et al., 2015). This is based on the electrochemical reaction between the chloride ions in sweat and stainless steel plate electrodes on which the subject's hands and feet are placed by combining direct current stimulation and reverse iontophoresis.

The hypothesis was that the ESC measured with SUDOSCAN, may also detect earliest stages of cardiovascular autonomic dysfunction in T1D. Thus, the main objectives of this study were to evaluate the associations between established measures of CAN and ESC as an indirect measure of sudomotor dysfunction in patients with T1D, and whether this measure could also be used as a reliable tool to evaluate longitudinal changes in the small fiber function in these patients. In addition, we aimed to evaluate the potential role of several risk factors in promoting these deficits.

2. Methods

2.1. Study design

Longitudinal prospective study in 37 T1D subjects followed for 12 months and 40 age-matched healthy control (HC) subjects.

2.2. Study population

T1D subjects were recruited from an ongoing clinical trial (NCT01170832) designed to evaluate the natural history of CAN and myocardial dysfunction in T1D at the University of Michigan Health System. Recruitment for this study began in August 2010 and ended in May 2013. Major inclusion criteria for the T1D subjects were: T1D as defined by the American Diabetes Association diagnostic criteria (Standards of medical care in diabetes-2015: summary of revisions, 2015), duration >5 years, age 18–65 years, and no history of any complications at baseline. HC were age-and-gender matched with the T1D subjects at the start of the SUDOSCAN study, but the controls had normal glucose tolerance, normal blood pressure, and normal lipid profile.

Major exclusions were pregnancy or nursing, history of any cardiovascular disease (confirmed by stress test and cardiology evaluations), history of previous kidney, pancreas or cardiac transplantation, history of drug/alcohol abuse, and current use of any agents or drugs that interfere with the uptake or metabolism of catecholamines.

The study was approved by the Institutional Review Board of the University of Michigan and all subjects signed a written informed consent.

2.3. Evaluations

All evaluations were performed in the morning after an overnight fast. Height was measured in centimeters (cm) using a stadiometer, and weight in kilograms (kg) using a standardized calibrated scale. Sitting systolic and diastolic blood pressure (BP) was obtained after at least 10 min of rest. Fasting blood samples were obtained for glucose, metabolic and lipid panel [total cholesterol, calculated high-density lipoprotein cholesterol (HDLc), triglycerides, calculated low-density lipoprotein cholesterol (LDLc)] and processed by the University of Michigan Health System laboratory via Advia 1800 (Siemens, Erlangen, Germany), and hemoglobin A1c (HbA1c) was measured by high performance liquid chromatography (TOSOH Bioscience, San Francisco, CA).

2.3.1. Assessment of sudomotor function

Electrochemical skin conductance was evaluated in the T1D subjects at baseline and 12 months, and in healthy control subjects once with the SUDOSCAN device (Impeto Medical: Paris, France) as previously described (Yajnik et al., 2012; Mayaudon et al., 2010; Gin et al., 2011; Hubert et al., 2011; Vinik et al., 2015; Casellini et al., 2013; Smith et al., 2014; Selvarajah et al., 2015; Eranki et al., 2013). Briefly, ESC is measured via reverse iontophoresis, an electrochemical reaction between the chlorides in sweat and stainless steel electrodes at low direct current (DC) voltage. The SUDOSCAN is composed of 2 sets of electrodes for hands and feet connected to a computer for recording and data management. Measurements are performed while the participants stand for 3 min placing their hands and feet on the plate electrodes. Four combinations of 15 different DC incremental voltages (<4 V) are applied. The device measures an ESC score for each hand and foot and provides a percent asymmetry between left and right limbs. No special preparations of subjects are required. All data were collected with two SUDOSCAN devices operated by the same trained technicians in the same fashion (37 T1D and 9HC with one device and 31 HC with the second device) During the study Impeto Medical remotely monitored these devices and updated their software.

2.3.2. Assessment of CAN

CAN was assessed at baseline in both groups, and at 12 months in the T1D patients. Subjects were asked to avoid caffeine and tobacco products for at least 8 h prior to testing, and hold any medication (except for basal insulin) until testing was completed. Subjects who experienced a hypoglycemic episode after midnight [blood glucose ≤50 mg/dl (2.77 mmol/l)] prior to the testing were rescheduled.

2.3.2.1. Left ventricle (LV) sympathetic innervation with positron emission tomography (PET) with sympathetic analogue [11C] meta-hydroxyephedrine (HED). The PET scans were done at baseline in T1D as previously described (Stevens et al., 1999; Raffel & Wieland, 2001). All PET studies were performed on a Siemens/ECAT Exact HR+ PET scanner. After positioning the subject in the PET scanner (Siemens, Erlanger, Germany) gantry, 2.0 mCi of [13N] ammonia was injected intravenously (IV) and a brief PET scan acquired to visualize the heart. Thirty minutes later, 20 mCi of [11C] HED was injected IV as a 60 min dynamic PET data acquisition sequence was started as previously described (Stevens et al., 1999; Raffel & Wieland, 2001).

Following image reconstruction, software was used to reorient and reslice the raw transaxial PET data into cardiac short-axis view data sets. The LV wall is divided into 60 regions to generate 480 independent LV regions. The measured [11C]HED radioactivity concentration in each sector in the final image frame (40–60 min) was normalized to the calculated integral of the total radioactivity in the blood pool throughout the PET study to obtain a [11C]HED "retention index" (RI, units: ml blood/min/ml tissue) for each LV sector. Polar maps of regional [11C]HED retention was generated and saved for visual inspection of [11C]HED retention deficits. A quantitative measure of the degree of