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Short communication

Reduced spontaneous sympathetic nerve activity in multiple sclerosis patients

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ABSTRACT

For the first time, we obtained direct intra-neural measurements of muscle sympathetic nerve activity (MSNA) in relapsing–remitting multiple sclerosis (MS) patients to test the hypothesis that spontaneous resting MSNA is reduced in MS patients compared to age, sex-matched healthy controls. Spontaneous MSNA (microneurography; peroneal nerve), plasma norepinephrine, arterial blood pressure (finger photoplethysmography), and heart rate were measured at rest in three groups: 1) relapsing–remitting MS patients on disease modifying therapy only (MS-DT; n = 6); 2) relapsing–remitting MS patients on disease modifying therapy and medications for MS-related symptoms that are known to effect the central nervous system (MS-DT/ST; n = 5), and 3) healthy age and sex-matched controls (CON; n = 6). Compared to the CON group, MSNA burst frequency (bursts/min) was significantly lower in both MS-DT (P = 0.027) and MS-DT/ST groups (P = 0.003). Similarly, MSNA burst incidence (bursts/100 heartbeats) was significantly reduced in both MS-DT (P = 0.049) and MS-DT/ST groups (P = 0.004) compared to the CON group. Burst frequency and burst incidence were not different between MS-DT and MS-DT/ST groups. Resting plasma norepinephrine was also significantly lower in both MS-DT (P = 0.039) and MS-DT/ST groups (P = 0.021) compared to the CON group. Reduced MSNA may signify an important dysfunction in autonomic control of cardiovascular function in patients with MS.

1. Introduction

Multiple sclerosis (MS) has been shown to impair autonomic control of cardiovascular function [1,6,9–11] and this dysfunction may increase with disease progression and increased clinical disability [4,9]. Studies suggest that upwards of 50% of individuals with MS may experience symptoms of orthostatic dizziness [5,14]. Although impaired sympathetically-mediated vasomotor control has been suggested to be responsible for the symptoms of orthostatic dizziness observed in MS patients [5,11] this has not been directly tested. Due to the obvious health-related concerns of autonomic dysfunction in individuals with MS, characterization of resting sympathetic outflow would provide a novel therapeutic target to alleviate symptoms associated with MS (dizziness, light headedness, thermal sensitivity, etc.) Sympathetic outflow to vasculature supplying skeletal muscle, or muscle sympathetic nerve activity (MSNA), can be recorded using microneurography [13]. However, to date, no direct measurements of resting sympathetic neural function have been reported in individuals with MS. The goal of this investigation was to obtain direct intra-neural measurements of MSNA in MS patients and to test the hypothesis that spontaneous resting MSNA is reduced in MS patients compared to healthy control subjects.

2. Methods

2.1. Human subjects

Participants from the following three groups were investigated: 1) individuals with clinically definite relapsing–remitting MS currently treated with disease modifying therapy only [MS-DT; n = 6 (4 females, 2 males); age = 38 ± 7 yrs; height = 173 ± 14 cm; weight = 70 ± 14 kg, duration from MS diagnosis = 7 ± 4 yrs]; 2) individuals with clinically definite relapsing–remitting MS currently on disease modifying

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therapy and medications for MS-related symptoms that are known to effect the central nervous system (i.e., anti-depressants, psychostimulants, anti-convulsants and anti-spasmatics) [MS-DT/ST; n = 5 (4 females, 1 male) age = 38 ± 7 yrs; height = 166 ± 8 cm; weight = 59 ± 11 kg, duration from MS diagnosis = 8 ± 4 yrs], and 3) healthy age and sex-matched controls [CON; n = 6 (4 females, 2 males); age = 36 ± 7 yrs; height = 169 ± 10 cm; weight = 65 ± 18 kg]. Participants were normotensive (supine blood pressures <140/90 mm Hg) and had no known cardiovascular disease. Subjects refrained from caffeine, alcohol and intensive exercise 24 h before the study. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Participants provided informed written consent prior to testing.

2.2. Instrumentation and protocol

All experiments were performed at a constant ambient room temperature (23–24 °C) with the subject in the supine position. Heart rate was monitored using ECG interfaced with a cardiotachometer (CWE, Ardmore, PA, USA). Beat-by-beat blood pressure was measured by continuous finger cuff photoplethysmography (Finometer, FMS, Amsterdam, The Netherlands) with resting values verified by brachial artery auscultation (SunTech, Medical Instruments Raleigh, NC, USA). Multiunit recordings of postganglionic MSNA were obtained by inserting unipolar tungsten microelectrodes percutaneously through the intact, un-anesthetized skin and positioned into muscle nerve fascicles of the peroneal nerve near the fibular head [13]. The nerve signal was processed by a pre-amplifier and amplifier (Department of Bioengineering, University of Iowa, Iowa City, IA, USA), band pass filtered (700–2000 Hz), rectified and integrated (time constant, 0.1 s) to obtain a mean voltage neurogram. The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria [13]. For the MS groups, due to their inherently low MSNA, more frequent repositioning of the recording microelectrode and more frequent use of sympatho-excitatory maneuvers (i.e., end expiratory breath holds) were utilized during instrumentation prior to obtaining recordings to ensure an optimal recording site.

Resting blood samples were drawn from a venous catheter placed in the forearm for the measurements of plasma norepinephrine, a general index of global sympathetic outflow. Blood samples were obtained from 4 patients in the MS-DT group, 4 patients in the MS-DT/ST group, and 5 patients in the CON group. Plasma norepinephrine concentrations (pg/ml) were measured using high-precision liquid chromatography by an independent laboratory using standardized procedures.

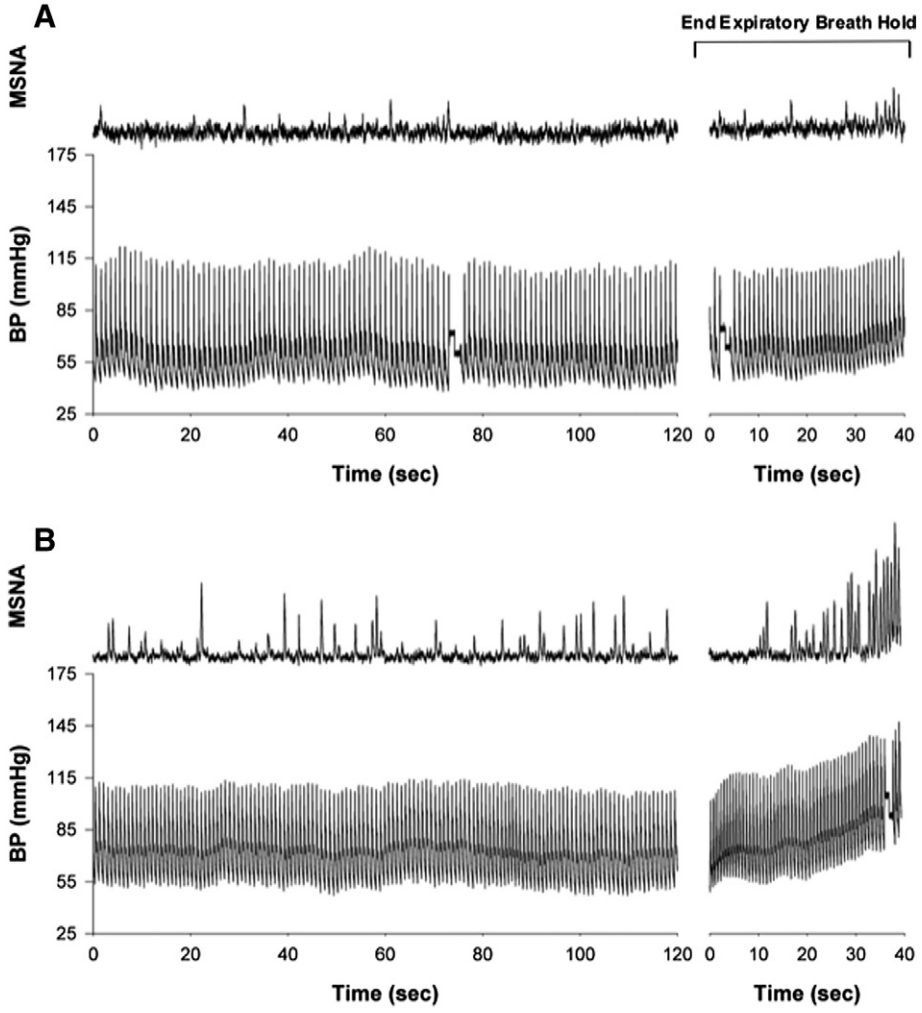

Fig. 1. Original recordings of muscle sympathetic nerve activity (MSNA) and arterial blood pressure (BP; Finometer) during 2 min of supine rest and in response to an end expiratory breath hold in an individual with clinically diagnosed relapsing–remitting MS currently on disease modifying therapy only (MS-DT; panel A) and a healthy age and sex-matched control (CON; panel B). An end expiratory breath hold is a common sympatho-excitatory maneuver used during microneurographic instrumentation to determine successful acquisition of an adequate MSNA recording site.