Sleep Medicine 34 (2017) 7–12

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Cardiovascular fitness in narcolepsy is inversely related to sleepiness and the number of cataplexy episodes

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ARTICLE INFO

Article history:
Received 3 December 2015
Received in revised form
17 November 2016
Accepted 16 February 2017
Available online 11 March 2017

Keywords:
Exercise stress test
Cardiopulmonary fitness
Narcolepsy with cataplexy
Narcolepsy without cataplexy
Influence of disease severity

ABSTRACT

Objective: Cardiopulmonary fitness depends on daily energy expenditure or the amount of daily exercise. Patients with narcolepsy spent more time being sleepy or asleep than controls; thus we may speculate that they have a lower quantity and quality of physical activity. The aim of the present study was thus to test the hypothesis that exercise tolerance in narcolepsy negatively depends on sleepiness.

Patients and methods: The cross-sectional study included 32 patients with narcolepsy with cataplexy, 10 patients with narcolepsy without cataplexy, and 36 age- and gender-matched control subjects, in whom a symptom-limited exercise stress test with expired gas analysis was performed. A linear regression analysis with multivariate models was used with stepwise variable selection.

Results: In narcolepsy patients, maximal oxygen uptake (VO_{2peak}) was 30.1 ± 7.5 mL/kg/min, which was lower than 36.0 ± 7.8 mL/kg/min, $p = 0.001$, in controls and corresponded to 86.4% ± 20.0% of the population norm (VO_{2peak}%) and to a standard deviation (VO_{2peak}SD) of −1.08 ± 1.63 mL/kg/min of the population norm. VO_{2peak} depended primarily on gender ($p = 0.007$) and on sleepiness ($p = 0.046$). VO_{2peak}% depended on sleepiness ($p = 0.028$) and on age ($p = 0.039$). VO_{2peak}SD depended on the number of cataplexy episodes per month ($p = 0.015$) and on age ($p = 0.030$).

Conclusions: Cardiopulmonary fitness in narcolepsy and in narcolepsy without cataplexy is inversely related to the degree of sleepiness and cataplexy episode frequency.

1. Introduction

Narcolepsy is a chronic neurological disease that is characterized by excessive daytime sleepiness and is divided into narcolepsy with cataplexy (NC) and narcolepsy without cataplexy (NwoC), due to differing etiologies [1]. NC occurs due to the loss of hypocretin (orexin) neurons in the lateral hypothalamus [2]. In addition to sleep and wakefulness regulation, hypocretin plays an important role in food intake regulation and metabolism. The etiology of NwoC is not well understood, and NwoC is not characterized by hypocretin deficiency in the cerebrospinal fluid.

Patients with narcolepsy have a lower quality of life compared to other neurological patients. On the Short Form–36 questionnaire, the dimensions “physical functioning,” “vitality,” and “general health perception” have been found to be the main domains of health-related decreased quality of life [3]. Exercise tolerance is the strongest prognostic marker of all-cause mortality in the general population [4] and in different chronic diseases, for example, obesity, coronary artery disease, heart failure, and cancer [5]. Exercise tolerance depends on daily energy expenditure or the amount of daily exercise. Patients with narcolepsy are reported to need more sleep during the daytime and are more fatigued than controls [6]; thus we may speculate that the main determinants of cardiopulmonary fitness in NC and NwoC are due to sleepiness and potentially to cataplexy episodes preventing patients from engaging in regular physical activity. The aim of the present study was to test the hypothesis that exercise tolerance in narcolepsy negatively depends on sleepiness.

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http://dx.doi.org/10.1016/j.sleep.2017.02.017

2. Methods

2.1. Study population

A total of 56 patients aged 18–65 years diagnosed with NC and NwoC, who were indicated for an exercise stress test before the initiation of an exercise program, were included in the present study (years 2013–2015). The age- and gender-matched control group was recruited from among participants of a preventive program for the general population to whom an exercise stress test was offered. All patients gave informed consent to participation in the study. The study was approved by the local ethical committee (40/11 IGA MZČR VFN), and was conducted in accordance with the Declaration of Helsinki.

Of the 56 subjects who agreed to participate in the study, 42 patients completed the cardiopulmonary exercise stress test (CPX). One patient had difficulty breathing through the mouthpiece and did not want to reschedule the test with a mask. Thirteen patients did not attend the scheduled CPX and thus were not included.

Of the 42 patients who completed the study, eight patients (19%) reported engaging in recreational sports. Five patients had arterial hypertension on monopharmacotherapy. One patient in the study population was treated with a β-blocker, another patient was treated with a statin, and two other patients were treated with a calcium channel blocker. Sixteen patients (38%) were current smokers and four patients (10%) were former smokers. There were no other diagnoses that could potentially affect the results of the CPX. Characteristics of the study population are summarized in Table 1, and the tests performed at narcolepsy diagnosis are summarized in Table 2.

All patients were previously diagnosed at our institution, and only those patients with an unambiguous diagnosis were invited to participate. All patients were diagnosed according to the International Sleep Disorders Classification, second edition [1]. In all patients, night polysomnography (8 h) and the 5-nap multiple sleep latency test (MSLT) were performed without any concurrent treatment that could influence sleep or cataplexy. Polysomnography was performed according to the American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events [7] and the MSLT according to AASM rules [8].

Results concerning sleep-related breathing disorders and periodic limb movements in sleep (PLMS) were retrieved from the diagnostic night polysomnography data to provide information about other sleep disturbances. Obstructive sleep apnea (OSA) was diagnosed according to polysomnography (PSG) criteria (apnea/hypopnea index ≥ 5). None of the patients fulfilled the diagnostic criteria for central sleep apnea [1]. Subjects were considered to have PLMS when the number of period leg movements per 1 h was ≥ 15 [7]. The mean latency between polysomnography and MSLT and the exercise stress test was 3.6 ± 4 years; however, information about general health status and pharmacological treatment was obtained at the date of the examination. The following information was selected and processed from the clinical records of all patients: age at data collection, age at symptom onset, body height and weight, Epworth Sleepiness Scale (ESS) score [9], cataplexy episode frequency per month (subjectively assessed), sleep latency during MSLT, sleep efficacy during night polysomnography, rapid eye movement (REM) sleep latency during polysomnography, percentage of slow-wave sleep during night polysomnography, and percentage of REM sleep during night polysomnography. Treatment with stimulants (modafinil and methylphenidate), antidepressants (selective serotonin reuptake inhibitors, venlafaxine, clomipramine, and tianeptine) and sodium oxybate at the time of the exercise test was as summarized in Table 2.

2.2. Cardiopulmonary exercise stress test

The CPX were carried out on a cycle ergometer (Ergoline e-Bike, GE Medical Systems, Milwaukee, WI, USA) at the same time, in the early afternoon. The work rate was corrected for body weight. We used a combined protocol with two consecutive 3-min steps, followed by a ramped increase in work intensity. The intensity of the first step was set to correspond to 0.5 Watt/kg (ie, 2.3 metabolic equivalents [METs]), increasing to 1.0 Watt/kg (ie, 4.7 METs) during the second step. Thereafter, a ramped increase in work intensity followed, consisting of 5 Watts/10 s, ie, 30 Watts/min, irrespective of body weight.

Blood pressure (BP) measurements were performed by an experienced nurse at the beginning of the third minute of each workload, and at each odd minute during the ramped increase. BP was measured manually by a standard sphygmomanometer using the auscultatory method. Systolic BP (SBP) was recorded at the appearance of the Korotkoff phase I sound, and diastolic BP (DBP) at the disappearance or muffling of the Korotkoff sounds (phase IV or V); preference was at the complete disappearance of the Korotkoff sound, and in the case of uncertainty, diastolic pressure was not noted. Heart rate (HR) in beats per minute (bpm) was measured from the electrocardiogram (ECG) recording by Cardiosoft v6.51 (GE Medical Systems, Milwaukee, WI, USA).

Analysis of expired gas was performed breath-by-breath using a Vmax Spectra 29s Cardiopulmonary Exercise Testing Instrument (SensorMedics Corporation, Yorba Linda, Canada). Flow and sensor calibration was performed before each test according to the device manual. The respiratory exchange ratio (RER; VCO_2/VO_2) and metabolic equivalent of tasks (METs; VO_2/basal oxygen demand [3.5 mL/kg/min]) were calculated from the measured variables.

Markers of cardiopulmonary fitness included VO_{2peak} (mean from the last 30 s of the exercise test), expressed in mL/kg/min, as a percentage of the national norm (VO_{2peak}%), as well as the number of standard deviations (SD) from the national norm (VO_{2peak}SD). These data were derived from the specific national data from the International Biological Program [10], as it is widely used in reporting fitness data, in which less than 85% and less than one SD are considered abnormal [11].

Table 1
Characteristics of study population.

	All narcolepsy	NC	NwoC	Control	Control vs all narcolepsy	NC vs NwoC
No.	42	32	10	36		
Age (y)	34.9 ± 10.0	35.0 ± 10.0	34.6 ± 10.6	35.3 ± 10.2	NS	NS
Gender (male/female)	16/26	12/20	4/6	15/21	NS	NS
Weight (kg)	88.0 ± 53.0	89.5 ± 15.3	83.4 ± 20.9	85.6 ± 20.3	NS	NS
Height (cm)	171.8 ± 9.1	171.4 ± 9.6	173.0 ± 8.0	174.3 ± 9.7	NS	NS
BMI	29.9 ± 5.7	30.6 ± 5.6	27.6 ± 5.7	28.1 ± 6.2	NS	NS

BMI, body mass index; NC, narcolepsy patients; NwoC, narcolepsy patients without cataplexy.