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Original article

Menopause, hormone replacement and RR and QT modulation during sleep

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Abstract

Background and purpose: Sleep affects the RR interval in electrocardiogram (ECG) recordings and ventricular repolarization differentially in men and women. Compared to men, pre-menopausal women have a more pronounced shortening of RR interval and prolongation of QT and QT corrected (QTc, by Bazett's formula) ECG waves during rapid eye movement (REM) sleep. The aim of the present study was to evaluate sleep-related RR and QT changes: (1) with the physiological decline in female hormones occurring with menopause, and (2) after hormone replacement therapy with estrogen and progesterone (HRT).

Patients and methods: We analyzed ECG recordings from 14 post-menopausal women (48–61 years old) who underwent polysomnography before HRT (T1) and after 6 months of HRT (T2) with estrogen and progesterone. Eight of the post-menopausal women (48–54 years) were also compared to eight age-matched pre-menopausal women. In all subjects, mean RR interval, mean QT interval and QTc, were obtained from 1-min recordings selected from wakefulness, stage 2 and REM sleep.

Results: Pre-menopausal and post-menopausal women showed similar changes in RR, QT and QTc intervals from wakefulness through sleep. Specifically, in both pre-menopausal and post-menopausal women the RR interval was shorter during REM sleep compared to wakefulness ($P=0.009$) and stage 2 sleep ($P=0.001$); the QT interval was more prolonged during stage 2 ($P=0.002$) and REM ($P=0.006$); and the QTc interval was significantly prolonged during stage 2 ($P=0.01$) and REM ($P=0.0003$) sleep compared to wakefulness.

Among post-menopausal women, both before and after HRT (T1 and T2), RR interval shortened significantly during REM compared to wakefulness ($P=0.03$) and to stage 2 ($P=0.002$); the absolute QT interval was longer during stage 2, compared to both wakefulness ($P<0.001$) and REM ($P<0.001$); the QTc interval was increased during REM sleep compared to wakefulness ($P=0.003$).

Conclusions: Sleep-related RR and QT changes in women are not altered by menopausal status nor by post-menopausal hormonal replacement with estrogen and progesterone.

Keywords: Sleep; Menopause; RR interval; QT interval; Gender; Hormones

1. Introduction

Previous studies have reported that gender independently influences the autonomic control of sinus node function and ventricular repolarization [1–5]. Women have shorter resting RR intervals, i.e., a shorter duration of the cardiac cycle at the electrocardiogram (ECG), compared to men [1–3]. Women also have longer QT and QTc intervals (i.e., QT corrected by the RR) at the ECG, to express longer duration of cardiac

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repolarization [3,4]. Women are also more susceptible to pathological QT prolongation and ventricular arrhythmias when exposed to medications affecting ion currents implicated in cardiac repolarization [6]. The mechanisms underlying these gender-related differences remain unclear.

Clinical [7] and experimental [8,9] data suggest that androgens play a protective role in shortening the cardiac repolarization phase and hence the duration of the QTc interval in men. However, other data suggest that female sex steroids may be responsible for prolongation of cardiac repolarization in women [10].

Recently, it has been shown that gender influences both autonomic control of sinus node function and cardiac repolarization during sleep [2,5]. Compared to men, pre-menopausal women have a more pronounced shortening of RR interval during REM sleep. REM is associated with paradoxical prolongation of QT and QTc intervals [5]. Whether sex hormones may contribute to this gender difference is not known.

We therefore examined whether sleep-related changes in RR and QT intervals are affected by menopausal status and the decline of female hormones after menopause, and whether they might be affected by post-menopausal hormone-replacement therapy with combined estrogens and progesterone (HRT).

2. Methods

2.1. Subjects and study design

We previously studied the effects of HRT with combined estrogens and progesterone on sleep in 21 post-menopausal women [11]. In 14 subjects (mean age 53 ± 3, range 48–61 years), the electrocardiogram (ECG) recordings were suitable for RR and QT analysis. All subjects included in the study were healthy women whose post-menopausal status was defined by amenorrhea for at least 6 months, presence of menopausal symptoms (hot flashes, night sweats and redness of the face) and levels of follicle-stimulating hormone >40 IU/L and estradiol <110 ng/L. Excluded were women with a previous hysterectomy or bilateral oophorectomy, endocrinopathy, alcohol or drug abuse, specific sleep disorders and the use of medications likely to influence sleep, vigilance or the autonomic nervous system.

Polysomnography was performed on two consecutive nights before treatment and after 6 months of HRT with conjugated estrogens (Premarin 0.625 mg) for 25 days (days 1–25 of each 30 day-cycle) and medroxyprogesterone acetate 5 mg (MPA) or micronized progesterone 200 mg for 14 days (days 12–25). Polysomnographic studies on HRT were performed between nights 22 and 25 of each subject's 30 day-cycle (while still on progesterone). Blood samples for the assessment of estradiol, progesterone and 17-hydroxyprogesterone levels were taken at the time of enrollment and before sleep studies at T2 [11].

A sub-group of eight post-menopausal women aged 48–54 years were also compared to age-matched (47–53 years old) pre-menopausal women. Pre-menopausal women were studied during the luteal phase of their regular menstrual cycle. Exclusion criteria were as mentioned above and further included the use of hormone/estrogen therapy within 4 weeks of study enrollment.

All subjects provided written informed consent. The study was approved by our local hospital ethics committee.

2.2. Data recording and analysis

Polysomnography was performed according to a standard clinical protocol, with recording of electroencephalogram (EEG) (C3-A2, O2/A1), submental and anterior tibialis electromyography (EMG), electro-oculography (EOG), oronasal airflow (thermocouples), thoracic and abdominal strain gauges, oxygen finger probe and one lead ECG (Lead I). Recordings were scored for sleep stages according to the standard method established by Rechtschaffen and Kales [12], using 20-s epochs. Micro-arousals and sleep-disordered breathing were scored according to American Sleep Disorders Association recommendations [13,14]. For both T1 and T2 (treatment phase before and after HTR, respectively), only data from the second night were used in the analyses, the first night serving as an adaptation to the laboratory conditions.

Polysomnographic variables included sleep latency, sleep efficiency (total sleep time divided by the total time in bed), the percentage of each stage of sleep, micro-arousal index (number of micro-arousals per hour of sleep), periodic leg movements (PLM) index (number of periodic leg movements per hour of sleep) and apnea/hypopnea index (number of apneas and hypopneas per hour of sleep).

ECG recordings were used for the computation of the RR and QT intervals. ECG recordings with stable sinus rhythm and QRS axis during the night and clearly detectable end of the T wave were considered. One-minute recordings of ECG signals were selected from inactive wakefulness and each stage of sleep:

(1) between 11 PM and 2 AM, to reduce any possible bias due to time of inactivity on RR and QT intervals [15];
(2) one minute after the beginning of each stage and at least one min away from arousals;
(3) only in the presence of stable breathing patterns, in order to avoid any QT changes associated with breathing instability;
(4) segments representative of REM were selected in order to include similar proportion of tonic and phasic REM (50:50).

Data were analyzed by one observer (P.A.L.), blinded to group (pre- and post-menopausal) and treatment phase (T1 or T2). All recordings were automatically analyzed by ScopeWin QT software (which allows the automatic