

Protective effect of metoprolol on arrhythmia and heart rate variability in healthy people with 24 hours of sleep deprivation

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Abstract

Purpose Sleep deprivation, which is a strong stressor, can greatly affect the cardiovascular system of rescue workers. This study aimed to investigate the effect of 24-h sleep deprivation on heart rate variability (HRV) in young healthy people and the protective effect of metoprolol on arrhythmia.

Methods Sixty young, healthy subjects (6 women and 54 men), aged 25±4.5 years, were enrolled in this study. All participants received 24-h continuous ambulatory electrocardiogram monitoring. Arrhythmia, time, and frequency domain parameters were analyzed in subjects at the following three stages: normal sleep stage, sleep deprivation stage, and metoprolol treatment before sleep deprivation stage.

Results After 24-h sleep deprivation, the high frequency (HF) of HRV was significantly decreased ($p<0.05$), low frequency (LF) was remarkably increased ($p<0.05$), and LF/HF was significantly increased compared with those in normal sleep ($p<0.05$). Some subjects presented with mild palpitation due to premature atrial complexes and premature ventricular complexes. At the metoprolol treatment stage, compared with the sleep deprivation stage, LF and LF/HF were significantly reduced, HF of HRV was elevated ($p<0.05$), and the total amount of premature atrial and ventricular complexes was decreased.

Conclusion The underlying mechanism of arrhythmia and HRV alteration after 24-h sleep deprivation could be attributable to lower vagal activity and elevated sympathetic activity. Metoprolol improves the change in autonomic nervous

system activity after 24-h sleep deprivation, which may be responsible for its protective role on arrhythmia in healthy subjects undergoing sleep deprivation.

Keywords Sleep deprivation · Arrhythmia · Heart rate variability · Metoprolol

In the setting of earthquakes, floods, or fire disasters, rescue workers usually carry out their work without sleep. Sleep deprivation (SD), which is a strong stressor, can exert a large effect on the cardiovascular system of rescue workers. It has been reported that SD is associated with increased arrhythmogenicity and disturbed cardiac autonomic control [1]. Heart rate variability (HRV) is acknowledged as a reliable marker of cardiac autonomic control, and the frequency of premature ventricular complexes can be an indicator of arrhythmogenicity. It is known that metoprolol, a class II antiarrhythmic agent, is currently used in clinical practice for the treatment of arrhythmia and hypertension, as well as for improving cardiac autonomic function. Previous studies on the pathophysiology of people with SD receiving beta-blockers are rare. This study aimed to investigate (1) the changes in heart rate variability and occurrence of cardiac arrhythmia by 24-h continuous ambulatory electrocardiogram (ECG) (24-h Holter) in young, healthy subjects undergoing complete SD and (2) the effects of metoprolol on HRV and arrhythmia after this agent was administered prophylactically before SD.

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1 Methods

1.1 Study population

Subjects aged between 18 and 30 years of both sexes were recruited by advertisement from the army. Sixty subjects (6 women and 54 men), aged 25±4.5 years, were enrolled, and

all participants completed the protocols. All subjects gave written, informed consent in accordance with the PLA General Hospital before taking part in this study. All participants received financial compensation for participation. This study was carried out in the clinical investigation unit of the PLA General Hospital. Participants were free of any medical conditions (e.g., hypertension, diabetes mellitus, and hyperthyroidism) and medication known to affect cardiovascular, metabolic, gastrointestinal, or immune function (including over-the-counter medication). Participants who suffered from sleep, depression, or anxiety disorders were excluded from the study according to self-reported pre-study questionnaires and written confirmation from their general practitioner. All subjects were nonsmokers at the time of the study and did not consume alcohol.

1.2 Heart rate variability

Sixty participants received Holter monitoring using a 12-channel ambulatory ECG recorder (Pacerecorder Model MIC-12H, Beijing Jinco Medical Co., Ltd) with a sampling rate of 250 Hz (4 ms). The P waves and QRS complexes were automatically classified and manually verified as normal sinus rhythm, premature atrial or premature ventricular complexes, or noise by comparison with adjacent waves. The R–R intervals were deduced from the adjacent normal sinus beats (i.e., N–N intervals). For the entire study population, time domain measurements, including mean N–N intervals, standard deviation of N–N intervals (SDNN), and root-mean-square successive differences (RMSSD), were calculated automatically every 5 min. The power spectrum densities were estimated by Welch's averaged periodogram method, while extremely low-frequency (VLF) power (0.01–0.04 Hz), low-frequency (LF) power (0.04–0.15 Hz), and high-frequency (HF) power (0.15–0.4 Hz) were derived for each 5-min segment. HF power is considered a function of cardiac parasympathetic nervous system activity to the heart [2]. LF, although not modulated by a single arm of the autonomic nervous system [3], is considered to be normalized for total power as a representative index of sympathetic activity to the heart [4–6]. The LF-to-HF power ratio is considered an index of the balance of sympathovagal input to sinoatrial node activity and has been found to be representative of sympathetic to parasympathetic balance in both physiological and pathophysiological conditions [2, 5–8].

1.3 Mean arterial pressure

Patients rested in the supine position while blood pressure was measured each hour from the right arm by an automatic cuff recorder (Critikon, Dinamap 1846 SX, USA).

2 Protocol

No caffeine or alcohol was allowed from the 48 h preceding the laboratory studies to the completion of the study. Enrolled subjects reported to the sleep laboratory at 07:30 hours after obtaining their normal sleep at home the previous night. Each subject remained awake in the sleep lab from 17:00 hours of day 1 to 17:00 hours of day 2 at the stage of SD. All participants had a designated bedroom for the entire study. All physiological measurements were performed in the bedroom with temperature of 22 °C and illumination of 100 lx during the study. Subjects were continuously monitored by a video camera. The subjects displaying sleep onset were immediately aroused and kept awake by verbal encouragement. Caloric and fluid management was individualized according to estimated daily needs. However, snacks were permitted to be eaten in the lab. Subjects were permitted to read, watch video movies on a DVD player, play video games, do job-related work, including using the computer and Internet, and converse with the staff or visitors.

Subjects underwent the following three stages: normal sleep, SD, and metoprolol treatment before SD. At the normal sleep stage, 24-h Holter monitoring was applied to all subjects. At the SD stage, we examined subjects who received another 24-h Holter examination at the sleep 1 month after the first stage. At the third stage, subjects accepted metoprolol administration 3 days previously and underwent SD again, which was scheduled 1 month later following the second stage, and data derived from 24-h monitoring were analyzed. Metoprolol was given in the morning (08:00–09:00 hours) and at the afternoon (17:00–18:00 hours), and the dosage was 25 mg every time.

3 Statistical analysis

Continuous variables are expressed as the mean \pm standard deviation. Continuous variables were compared with the Student's *t* test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were compared by χ^2 test. A *p* value of <0.05 was considered statistically significant.

4 Results

The characteristics of the study population are given in Table 1. The body mass index of the participants ranged from 22 to 23.1 kg/m². They usually needed 7 to 10 h of sleep daily.

At the normal sleep stage, some of the subjects (*n*=5) complained of sleep disruption due to blood pressure measurements, but it did not generally affect the normal sleep of subjects. At the metoprolol treatment before SD stage, a few

Table 1 Population characteristics

	Subjects (n=60)	
	Male	Female
Sex	54 (90 %)	6 (10 %)
Age (years)	26±3.7	24±2.8
Height (m)	1.71±0.03	1.68±0.02
Weight (kg)	66±2.8	63±2.8
BMI (kg/m ²)	22.5±0.3	22.3±0.4
Normal duration of sleeping time (h)	7.5±0.7	7.8±1.1

Data were presented as mean ± standard deviation unless otherwise indicated

BMI body mass index

of the subjects complained of mild fatigue (n=2), headache (n=1), and constipation (n=1) after the administration of metoprolol. Daily life was not significantly affected by this drug.

After SD, heart rate, mean blood pressure, LF, and LF/HF of HRV were significantly increased at the SD stage compared with those in the normal sleep stage (p<0.05). There was also a significant decrease in HF, VLF, SDNN, and RMSSD of HRV at the SD stage compared with those in the normal sleep stage (p<0.05). The subjects suffered from frequent premature atrial and ventricular complexes after SD. At the third stage, after prophylactic treatment of metoprolol, heart rate, mean blood pressure, LF, and LF/HF were significantly decreased compared with those in the SD stage, and HF, VLF, SDNN, and RMSSD of HRV were also elevated (p<0.05). The frequency of premature atrial complexes and premature ventricular complexes was reduced with treatment of metoprolol compared with that in the SD stage (Table 2).

The duration of experimental time was divided into two periods: night time and day time. Night time was defined as from 17:00 hours of day 1 to 05:00 hours of day 2 and day time was 05:00 hours of day 2 to 17:00 hours of day 2. With a prolonged SD, especially at day time compared with the night time, LF was significantly increased (p<0.05; Fig. 1), and HF was remarkably decreased after SD (p<0.05; Fig. 2). With the progression of SD, the participants suffered from more atrial premature beats and ventricular premature beats (Figs. 3 and 4).

5 Discussion

In this study, we identified the changes regarding HRV parameters among three different stages. We found that HF, VLF, SDNN, and RMSSD were significantly decreased, and LF and LF/HF were remarkably elevated among participants

with SD compared with the same individuals during normal sleep. After the prophylactic administration of metoprolol before SD, HF, VLF, SDNN, and RMSSD were recovered, and LF and LF/HF were nearly reduced to the original values among SD participants.

Spectral analysis techniques have been used to determine changes in central nervous system activity. Power in specific frequency bands can be related to parasympathetic and sympathetic nervous system activity. Specifically, relative power in HF areas, usually from 0.15 to 0.5 Hz, has been used to infer parasympathetic nervous system activity. A range of lower frequencies from 0.05 to 0.15 Hz has typically been related to a combination of parasympathetic and sympathetic influences [9–11]. Because LF power is a combination of sympathetic and parasympathetic effects, investigators frequently infer sympathetic nervous system activity from the ratio of low (parasympathetic and sympathetic) to high (predominantly sympathetic) power so that parasympathetic power is extracted out of the ratio to some extent [10, 12, 13], leaving a better indicator of sympathetic activity. VLF, SDNN, and RMSSD are also considered as representative indices of parasympathetic nervous system activity [14]. Acute SD is associated with increased sympathetic activity and decreased parasympathetic modulation [15]. In addition, sleep disturbance may also result in sympathovagal imbalance [15, 16] and an increase in premature ventricular complexes [16]. Lower HF, VLF, SDNN, and RMSSD reflect lower parasympathetic activity, and higher LF and LF/HF indicate higher sympathetic activity. All these factors are associated with a higher risk of cardiovascular

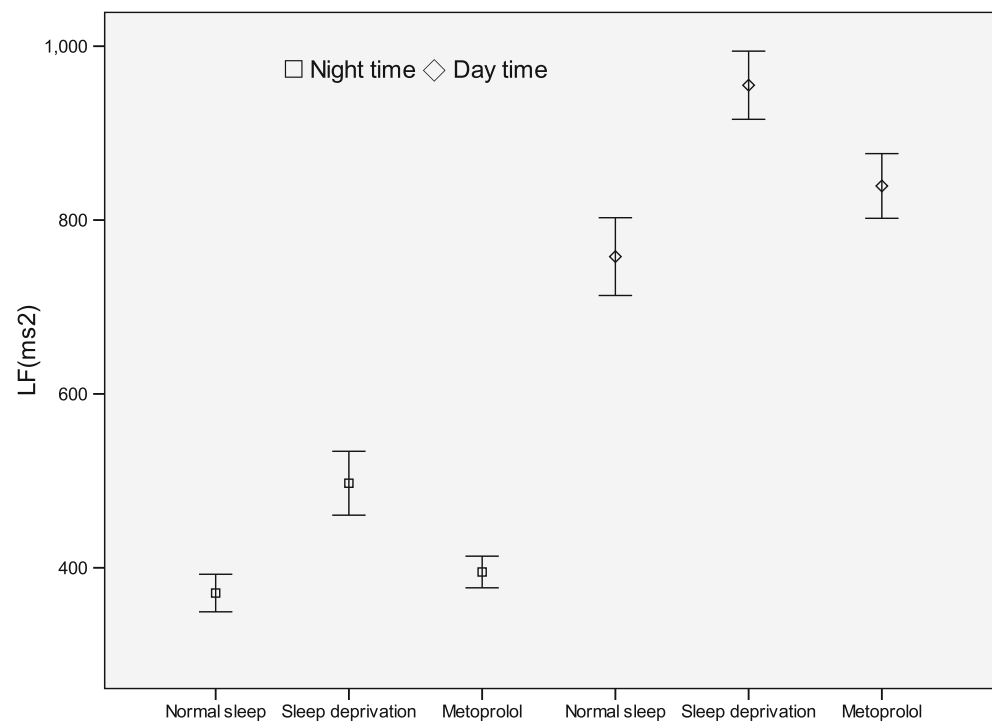
Table 2 Changes in arrhythmia and HRV parameters during three stages

Parameter	Normal sleep (n=60)	Sleep deprivation (n=60)	Metoprolol (n=60)
AHR (beats/min)	68±18	78±18*	69±17**
MAP (mmHg)	115±9	120±8*	116±6**
PAC (beats/h)	1±1	4±2*	2±1**
PVC (beats/h)	1±1	3±2*	1±1**
HF (ms ²)	787±393	614±390*	691±417**
LF (ms ²)	1,129±443	1,383±675*	1,148±356**
VLF (ms ²)	24,932±19,932	20,917±19,232*	23,200±19,374**
LF/HF	1.85±0.97	2.63±0.94*	2.22±1.01**
SDNN (ms)	151±46	129±34*	144±34**
RMSSD (ms)	52±22	45±21*	49±17**

AHR average heart rate, MAP mean artery pressure, PAC premature atrial complexes, PVC premature ventricular complexes, HF heart failure, LF low frequency, VLF very low frequency, LF/HF low frequency/high frequency, SDNN standard deviation of N–N intervals, RMSSD root-mean-square successive differences

*p<0.05, sleep deprivation vs normal sleep; **p<0.05, metoprolol vs sleep deprivation

Fig. 1 The change of LF through the three stages. Night time is characterized as 17:00 hours of day1 to 05:00 hours of day2. Day time is characterized as 05:00 hours of day2 to 17:00 hours of day2. Data were presented as mean \pm standard deviation ($n=60$)



disease [14, 17]. The current study found that premature atrial complexes and premature ventricular complexes were significantly increased in participants with 24-h SD. The change in arrhythmia after 24-h SD has been found to correlate with elevated sympathetic activity [17]. Therefore, in our study, the above-mentioned findings are consistent with results of a previous research.

Metoprolol can bind to beta-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both β_1 and β_2 adrenoceptors, and the predominant receptor type in number and function is β_1 . Metoprolol acts by blocking the effects of catecholamines at β_1 -adrenergic receptors, thereby decreasing sympathetic activity on the heart. Metoprolol is useful in the treatment

Fig. 2 The change of HF through the three stages. Night time is characterized as 17:00 hours of day1 to 05:00 hours of day2. Day time is characterized as 05:00 hours of day2 to 17:00 hours of day2. Data were presented as mean \pm standard deviation ($n=60$)

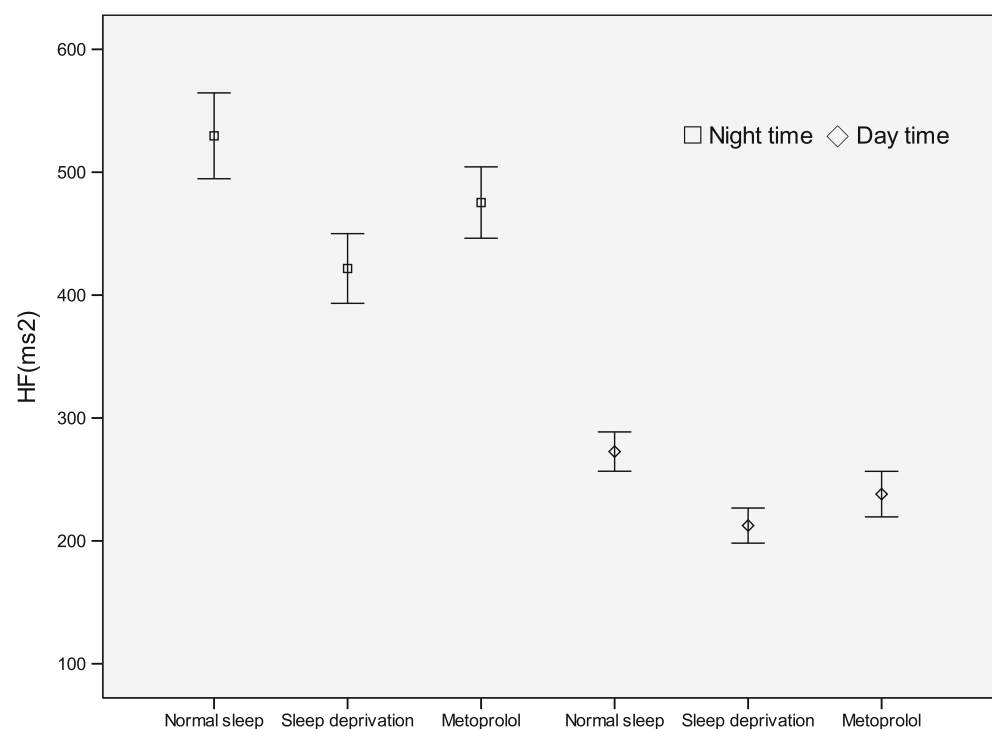
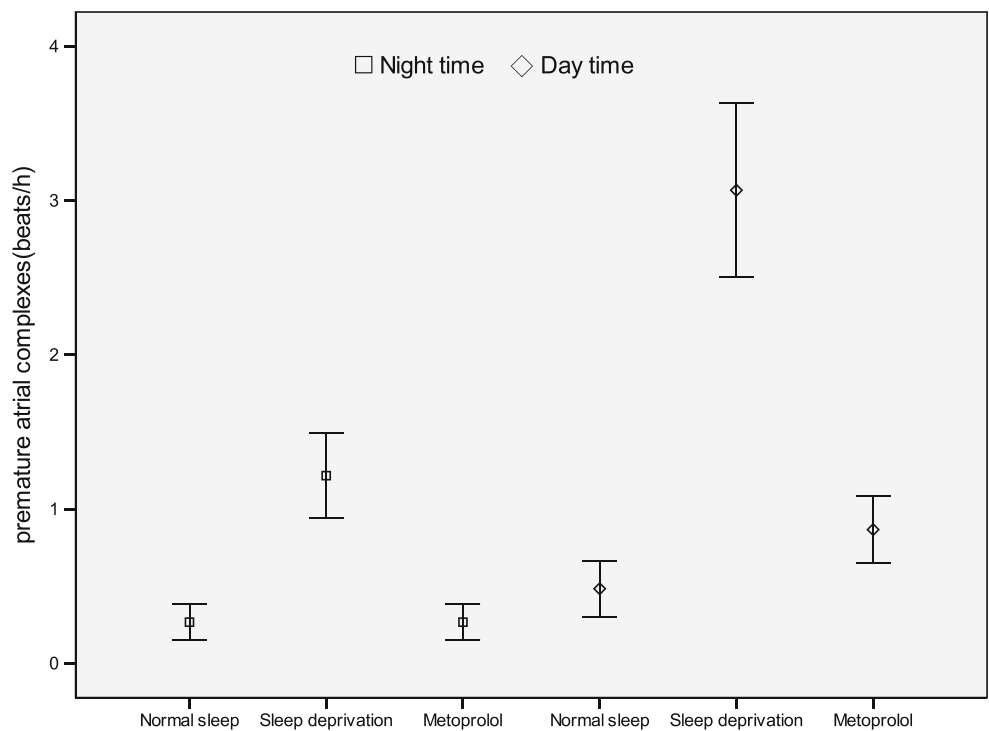


Fig. 3 The change of premature atrial complexes through the three stages. Night time is characterized as 17:00 hours of day 1 to 05:00 hours of day 2. Day time is characterized as 05:00 hours of day 2 to 17:00 hours of day 2. Data were presented as mean \pm standard deviation ($n=60$)

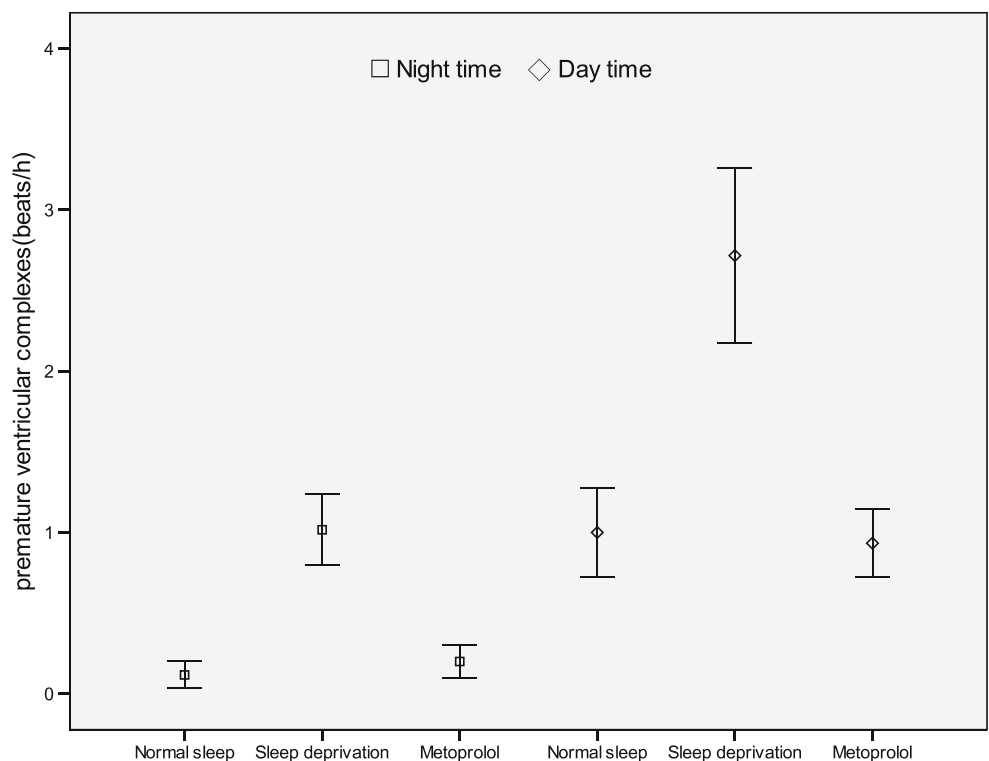


of supraventricular and ventricular tachycardia. In the current study, at the third stage after administration of metoprolol, an increase in HF, VLF, SDNN, and RMSSD reflected a recovery of parasympathetic activity, and a decrease in LF and LF/HF indicated the return of sympathetic activity. Therefore, beta-

blockers can play an important role in the prevention of arrhythmia in healthy people with 24-h SD.

In conclusion, the mechanism of alteration of arrhythmia and HRV after 24-h SD could be related to lower vagal activity and elevated sympathetic activity. Metoprolol can

Fig. 4 The change of premature ventricular complexes through the three stages. Night time is characterized as 17:00 hours of day 1 to 05:00 hours of day 2. Day time is characterized as 05:00 hours of day 2 to 17:00 hours of day 2. Data were presented as mean \pm standard deviation ($n=60$)



improve this change in the autonomic nervous system after 24-h of SD, and it can play a preventive role of arrhythmia in healthy people with SD. The main limitations of this study are the small number of subjects and a non-placebo-based study protocol was carried out.

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Editorial Commentary

Sleep deprivation can have an adverse effect on markers of arrhythmia susceptibility such heart rate variability (HRV). This study shows that the beta-adrenergic blocker metoprolol ameliorates sleep deprivation changes on HRV and may therefore be advantageous for reducing arrhythmia propensity in sleep-deprived individuals.