Original Article

Chronic Sleep Deprivation and Ventricular Arrhythmias: Effect of Sympathetic Nervous System

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Abstract

Background: Chronic sleep deprivation through activation of sympathetic nervous system leads to destructive effect on different body organs. We assessed the effect of chronic sleep deprivation on incidence of ischemia/reperfusion-induced ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) and the role of the sympathetic nervous system in this respect.

Materials and Methods: A total of 24 Rats were randomly divided into four groups of six; 1) ischemia/reperfusion group (IR): 30 minutes ischemia followed by 60 minutes reperfusion was induced, 2) control group (CON): rats has been placed in large multiple platforms for 72h prior to ischemia and reperfusion, 3) Chronic sleep deprivation group (SD): 72h sleep deprivation was induced by using small multiple platform prior to ischemia and reperfusion, 4) Sympathectomy group (SYM): chemical sympathectomy was done 24h before to chronic sleep deprivation and then underwent ischemia and reperfusion. The heart isolated and perfused by langendorff apparatus. After thoracotomy and aorta cannulation, the hearts perfused in the langendorff apparatus using krebs-Henseleit buffer. Hearts were allowed to recovery for 15 min. After recovery period, 15 minutes was considered as baseline prior to 30 minutes ischemia followed by 60 minutes reperfusion. Two thin stainless steel electrodes fixed on the ventricular apex and right atrium for recording the lead II of electrocardiogram (ECG).

Results: There were no significant differences in heart rates between groups, and ventricular tachycardia significantly increased in chronic sleep deprivation group as compared with IR group in ischemia period. Sympathectomy significantly reduced ventricular tachycardia incidence when compared with SD. There is no difference in incidence of ventricular tachycardia between control group and IR group. The incidence of ventricular fibrillation during early reperfusion was significantly augmented ($p<0.05$) in sleep deprivation group as compared with IR group and Sympathectomy significantly could reverse ventricular fibrillation incidence to IR group level as compared with SD group ($p<0.05$).

Conclusion: Induction of 72h sleep deprivation prior to ischemia and reperfusion increased the probability of ventricular tachycardia and ventricular fibrillation occurrence during ischemia and reperfusion and chemical sympathectomy could eliminate this effect.

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Received: December 19, 2015
Accepted: December 27, 2015

Keywords: Sleep deprivation, ventricular arrhythmias, sympathectomy, rat heart

Please cite this article as: Choopani S, Imani A, Faghihi M, Askari S, Edalatyzadeh Z. Chronic Sleep Deprivation and Ventricular Arrhythmias: Effect of Sympathetic Nervous System. J Cell Mol Anesth. 2016;1(2):56-61.

Introduction

Sleep as a physiological process affects different biological systems. Its integrity is necessary for maintaining health and homeostasis in human. Autonomic nervous system (ANS), has a critical role in different sleep stages (1). Insufficient sleep is a common problem in modern society, and it has been estimated that about one in five adults are affected by sleep problems (2). Chronic sleep restriction has adverse effects on cardiovascular system, immune responses, hormonal pathways, and thermoregulation. Human studies represent that sleep deprivation can increase activation of the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal axis (HPA), and the immune system. Sgoifo *et al*, reported that after 48-h sleep deprivation, heart rate and HPA activity considerably augmented. Some studies have shown that 48h sleep deprivation cause imbalance between parasympathetic and sympathetic tones which changes electrocardiographic patterns (3)**.** Sleep deprivation by increasing sympathetic activity leads to increase in percent low-frequency and a decrease in percent high-frequency component of heart rate variability (HRV), increase in low-frequency band of blood pressure variability (BPV), and increase in serum norepinephrine as well as a reduction in maximum endothelial dependent vasodilation. Also five night of partial sleep deprivation is adequate factor to significant increase in sympathetic activity and venous endothelial dysfunction (4).

Despite growing advances against heart disease over the past 50 years, myocardial infarction remains a leading cause of death in united states (5). The development of ventricular arrhythmias and the loss of myocardial contractility are all relevant as clinical consequences of occlusive coronary disease (6). Restitution of the blood supply to an ischemia area that is known as myocardial reperfusion in addition to its cardioprotective effect, can cause myocardial injuries arrhythmias and contractile dysfunction (7).

The autonomic nervous system plays key role in the regulation of cardiac electrophysiology and arrhythmogenesis. The mechanisms by which autonomic activation can induce arrhythmogenic or antiarrhythmic effects are complex and are different for each type of arrhythmias (8). It was found that stimulation of the vagus nerve in rats, dogs, and cats, can prevent ventricular arrhythmias during myocardial ischemia associated with enhanced cardiac sympathetic activity (7).

Since little is known about potential properties of chronic sleep deprivation to facilitate incidence of ventricular arrhythmias, we hypothesized that chronic sleep deprivation through increasing the sympathetic nervous system leads to increase the incidence of ventricular of tachycardia (VT) and ventricular fibrillation during ischemia and reperfusion.

Methods

Experimental animals and ethical approval

Adult Male wistar rats with body weight between 250-300 gr. were housed in an animal room with 12h light/dark cycle at 22±2°C and free access to food and water. All experiments were conducted in accordance with the institutional guidelines of Tehran University of Medical Sciences (Tehran, Iran) and the National Institutes of Health guidelines for the care and use of laboratory animals.

Surgical procedure for heart isolation

Rats were anesthetized with pentobarbital sodium (50 mg/kg; intra-peritoneal) and administered heparin sodium (500 IU; intra-peritoneal). After thoracotomy and aorta cannulation, the hearts perfused in the langendorff apparatus using krebs-Henseleit buffer containing: $NaHCO_3$ 25; KCl 4.7; NaCl 118/5; $mgso_4$ 1/2; KH_2PO_4 1/2; glucose 11; CaCl 2/5. The perfusion pressure was maintained at 70cm H_2O. The perfusate was bubbled with a 95% O_2 and 5% CO_2 gas mixture, and the bubbling rate was adjusted to maintain a physiological PH (7/35-7/45). The perfusate temperature was maintained at 37°c. Tow thin stainless steel electrodes fixed on the ventricular apex and right atrium for recording the

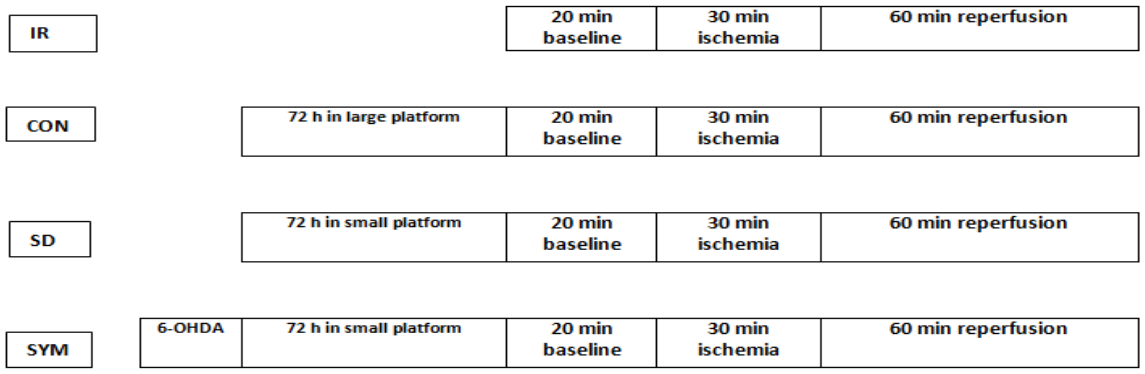

Fig. 1. Schematic diagram of the experimental protocol. IR: ischemia-reperfusion, CON: Control, SD: sleep deprivation, SYM: sympathectomy**.**

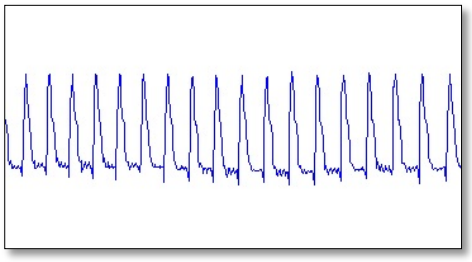

Fig. 2. Ventricular tachycardia.

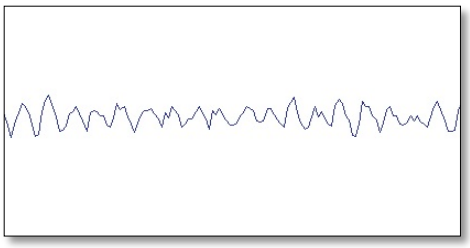

Fig. 3. Ventricular fibrillation.

lead II of electrocardiogram (ECG).

For induction of regional ischemia a surgical needle was passed all round the origin of the left anterior descending coronary artery (LAD), and the ends of the structure were passed through a pipette tip to form a snare. Regional ischemia was induced by tightening the snare and reperfusion was performed by releasing the ends of the structure. After recovery period, 15 minutes was considered as baseline prior to 30 minutes ischemia followed by 60 minutes reperfusion.

Induction of chronic sleep deprivation

The modified multiple platform method (MMPM) was selected to induce chronic sleep deprivation (CSD). Briefly, rats were placed in a water tank (125×44×44 cm.) containing 8 circular platforms, 6.5 cm. in diameter (small platform) for induction of chronic sleep deprivation. Another tank containing 4 circular platforms, 14 cm. in diameter (large platforms) was used for control group. The tank was filled with water until approximately 1 cm. below of platforms top. The rats were allowed to move around freely inside the tank. Muscle atonia due to sleeping led to falling from small platforms the water and awaked the animal. Rats on large platforms could sleep. The large platforms were used for assessing stress due to tank. Food and water were free for using by animals.

Experimental Protocol

The experimental protocol has been shown in figure 1. The hearts were subjected to a stabilization period with krebs-Henseleit buffer perfusion for 20 min. baseline period followed by 30 min. of regional ischemia and 60 min. of reperfusion. All animals were randomly divided into four groups; IR group: rats underwent 30 min. ischemia reperfusion (n=7), CON: control group (n=6), rats has been placed in large multiple platforms for 72h prior to ischemia reperfusion, SD: chronic sleep deprivation group (n=10), 72h sleep deprivation was induced by using small multiple platform prior to ischemia reperfusion. SYM: Sympathectomy group (n=4), 24h before to sleep deprivation, chemical sympathectomy was done by single subcutaneously injection of 6-Hydroxydopamine (100 mg/kg).

Assessment of ventricular arrhythmia

Basis on the Lambeth conventions, ventricular ectopic beats (VEBs) were selected as obvious premature QRS complexes. Ventricular tachycardia (VT) was determined as the occurrence of for or more consecutive VEBs. Ventricular fibrillation (VF) was appeared as unidentifiable and low voltage QRS complexes (Figure 2 and 3).

Ventricular fibrillation may be sustained or may revert spontaneously to a normal sinus rhythm. VF lasting for more than 5 minutes was considered as irreversible.

The severity of arrhythmias was quantified by the following scoring system:

0. 0-50 VEBs with no other arrhythmias over the 25-minute ischemia period,
1. Only 50-500 VEBs,
2. More than 500 VEBs, or one episode of spontaneously reversible VT or VF,
3. 2-30 episodes of spontaneously reversible VT and/or VF
4. More than 30 episodes of spontaneously reversible VT and/or VF
5. Irreversible VF

Statistical analysis

Heart rates were expressed as the Mean±SEM. Tow way ANOVA test was performed for heart rate analyses between groups during baseline, ischemia and reperfusion periods. The arrhythemia scores were analyzed with kruskal-wallis test, and the incidences of VT or VF were compared using the fisher exact test. Significant differences were determined as $p<0.05$.

Results

Heart rate

Heart rate was continuously recorded during the experiments and calculated for 5 minutes at the end of baseline, ischemia and reperfusion. There were no differences between baselines of all groups. Only, heart rate during reperfusion were decreased significantly in IR and CON group ($p<0.05$) as compared with their baselines.

Number of Ventricular tachycardia (VT) episodes during ischemia

In this model of regional ischemia, severe ventricular arrhythmias peaked after 7-15 minutes of left descending artery (LAD) occlusion. Ventricular tachycardia significantly increased in chronic sleep deprivation group as compared with IR group ($p<0.05$, %55 and %15 respectively). Sympathectomy

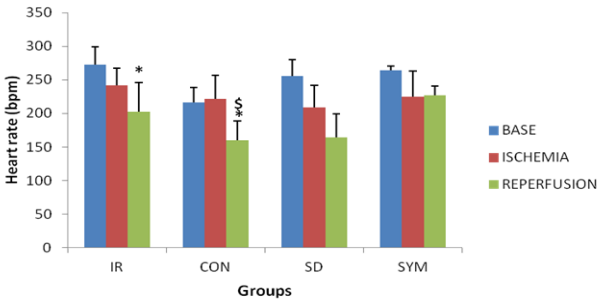

Fig. 4. Heart rate (bpm) in groups. IR: Ischemia reperfusion group, CON: Control group, SD: Sleep deprivation group, SYM: Sympathectomy group.*$p<0.05$ when compared with baseline, $ $p<0.05$ when compared with ischemia.

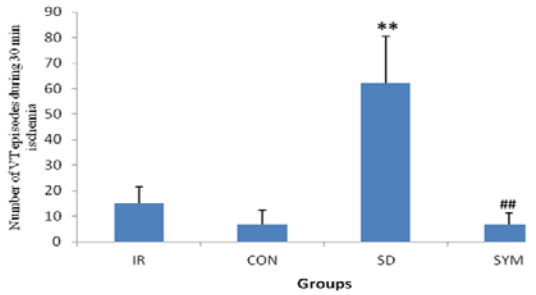

Fig. 5. The number of VT episodes during ischemia period. IR: Ischemia reperfusion group, CON: Control group, SD: Sleep deprivation group, SYM: Sympathectomy group.
**$p<0.01$when compared with IR, ## $p<0.01$ when compared with SD group.

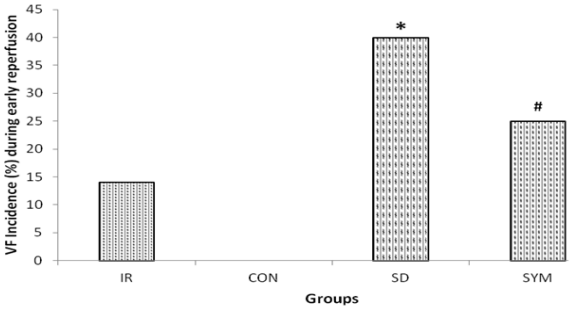

Fig. 6. The incidence of VF during early reperfusion period in groups. IR: Ischemia reperfusion group, CON: Control group, SD: Sleep deprivation group, SYM: Sympathectomy group. *$p<0.05$ as compared with IR group, # $p<0.05$ as compared with SD group.

in SYM group significantly reduced VT incidence when compared with SD group ($p<0.05$, 7% in sympathectomy group). There is no difference in VT incidence between control group (7%) and IR group.

Incidence of Ventricular fibrillation (VF) during reperfusion

The incidence of VF during early reperfusion was significantly increased ($p<0.05$) in sleep deprivation group (40%) as compared with IR group (14%). Sympathectomy significantly could decrease VF incidence (25%) as compared with SD group ($p<0.05$).

Discussion

In this study, we have shown that regional cardiac ischemia reperfusion after 72h chronic sleep deprivation could not change heart rate. The heart rate is a parameter that might play role in arrhythmogenesis. It is considerable that ischemia-induced arrhythmias originate from the boundary zone between the normal region and ischemic area in the boundary zone and shortening of action potential duration (APD) during ischemia will be accompanied by a shortening of refractoriness, which would be pro-arrhythmic (9).

72h of REM sleep deprivation causes to a significant increase in systolic and mean arterial pressure and a relative but non-significant increase in myocardial consumption index, however, it had no effect on the HR of rats (10). Also, it has been shown that 1 week of continuous night shift had no significant effect on the mean heart rate (11). Kato *et al*, reported that a one night of sleep deprivation was related to increased BP and decreased muscle sympathetic nerve activity, but it had no effect on the HR (12). On the other hand, acute sleep deprivation leads to a greater sympathetic influence on the autonomic control of the heart. Endogenous circadian rhythmicity effect on autonomic control of heart rate and the timing of these endogenous rhythms can be altered by extended sleep/rest episodes and associated changes in photoperiod (13).

The present study indicates that the chronic sleep deprivation augmented the number of ventricular tachycardia episodes during ischemia period. It is assumed in ischemic myocardium that catecholamines are involved in exacerbating of arrhythmias by increasing automaticity and stimulation of activity, but it has been shown that there is no association between circulating catecholamines and incidence of arrhythmias in clinical and experimental literatures (9). In our study, chemical sympathectomy could improve ischemia and reperfusion induced ventricular arrhythmias. Moreover, it has been shown that REM sleep deprivation increases PVC (premature ventricular contraction) but not life-threatening ventricular arrhythmias such as VT and VF(10).

Ventricular arrhythmias that result in sudden cardiac death (SCD) are significant unsolved clinical problems. Experimentally, sympathetic stimulation induces changes in ECG repolarization and by decreasing in the threshold, facilitates the initiation of VF. These effects are exaggerated in the presence of cardiac ischemia. The ischemic and infarcted myocardium becomes a substrate exquisitely sensitive to arrhythmia triggers because of regional cellular and tissue remodeling heterogeneity of sympathetic nervous system innervation. Cao et al., reported that patients with a history of ventricular arrhythmias had augmented sympathetic nerve sprouting (mainly in the border of normal myocardium and scar tissues) as compared to patients with similar structural heart disease without arrhythmias (8). Sympathetic nerve sprouting itself can lead to increased incidence of VF without related cardiac ischemia. Increased sympathetic activity, as suggested by heart rate variability analysis, was found to be in the 30 minutes before the onset of ventricular tachyarrhythmia (8). In another study unexpected ventricular tachycardia or ventricular fibrillation have obviously augmented cardiac sympathetic activity compared with appropriate reference groups, based on measurements of the rate of overflow of the sympathetic neurotransmitter, noradrenaline, from the heart to plasma. These clinical findings support a role for cardiac autonomic dysfunction, specifically sympathetic activation and vagal withdrawal, in arrhythmogenesis. Several human studies suggested that sleep loss may effect in elevated catecholamines, increased heart rate and blood pressure, and a shift of sympathovagal stability toward sympathetic dominance. When occurring continually, restricted or disrupted sleep may finally increase the susceptibility

to cardiac electrical instability and coronary heart disease (14). On the other hand, it has been reported that sleep deprivation, ranging between 30h and 72 h, do not make significant changes in response patterns of plasma catecholamines, heart rate, and blood pressure during a subsequent exercise challenge (14). There are several biological interpretations for the increased risk for cardiac heart disease associated with sleep deprivation. Hypertension, increased sympathetic nervous system activity, heart rate, vasoconstriction and salt retention also are side effects of sleep deprivation (10).

Conclusion

Induction of 72h sleep deprivation prior to ischemia and reperfusion increased the probability of VT and VF occurrence during ischemia and reperfusion and chemical sympathectomy could eliminate this effect.

Acknowledgment

This study was performed as an MSc thesis by financial support of Tehran University of Medical Sciences.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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