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Original Article

Effect of nasal airflow on respiratory pattern variability in rats

Saeed Pazhoohan*, Fatemeh Abbasi Feijani, Farnaz Mehrabbeigi, Mohammad Reza Palizvan, Saeed Hajihashemi

Department of Physiology, Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran

ABSTRACT

Introduction: The nasal airway a common route for normal breathing. Difficulty in nasal breathing due to nasal blockage is associated with abnormal respiratory pattern during sleep. The aim of this study was to investigate whether alteration in nasal airflow can change respiration pattern variability.

Methods: Healthy male Wister rats were randomly divided into 4 groups including: control, saline, nasal obstruction and nasal cavity lidocaine anesthesia. The animals underwent bilateral nasal obstruction using cauterization and locally nasal cavity anesthesia using 10% lidocaine. Respiration of conscious animals recorded using whole-body plethysmography.

Results: Respiratory signal analysis revealed a dramatic increase in variability of respiratory rhythm that quantified with increase in the standard deviation of inter-breath interval, inspiration time and mean of IBI, expiration and expiration to inspiration time ratio in both nasal obstruction and nasal anesthetized animals. Additionally, Power spectral density analysis showed higher variability in respiratory frequency, which characterized with broader dominant frequency and periodic respiratory pattern in nasal obstruction animals.

Conclusion: These results proposed that, nasal airflow influences respiratory pattern variability. Nasal cavity flow receptors may contribute for these observations.

Keywords:
Nasal obstruction
Respiratory pattern
Nasal airflow
Apnea

Introduction

Breathing is a highly dynamic and rhythmic motor activity, which is essential for sustaining homeostasis and life in all mammals (Feldman et al., 2013). Dynamic and variable behavior of breathing likely originates from internal regulatory mechanisms, but these are also affected by a variety of environmental triggers to optimize the efficiency of gas exchange (Frey et al., 2011; Peng et al., 2002). Both respiratory rate and volume continuously fluctuate under non-equilibrium steady-state conditions (Suki et al., 2011) in order to maintain adaptability to environmental stimuli (Thamrin and Frey, 2009). A shift in variability of a system may be associated with disease state. Therefore, disease may be expressed by changes

* Corresponding author: Saeed Pazhoohan, S.pazhoohan@arakmu.ac.ir
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in the variation of respiratory parameters either to reduced variation or to increased variation (Frey et al., 2005; Raoufy et al., 2016). Analyzing these variations carry information on the adaptability of the respiratory system and may provide a new insight into the characteristics of respiratory diseases (Frey et al., 2011).

The nasal airway not only has main role in olfaction and air conditioning function, but also plays an important role in the regulation of respiration by providing a passage for airflow (Tanaka and Honda, 1989). Change in the respiratory route is non-physiological conditions, which can change the normal breathing (Douglas et al., 1983; Michels Dde et al., 2014). Occlusion of the nasal passages may lead to apnea in adult (Magliulo et al., 2019), young children (Patino et al., 2013) and newborn humans (Katz et al., 2012) and lambs (Harding et al., 1987). A small change in nasal patency, significantly affects breathing patterns (Guilleminault et al., 2019), which may produce hypopnea, apnea and snoring episodes during sleep (Basner et al., 1989). In addition, nasal obstruction has often been suggested as a cause of death in sudden infant death syndrome (Thach, 2018).

Apnea is a breathing disorder characterized by repetitive cessation in breathing, caused by changed control of breathing (central sleep apnea) or airway occlusion (obstructive sleep apnea). The prevalence in the overall adult population ranged from 9% to 38% and is higher in men than women. It prevalence increased with age, in both genders (78% in women and 90% in men). Also, sleep apnea prevalence was greater in obese men and women (Senaratna et al., 2017). Numerous Previous studies have reported a connection between nasal patency disorders and abnormal breathing pattern such as snoring and apnea (Atkins et al., 1994; Craig et al., 1998; Michels Dde et al., 2014), However, the exact nature of this relationship is not yet known.

Therefore, we wondered whether alteration in nasal airflow change respiration pattern variability in awake rats. In the present study, we investigated the effect of complete nasal obstruction and nasal cavity anesthesia on respiration pattern variability.

Materials and methods

Animals

Thirty adult pathogen-free male Wistar rats, weighting 220±20g, were purchased from the Pasteur Institute (Tehran, Iran). Animals were housed in groups of 4 per cage, with free access to food and water in a temperature-controlled room (22–24°C) and 12h light/dark cycle. All procedures were approved by the ethics committee of the Arak University of Medical Sciences (IR.ARAKMU.REC.1397.100).

Nasal obstruction protocol and experimental groups

Rats were randomly divided into four experimental groups: control (CONT, n=8), bilateral nasal obstruction (BNO, n=7), nasal cavity anesthesia (NA, n=7) and saline (n=8). All animals were anesthetized via hypothermia (10min at -18°C) and those in the BNO group underwent left and right side nasal obstruction via cauterizing the external nostrils, the most common and simplest procedure used for the establishment of nasal obstruction in rodents (Funaki et al., 2014; Ogawa et al., 2018). The tissue surrounding the external nostril was burned by placing a small vessel cauterizer on the nostril to occlude the nasal route without causing mechanical damage to the olfactory mucosa. After cauterization, animals were kept warm (37°C) for 30min and then returned to their cages. The nostrils were coated with 3% chlortetracycline to prevent infection and animals were allowed to recover for 7 days; then nasal obstruction was confirmed by observation. The CONT group underwent a sham operation involving the cauterizing instrument was placed approximately 2mm above the left and right side of nostril. In NA group nasal cavity anesthesia was induced by a modified anesthesia protocol (Douglas et al., 1983; Mohammadkarimi et al., 2014). For this purpose, 5µl of 10% lidocaine (Sina Darou Laboratories Company) was administered during inspiration into each nasal cavity. In control group animals received an equal volume of normal saline in each nostril.

Respiratory recording

The respiratory signal was recorded by whole-body plethysmograph (BIODAC-R172, Trita Wavegram Co., Iran) as described in our previous study (Sadeghi et al., 2022). Briefly, the apparatus included a cylindrical chamber made of transparent Plexiglas with oppositely aligned inlet and outlet ports in each side. Ambient air continuously was pumped into the chamber at a controlled flow rate (4l/min) in order to prevent any change of CO_2 in the plethysmograph. Chamber's outlet was linked to recording system by means of polyethylene tubing. The duration of each recording was 30min. The

respiration of conscious rats was recorded one day after the nostril blockage was confirmed. In CONT group, respiratory signal was recorded one week after of sham operation. Also, in NA and saline groups respiratory recoding was performed 5min after intranasal administration of lidocaine or saline respectively. In order to allow the rats to get accustomed to the recording chamber animals were positioned in the recording box one hour per day for 5 days prior to the beginning of experiments. On the experiment day, animals were gently introduced into the recording box. Also, in order to reduce the effects of circadian rhythms on breathing, all records were carried out between 11 AM and 14 PM.

Assessment of respiratory variability

Data collection

The respiratory signal was recoded at 1KHz sampling rate, filtered between 0.1Hz to 5Hz, using whole-body plethysmograph system and stored on a PC for offline analysis. Twenty min of respiratory signal that had lower artifact was selected for analysis. For each rat we determined a set of respiration parameters. The inter-breath interval (IBI) time series was calculated using a program written in MATLAB (MathWorks, R2016a). The peaks of each signal were detected and visually checked, and then the peak-to-peak intervals were considered as the IBI time series (Figure 1a). Since we expected abnormal breathing patterns to manifest also by alteration in the inhaling and exhaling part of the respiratory cycle, therefor we calculated the mean of inspiration, expiration time and expiration to inspiration time ratio. Inspiration and expiration are recorded by establishing start-inspiration and end-expiration, as the box pressure/time curve crosses the zero line. Therefore, inspiration phase was defined as the time lapse between two point when the box pressure/time curve is the below of the zero line. While the expiration was determined as the time interval between two points when the pressure/time curve is above the zero line (Figure 1a).

Variability analysis

The mean IBI, respiratory variability, respiratory rate, expiration, inspiration and expiration to inspiration time ratio and standard deviation (CV) were calculated for all animal using a programme in MATLAB. In addition, for evaluation of respiratory frequency variability, the power spectral density of the respiratory signal was calculated using Welch's algorithm (Zamoscik et al., 2018). To quantitatively analyze the power spectrum, a criterion named dominant frequency interval was defined, which is measured by considering the bin number of frequency component that their power spectrum values are higher than 10% of the maximum value of the power spectrum. Higher variability of respiration signal may be reflected by broader dominant frequency compared to the dominant frequency of less variable respiration signals. We also computed the maximum peak frequency of the power spectral analysis.

Blood gas analysis

Blood samples were obtained through tail artery of rats under ketamine/xylazine anesthesia into heparinized syringes. In CONT group, blood samples were collected 7 days after of sham operation. in NA and saline groups blood samples were collected 5min after intranasal administration of lidocaine or saline respectively. Also, blood samples of BNO rats was obtained one day after the nostril blockage confirmation. Blood samples were taken for the analysis of pH, PCO_2 and PO_2 via blood gas analyzer system.

Statistical analysis

The GraphPad Prism V6.07 (GraphPad Software, San Diego, CA) was used for statistical analysis of data. Results are expressed as mean±SEM. Comparisons among groups were performed using the One-way ANOVA and followed by post hoc Tukey's test.

Results

Respiratory variability analysis

An exemplary of respiration time courses is shown for each group in Figure 1b. Respiratory pattern in BNO group display a periodic pattern that characterized by a gradual increase in the pressure of box, followed by a progressive decrease in the box pressure that occurs repeatedly during the time. However, this pattern was not observed in other groups.

Following on from the previous result, the effects of nasal obstruction and anesthesia on the respiratory variability were studied. Rats in both BNO and NA groups have significantly higher variability in respiratory pattern. In BNO and NA groups, the mean of IBI (P<0.007), expiration time (P<0.01), expiration and inspiration time ratio (P<0.013), were significantly increased compared

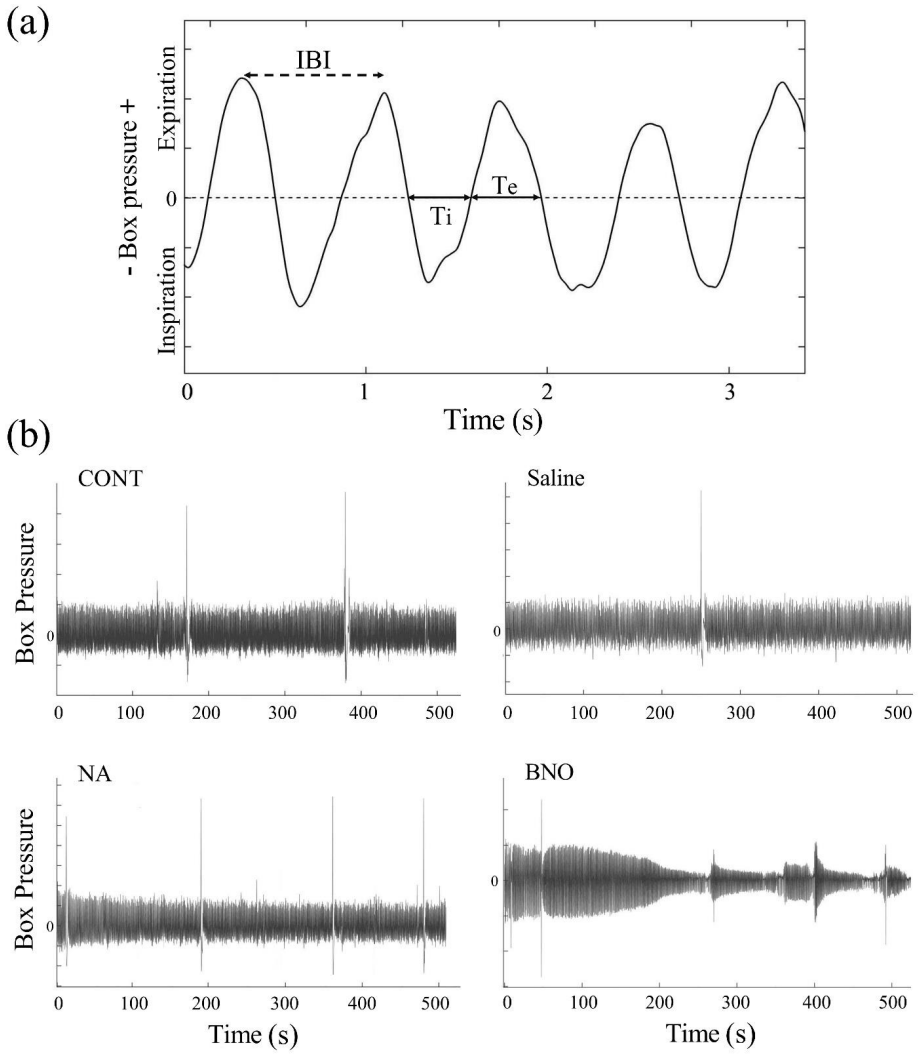

FIGURE 1. Respiratory pattern in a representative in rats. (a) Representative parts of the respiratory signal. (b) Exemplary 10min respiration recordings of experimental groups. IBI: inter-breath interval; Ti: inspiration time; Te: expiration time; CONT: control (CONT); NA: nasal anesthesia; BNO: bilateral nasal obstruction.

to saline and control groups. Also, mean respiratory rate (P<0.01) in the BNO and NA groups was lower than CONT and saline groups. CV of IBI was significantly higher in rats of BNO group compared to rats in CONT and Saline groups (P<0.006 and P<0.039, respectively). In NA group, CV of IBI was significantly higher than CONT group (P<0.023). Also, CV respiratory rate in BNO animals were significantly lower than CONT and saline animals (P<0.011 and P<0.001, respectively). Moreover, CV of inspiration in BNO group was significantly higher than both CONT and saline group (P<0.001 and P<0.007, respectively). Whereas, statistical analysis showed no significance difference in CV of expiration to inspiration time ratio among the experimental groups (P>0.05, Table 1).

In order to provide an impression of these altered respiratory patterns, Figure 2a displays exemplary frequency analyses from experimental groups. Animals in BNO and NA groups showed lower maximum peak frequency (P<0.01) compared to CONT and saline groups. In addition, power spectral density analysis of the respiratory signal showed that the BNO group had more dominant frequency above threshold and lower maximum peak frequency (P<0.01), which can also be seen as a higher variability in the respiratory pattern compared to CONT and saline (Figures 2b and c).

Arterial blood gas analysis

The descriptive statistics presented in Table 2 showed that, PaO_2 level in BNO group was significantly decreased compared with the other experimental groups (P<0.01). However, there were no significant differenc-

TABLE 1: Respiratory parameters of experimental groups with statistics from ANOVA.

	Mean± SEM				P value				F
	CONT	NA	BNO	Saline	CONT-NA	CONT-BNO	Saline-NA	Saline-BNO	BNO-NA	
Mean IBI	0.57±0.015	0.016 ± 0.66	0.019 ± 0.65	0.56±0.014	0.001	0.007	0.0005	0.002	0.92	(26 ,3) 0.4181
Mean RR	110.5±3.3	90.5±2.1	93.6±3	107.2±2.6	0.0002	0.001	0.001	0.012	0.86	(3,26) 1.100
Mean Exp	0.28±0.012	0.34±0.011	0.37±0.014	0.29±0.007	0.0001	0.001	0.011	0.0004	0.57	(26 ,3) 0.4616
Mean Ins	0.251±0.006	0.276±0.006	0.281±0.011	0.266±0.008	0.156	0.068	0.845	0.602	0.97	(26 ,3) 0.2674
Exp/Ins ratio	1.11±0.023	1.26±0.012	1.34±0.042	1.13±0.026	0.0054	0.0001	0.0130	0.0001	0.24	(26 ,3) 1.054
CV IBI	0.1±0.008	0.15±0.018	0.159±0.012	0.113±0.004	0.023	0.0066	0.11	0.0397	0.95	(26 ,3) 4.467
CV RR	0.026±0.003	0.028±0.003	0.01±0.0008	0036.± 0.029	0.9551	0.0117	0.9961	0.0019	0.004	(26 ,3) 4.831
CV Exp	0.14±0.01	0.24±0.023	0.2±0.016	0.2±0.029	0.0163	0.2088	0.5338	0.999	0.5	(26 ,3) 1.306
CV Ins	0.139±0.012	0.186±0.011	0.22±0.013	0.15±0.014	0.079	0.001	0.31	0.007	0.64	(26 ,3) 0.3121
CV Exp/Ins	0.318±0.07	0.31±0.025	0.49±0.089	0.36±0.057	0.999	0.2724	0.94	0.51	0.099	(26 ,3) 0.9404

Data are reported as mean±SEM for all variables. IBI: inter-breath interval; RR: respiratory rate; Exp: expiration; Ins: inspiration; CV: coefficient of variation; NA: nasal cavity anesthesia; BNO: bilateral nasal obstruction. The significance of differences between groups were assessed by a one-way ANOVA with a Tukey's post hoc test. n=8 for CONT and saline groups; n=7 for BNO and Na groups.

es in pH and pCO_2 values between experimental groups (P>0.05).

Discussion

In this study, we investigated the effect of nasal airflow on respiratory pattern variability. The major finding of this study was the absence of nasal airflow following the nasal occlusion and decrease the stimulatory effects of nasal airflow in nasal cavity by induction of local anesthesia increased variability of breathing pat-

TABLE 2: Arterial blood gases and acid-base balance values in experimental groups.

	Mean± SEM			
	CONT	NA	BNO	Saline
pH	7.34±0.01	7.37±0.02	7.32±0.03	7.34±0.02
PaO_2	92.59±1.2	93.33±1.6	82.00±2.02**, ## ,++	93.15±2.08
$PaCO_2$	44.85±1.9	43.23±1.45	61.20±9.713	45.53±2.761

Data are reported as mean±SEM for all variables. The significance of differences between groups were assessed by a one-way ANOVA with a Tukey's post hoc test. $^{*}P<0.01$ and $^{**}P<0.01$ compared to CONT group; $^{\#\#}P<0.01$ compared to saline group; $^{++}P<0.01$ compared to NA group.

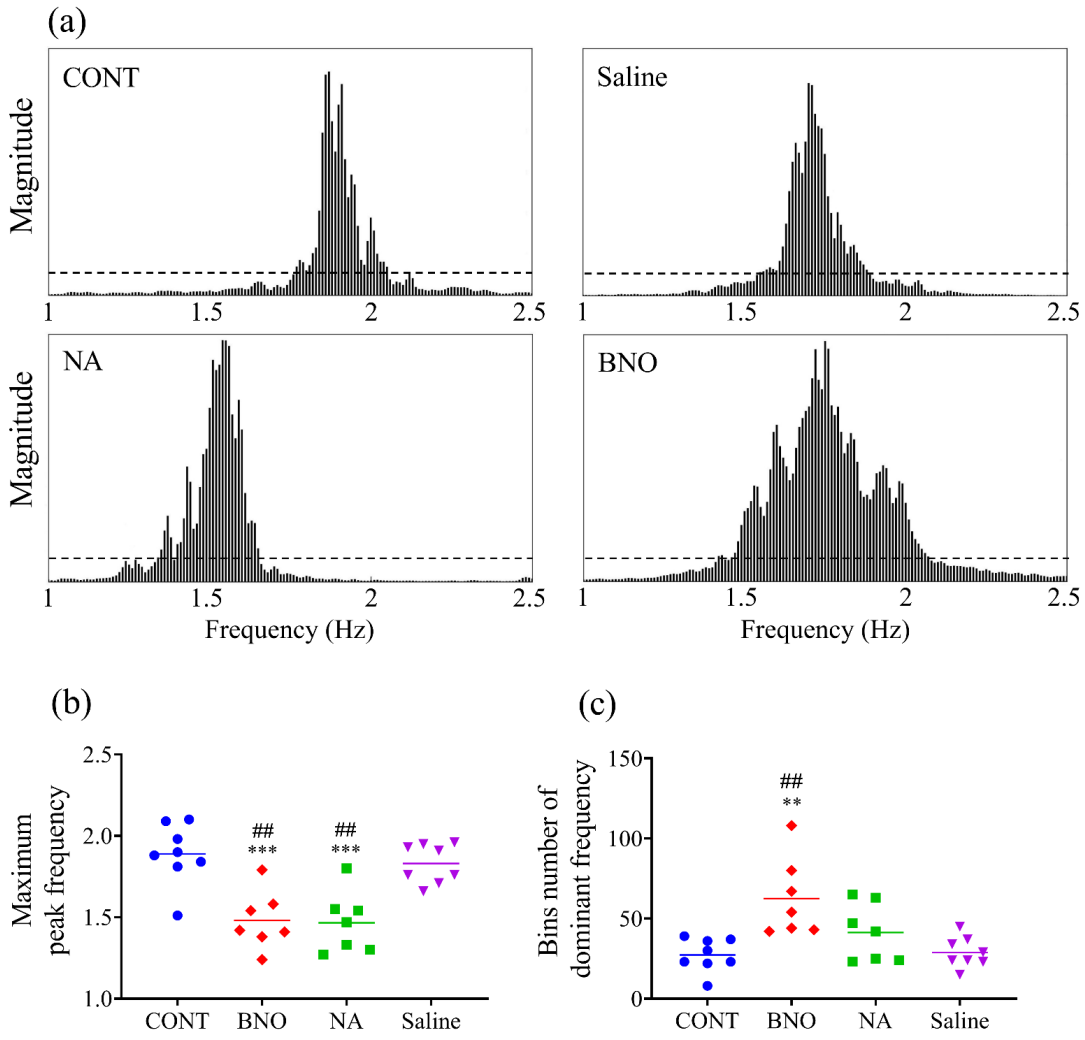

FIGURE 2. Welch's power spectral density estimates analysis of respiratory signals. (a) Exemplary Welch's power spectral density estimates of experimental groups. (b) maximum peak frequency. (c) number of frequency bins above the threshold. $^{**}P<0.01$ and $^{***}P<0.001$ compared to CONT group; $^{\#\#}P<0.01$ compared to saline. Dash line: represent of threshold 10% of the maximum frequency power.

tern in awake rats. Various inputs from peripheral and central source that integrated in brain stem, provide a background respiratory drive activity to maintain homeostasis and survival. If sensory inputs are changes, the respiratory neuron in respiratory control network in brain stem responds to these flow of information by

changing their firing activity and changes breathing pattern (Douglas et al., 1983; Jubran and Tobin, 2000; Perez and Tobin, 1985). Serval nose abnormality such as turbinate hypertrophy, septal deviation, nasal polyps and rhinitis by alteration in nasal airflow may cause or worsen of respiratory disorders such as apnea (Guilleminault et al., 2019; Rombaux et al., 2005). Recently, Some studies have reported a weak correlation between nasal resistance and breathing pattern alteration (Meen and Chandra, 2013).

The current findings have further demonstrated that there is a relationship between nasal patency and normal breathing pattern variability. Result from our analysis showed that, nasal obstruction significantly decreased respiratory rate and max peak frequency and increased expiration time and exp/ins ratio. Previous studies have also reported that mouth breathing decreases breathing frequency and increases expiration time during rest in normal subjects (Douglas et al., 1983; Guilleminault et al., 2019). In addition, increased CV of IBI, expiration, expiration to inspiration time and more dominant frequency of respiratory signal of BNO rats indicate higher variability of the respiratory control system. Moreover, periodic pattern of respiratory in BNO animals, demonstrate an instability in respiratory control.

Previous studies reported respiratory responses to hypercapnia and hypoxia were greater with mouth than nose breathing in awake normal men (Douglas et al., 1983). While results of a study conducted on children with obstructive sleep apnea (OSAS) due to adenotonsillar hypertrophy, showed a diminished ventilatory response to CO_2, compared with those children without OSAS symptoms (Strauss et al., 1999). Also, obese adolescents with OSAS have blunted respiratory responses to CO_2 during sleep (Yuan et al., 2012). These reports and our result proposed that alteration in breathing route may interfere with respiratory control mechanisms and changed the respiratory response to sensory inputs. However, the role of nasal airflow and nasal obstruction in the pathophysiology of breathing abnormality such as apnea is not clear and it seems to be attributed to some pathophysiological mechanisms. These includes, unsteady oral airway, Starling resistor model, role of nitric oxide and nasal ventilatory reflex (Michels Dde et al., 2014).

Furthermore, our results showed that nasal anesthesia, like nasal obstruction, alters the variability of respiratory pattern. Results of previous studies have shown that nasal mucosa anesthesia of healthy subjects resulted to a significant increase in the rate of obstructive and central apnea episodes (McNicholas et al., 1987; White et al., 1985). These data suggested that nasal cavity mechanoreceptor which play a pivotal key role in respiratory regulation and timing, and alteration in the activity of these receptors at least a considerable part of pathophysiology of apnea due to nasal patency disorders. It has been previously reported that olfactory sensory neurons in the mammalian nose not only detect chemical stimuli, but also detect mechanical stimuli (Grosmaitre et al., 2007). Nasal airflow by stimulating mechanoreceptors located in nasal epithelium entrains rhythmic neural activity in different brain areas such as piriform cortex, amygdala and hippocampus (Zelano et al., 2016). Guilleminault et al. (2019) demonstrated that, abnormal breathing patterns due to nasal flow-limitation in children are associated with EEG disturbances. Based on such evidence, it is suggested that, the sensory information raised form flow receptor in upper airway (nasal cavity), by adjusting of neuronal activity in different brain regions (Parsazadegan et al., 2018), may be involved in regulation of respiratory timing and drive (Douglas et al., 1983). It seems that this sensory information from nasal receptors, regulates the respiratory centers in the brainstem respond to changes in blood oxygen and carbon dioxide level within physiological range.

Also, our result demonstrated that paO_2 level was remarkably decreased in animals with nasal obstruction animals. Douglas et al. (1983) have previously reported that the ventilatory response to hypoxia and hypercapnia will be excessive, when nasal airflow is reduced. Furthermore, nasal obstruction severely impaired blood gas homeostasis in newborn lambs, which is associated with increase in level of PCO_2 and reduce of PO_2 and pH (Harding et al., 1987), that leads to abnormal respiratory pattern.

Conclusion

It is difficult to relate these findings to respiratory abnormality observed in patients during sleep. Perhaps the altered respiratory variability during nasal obstruction might be further affected by the decreased nasal air flow during sleep. Therefore, the results of this study showed that nasal air flow influences respiratory pattern variability.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest related to this work.

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