BREATHING FREQUENCY IN SLEEP RELATED
RESPIRATORY DISTURBANCES

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SUMMARY — In normal adults, breathing frequency (f) is highly reproducible within an individual ranging from 8 to 25 min-1; during sleep, f is known to change only minimally. This variable is rarely reported in studies of adults with various sleep related respiratory disturbances (SRRD). We occasionally observed a spectacular increase of f during sleep in patients with SRRD associated with hypopnea and O2 desaturation. We undertook a retro-spective study of 650 consecutive all-night polysomnographic recordings, in order to evaluate how often such an increase in breathing frequency occurs and with which factors it is associated. We excluded patients with major respiratory failure. We found 16 patients (11 males; mean ± SD, age: 45 ± 13 yrs; body mass index (BMI): 44±11 kg/m2) with f > 25 min-1 during sleep (tachypneic group, T). We performed a one-for-one matching for sex, age and BMI between the T and a control (C) group (age: 45±12 yrs; BMI 44±10 kg/m2), with similar sleep disturbances but normal f during sleep. We compared the f in each vigilance state by averaging five measurements of f, each of one minute duration in a stable period. We observed that: C patients showed no significant change in f in any vigilance state; T patients showed a higher f already during wakefulness (p<0.05) and f increased significantly in all sleep stages (<0.01). We compared the two groups for many clinical and polysomno-graphic variables. Significant statistical differences were observed for: f, arterial CO2 tension (PaCO2), vital capacity (VC), forced expiratory volume at one second (FEV1) and pulse fre-quency (PF).

KEY WORDS: breathing frequency, polysomnographic recording, sleep related respiratory disturbances.

Frequência respiratória observada em pacientes com problemas respiratórios associados ao sono.

RESUMO — Em adultos normais, a frequência respiratória (f) varia de 8 a 25 min-1 com grande reprodutividade intraindividual: durante o sono, f é quase invariável. Esta variável tem sido raramente referida em estudos de pacientes com problemas respiratórios associados ao sono (SRRD). A observação ocasional de espetacular aumento da f durante o sono em pacientes com SRRD, principalmente apnéias/hipopnéias associadas à desaturação da oxi-he-moglobina, nos levou a proceder a estudo retrospectivo de 650 exames consecutivos de polisso-nografia (PSG), com a finalidade de avaliar a frequência da ocorrência desta aceleração da f e dos prováveis fatores a ela associados. Foram excluidos deste estudo pacientes com insu-ficiência respiratória grave. Observamos a ocorrência deste fenômeno em 16 pacientes (11 homens com média de idade 45±13 anos, índice de massa corporal (BMI) 44±11 kg/m2) para os quais a f foi maior que 25 min-1 durante o sono (grupo de taquipnéicos, T). Realizamos comparação da f entre T e grupo controle (C) de pacientes de mesmo sexo e semelhantes

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idades (45±12 anos) e, BMI (44±10 kg/m2) e SRRD, em cada estado de vigilância, fazendo média de 5 contagens da f, cada uma feita durante 1 minuto e durante um período estável do determinado estado de vigilância. Observamos que: os pacientes do grupo C não apresentaram alteração significativa da f em qualquer estado de vigilância; os pacientes do grupo T já tinham f maior que os pacientes do grupo C (p < 0.05) quando acordados e esta aumentou significativamente em todos os estados do sono (p<0.01 f quando acordados vs f durante o sono, p < 0.001 T vs C durante o sono). Comparamos os dois grupos para vários parâmetros clínicos e polissonográficos. Diferença estatisticamente significante foi observada para os dados de: PaCO2 (pressão arterial do CO2), capacidade vital (VC), volume expiratório em 1 segundo (FEV1) e da frequência do pulso (PF) durante repouso (acordados) e durante o sono.

PALAVRAS-CHAVE: frequência respiratória, registro polissonográfico, problemas respiratórios relacionados ao sono.

RESPIRATORY PHYSIOLOGY DURING WAKEFULNESS AND SLEEP

1. Sleep organization. Wakefulness on the one hand is a state of cortical activation recognized by the occurence of alpha waves (during quiet periods) on the electroencephalogram (EEG) and increased muscle tone. The cortical activation is maintained by tonic activity of the reticular activating system, which both directly stimulates the cortex and also facilitates thalamic relay neuron passage of sensory information to the cortex. Sleep on the other hand is a state in which alpha activity is lost and muscle tone reduced. NREM sleep (stage 1-4) is characterized by inhibition of the reticular activating system, resulting in cortical suppression and functional deafferentation. In REM sleep, the reticular activating system is reactived, producing cortical stimulation. In contrast to wakefulness both sensory and motor functions are impaired during REM. There is both pre- and post-synaptic inhibition of afferent neurons resulting in raised arousal thresholds to external stimuli and post-synaptic inhibition of motor neurons which produces the postural atonia typical of REM sleep [11].

2. Ventilation. Feedback regulation through chemoreceptors is one of the two major mechanisms controlling ventilation. It adjusts ventilation to changes in the environment and metabolic rate. The other one is under volitional control, and can override, under certain limits, the metabolic one. This usually happens when the respiratory system is disturbed so as to change the partial pressure of O2 or CO2 in the blood, smooth adjustments in ventilation are expected [28]. The special attributes of the brain-stem respiratory neurons may not be inherent automaticity, but rather a consequence of their afferent inputs and their ability to convert these inputs into a rhythmic output. Thus, breathing rhythm would not be simply modulated by afferent respiratory stimuli but rather would be critically and fundamentally dependent on such stimuli [33]. The activation of each inspiratory burst (on-switch mechanism) is the critical event in the generation of the respiratory patterns and depends on adequate levels of afferent respiratory stimuli. The major influence of incoming afferent stimuli is to determine the timing of the onset of each respiration and, in so doing, to fix the duration of the preceding expiration, thereby generating the basic respiratory rhythm [33,39]. Under normal conditions, effective respiratory rhythmicity is critically linked to, and dependent on the need for removal of CO2; other respiratory stimuli exert a more secondary modulating influence, but do not in themselves generate the respiratory rhythm.

3. The effect of sleep stages on ventilation.

3.1. Breathing patterns: (1) Drowsiness or unsteady NREM sleep is characterized in many subjects by periodic breathing associated with swings in PO2 and PCO2, cortical EEG activity, systemic arterial pressure (AP), heart rate, O2 saturation (SaO2) and an overall moderate decrease in ventilation [29]. (2) The irre-

gularity of breathing at sleep onset consists of a regular waxing and waning of breathing amplitude. The oscillations may be of low amplitude resulting in alternating hyper- and hypoventilation or of large amplitude with apneas at the nadir of the oscillations. During the amplitude oscillations there are few changes, if any, in respiratory rate [12,45]. Apneas occur more frequently in the elderly and not only at the transition between wakefulness and sleep, but also tend to occur predominantely in sleep stages 1-2. They seem to be an exaggeration of the periodicity that is typical of sleep onset [6,37,44]. (3) Periodic breathing persists as long as sleep oscillates between arousal and stages 1 or 2. These oscillations seem to be mainly due to sleep instability at these stages and different setpoints of breathing regulation in wakefulness and sleep; the natural tendency of breathing regulation to be unstable probably aggravates this situation. It disappears when stable stage 2 or stages 3-4 are reached and systemic AP drops 20-30% below basal wakefulness values [13,43]. (4) REM sleep is characterized by erratic shallow breathing with irregularities both in amplitude and frequency. The heart rate becomes irregular and central apneas or hypopneas occur sporadically. Hipertensive peaks, sometimes reaching 30-40 mmHg, suddenly appear and continue for the whole length of REM sleep. These events are synckroncus with REM bursts and probably of central origin, related to the REM sleep process.

3.2. Ventilation. In normal healthy adults the minute ventilation (VE) decreases by a mean of 8.2 $\pm$ 2.3% from wakefulness to sleep and does not vary significantly between sleep stages [18,38,45]. The greatest decrease in ventilation has been observed during phasic REM sleep [11,14]. Mean inspiratory flow fell significantly but timing was unchanged [33,38]. Arterial oxygen saturation (SaO2) also fell and could be accounted for entirely by the associated reduction in ventilation. O2 (VO2) consumption and CO2 (VCO2) production also fell by 8.5 $\pm$ 1.6% and 12.3 $\pm$ 1.7% respectively during sleep and again did not differ between sleep stages. Ventilation correlated quite closely with VO2 and VCO2 during sleep with similar levels of correlation found for each sleep stage. These results are similar to those observed in younger [14,21] or older subjects [37,41].

3.3. Breathing frequency (f). Breathing frequency (f) varies significantly from one individual to an other but a remarkable stability is observed for the same subject [1,14,31,35-38,42]. For healthy awake subjects the mean is 8 to 24.8 breaths/min for the young and 8.14 to 18.06 breaths/min for the elderly (>65 years). In sleep f ranges from 9.9 to 23.6 breaths/min for the young and 5.16 to 19.64 breaths/min for the elderly. The lower respiratory frequency observed in the elderly was primarily due to a significantly longer inspiratory time compared with values observed in wakefulness and each sleep stages in the young [37]. In children, Guilleminault [16] describes the association of tachypnea with the rare occurrence or absence of apnea during sleep with or without a decrease of oxygen saturation which could be proposed as a marker of pathological breathing during sleep. Aubert-Tulkens et al [2] reported a case of a woman with obesity, loud snoring, restless sleep, hypersomnia, personality changes and systemic hypertension, who on polysomnographic examination revealed tachypnea of 35 breaths/min, continuous loud snoring and an SaO2 with periodic oscillations between 95-60%.

3.4. Upper airway. Breathing implies maintenance of a normal upper airway patency: many local reflexes at the naso-oro-hypopharyngeal and laryngeal level are thought to counteract the progressive development of the negative intrathoracic pressure generated by the inspiratory muscles (scaleni, intercostals, diaphragm) contraction. The reflexes involved in the maintenance of upper airway patency are, of course, activated just prior to the onset of the diaphragmatic contraction.

The passage from wakefulness to sleep is normally associated with an increased upper airway muscle tone. Whether the increase in upper airway resistance alone explains the decrease in ventilation during sleep is not yet clear [1,17,20,25,40,41].

4. Sex differences — Caterall and co-workers [5] reported that there was no sex difference in sleep disorders in subjects with normal body weight. In female subjects, disordered breathing was reduced during pregnancy [4] and increased after menopause [3]. Progesterone is known to be a respiratory stimu-

lant [11,22,46]. Obese women (but not obese men) show an increased response to both hypoxia and hypercapnia [27].

5. Diseased subjects. Tobin et al.[42] studied f in awake normal and diseased subjects and observed that respiratory rate was increased above the normal in smokers and in patients with COPD, restrictive lung disease and pulmonary hypertension but remained normal in asthmatic patients (11 to 22.2 breaths/min in normals, 12.1 to 43.7 breaths/min in diseased subjects).

PROPOSAL. The present study's main aim is to determine the frequency with which tachypnea occurs during sleep in patients referred to our laboratory (Sleep Laboratory, St Luc Training Hospital, Brussels, Belgium) for clinical assessment of sleep apnea syndrome. We were impressed by the fact that contrary to what is normally described in current literature on the subject, instead of reducing f during sleep, several subjects showed a spectacular increase in f. With this in mind, we undertook a retrospective study of 650 all night polysomnographic recordings (excluding patients with major respiratory failures) and found 16 patients who presented a significant increase of f during sleep ($p < 0.01$). We set up a control group (n=16) of patients with similar sleep disturbances but normal f during sleep, matched for sex, age and body mass index in an attempt to establish any distinguishing factors between them.

METHODS

Population. In a study of 650 consecutive all-night polysomnographic recordings, we found 16 patients who had f higher than 25 min-1 during sleep (T group). The main diagnosis of SRRD comprised 9 patients with sleep apnea-hypopnea syndrome, 3 with an overlap syndrome, 1 with a hypoventilation syndrome, 1 with Shy-Drager syndrome associated with snoring, 1 with chronic obstructive pulmonary disease (COPD) and 1 with major obesity associated with SaO_2 desaturations essentialy in REM sleep. We constituted a control group of patients (n=16) with similar SRRD (i.e. apnea-hypopnea, snoring, SaO_2 desaturations) but normal f during sleep, matched with T for sex, age and BMI (C group) and a group of young healthy subjects (15 males; age: 24 ± 2; BMI: 21 ± 2 (N group) for comparison with the T group.

Polysomnographic studies. The polysomnographic recordings were performed according to standard techniques [34]: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), oral and nasal airflow (thermocouples placed in front of mouth and nostrils), respiratory movements (strain gauge), breathing sounds, i.e., snoring (microphone attached to the skin over the larynx). These parameters were recorded on a polygraph at a paper speed of 15 or 10 mm/s.

Since 1986, transcutaneous oxygen saturation (SaO_2) (Nellcor pulse oxyleter N-100, Hayward, CA, USA) has also been recorded. The mean of ten measurements per second of SaO_2 and pulse frequency (PF) from the oximeter, along with the integrated signal from the microphone were stored in an intermediate data bank every 6 seconds. The file containing these measurements also held information on the exact time of the start of recording. This allowed us to correlate these data at a later stage along with other data, namely data of the vigilance stages and apneas. The desaturation index (DI) was taken as the number of the desaturations episodes $\geqslant 4\%$ expressed per hour of sleep.

Sleep staging was performed according to standard methods in 40 or 60 seconds epochs. Total sleep time (TST) was measured from the moment when the patient fell asleep until the final awakening, excluding wake time during sleep. The time of the various sleep stages was calculated as percentage of TST. Movement arousal index (MA) is the number of episodes of increase in EMG accompanied by alpha rhythm in the EEG for at least 2 seconds, during a sleep epoch, expressed per hour of sleep.

Study. We compared f (from airflow) in each vigilance state by averaging five measurements of f, each of one minute duration in a stable period for: (a) the T group (wakefulness vs stages 1, 2, 3, 4 and REM sleep); (b) the C group (idem to T group); (c) the N group (idem to T group) and T vs C group (in each vigilance state). We compared the T and C groups for other polysomnographic variables: % stage 1, 2, 3, 4 and REM sleep; MA; SaO_2; DI and PF and for some clinical variables: blood pressure (BP); blood gas (PaO_2 and $PaCO_2$); vital capacity (VC) and forced expiratory volume at one second (FEV1).

Statistical analyses. The t-paired test was used for analyses within groups. The t-test for two means was used for the comparisons between T vs C groups.

RESULTS

Analysis of the results highlighted the following elements:

1. by definition, T and C groups were well matched for age and BMI (mean±SD; age: 45±13 yrs vs 45±12 yrs; BMI: 44±11 kg/m2 vs 44±10 kg/m2);

2. T patients showed a higher f during wakefulness than C patients (23.4±6.5 min-1 vs 17.9±3.0 min-1; p<0.05);

3. C patients showed no significant modification of f in any sleep stage;

4. T patients increased f in all sleep stages (stage 1: 31.5±7.7 min-1; stage 2: 31.9±7.2min-1; stage 3: 31.0±6.0 min-1; stage 4: 30.3±6.5 min-1; stage REM: 29.3±4.0min-1; all p<0.01 vs wakefulness);

5. N subjects showed no significant modification of f in any vigilance stage;

6. T and C patients showed no significant difference for the distribution or the sleep stages;

7. N subjects showed a normal distribution of sleep stages: stage 1: 10.0±4.7; stage 2: 48.5±9.1; stage 3: 7.7±4.2; stage 4: 15.2±6.8; stage REM: 18.6±6.4 %TST;

8. T and C patients showed no significant difference for: MA, SaO2, DI, BP and PaO2;

9. N subjects showed a mean SaO2 during TST of 97.2±1.0% and a number of MA/hs of 12.0±6.1;

10. a significant statistical level of difference was observed between T vs C group for: PaCO2 (44.2±6.0 vs 39.1±3.1 mmHg p<0.05); VC (76.2±11.3 vs 83.2±7.8 percent predicted normal p<0.05); FEV1 (77.0±12.9 vs 86.3±10.0 percent predicted normal p<0.05); PF (awake: 84.2±13.3 vs 74.3±8.9 min-1; TST: 80.0±13.6 vs 69.8<9.6 min-1 p<0.05 for wakefulness and sleep) and f in all vigilance states (wakefulness p<0.05; stage 1, 2, 3 and 4 sleep p<0.001; REM sleep p<0.05) (see Fig. 1 and Table 1).
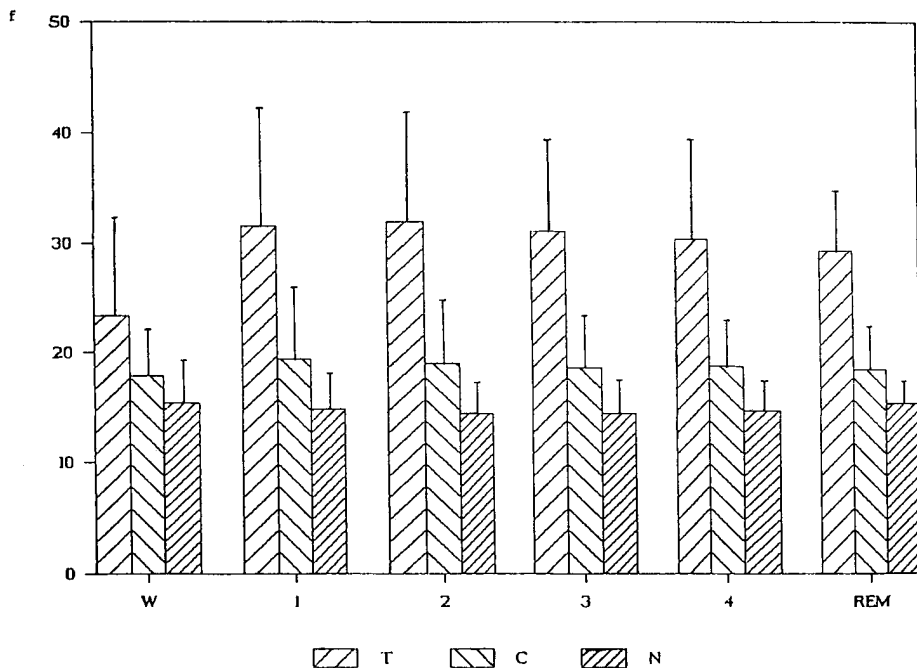

Fig. 1. Breathing frequency.

Table 1. Statistical significative level of comparison between the two patients population (T vs C) for: breathing frequency (f), PSG and clinical variables (see text).

Statistical analyses (T vs C)					
f		**PSG variables**			
W	- t= 2.13**	%1	- t= 0.88	SaO2 -	t= -1.10
1	- t= 5.22*	%2	- t= -1	D1 -	t= 0.32
2	- t= 6.01*	%3	- t= 0.51	MA -	t= -0.83
3	- t= 6.07*	%4	- t= -0.97	PF - W - t= 2.25**	
4	- t= 5.51*	%REM	- t= 0.26	TST - t= 2.27**	
REM	- t 2.31**				
		Clinical variables			
BP - Sys. - t= 0.19		PaO2 - t= 1.25		PaCO2 - t= 2.26**	
Dyas. - t= -0.06					
		VC - t= 1.73**		FEV1 - t= 1.94**	

Student't: $p < 0.001$ *; $p < 0.05$ **

COMMENTS

Discussion. An acceleration of f during sleep is rarely confirmed in a review of current literature. In females and children, tachypnea may be considered a marker of pathologic breathing during sleep; which could be associated with loud snoring, and oxygen desaturation with or without the occurence of apneas or hypopneas [2,16]. In this study, we found 16 patients from a population of 650 subjects (2.5%) who presented a significant acceleration of f during sleep. All but two of these patients (one female, BMI of 19.78 kg/m^2, who suffered from Shy-Drager syndrome and one male, BMI of 27.68 kg/m^2, who suffered from DPOC) suffered from morbid obesity and were referred to us for investigation of sleep apnea syndrome.

In relation to the main diagnosis of SRRD presented by our patients: The alveolar hypo-ventilation syndrome is defined as a combination of hypercapnia and alveolar hypoxemia. Nonspecific alveolar hypoventilation can occur secondary to damaged respiratory centers in the brain and can also be seen with drug intoxication (barbiturates, for example) and with abnormalities of breathing apparatus, as in muscular dystrophy, kyphoscoliosis, Pierre Robin syndrome, obstructice lung disease, etc. The Pickwickian syndrome, in its classic form includes obesity, hypersomnolence, periodic breathing with hypoventilation and cor pulmonale [15]. In obesity, the total lung volume and the functional residual capacity are diminished. The decrease in functional residual capacity is secondary to a marked diminution in expiratory volume. Because of the diminished volumes, the obese patient breaths closer to residual volume. This, coupled with a decreased tidal volume allows for earlier airway closure in areas of decreased ventilation [46]. Sleep studies indicate that the incidence of obstructive sleep-apnea (OSA), obesity-hypoventilation syndrome and desaturation in unselected, morbidly obese male patients is extremely high [19]. Obese children and adolescents are undoubtedly at risk as a group for OSA in adulthood [30]. Kunitomo et al [27] showed that there is no sex-related difference in ventilatory or occlusion pressure responses to hypoxia or hypercapnia in either obese subjects or normal control subjects. However, there is respiratory compensation with mass loading i.e. accumulation of fat about the chest wall that produce a decrease in chest wall and lung compliance [46] in obese women but not in obese men [9,27]. In obese women, an increased severity of oxygen desaturation and the appearance of sleep

apnea is often seen after the menopause. Progesterone has been considered as a protective hormone in females [46]. Among our tachypneic group, 4 women presented a morbid obesity and 2 were in a post-menopausal age. Harman et al [19] suggest that for obese men anatomic factors would appear to be important. Increased fatty tissue in the hypopharynx may predispose to obstructive apnea. Kopelman et al [23] believe that mechanical impedance of breathing due to abdominal adipose tissue combined with abnormal central respiratory control i.e. relatively depressed chemosensitivities [27] are the major factors responsible for the respiratory disturbances observed during sleep. All of our obese patients presented obstructive sleep apnea-hypopnea, periodic breathing or snoring associated with SaO_2 desaturation.

In patients with Shy-Drager syndrome, there is evidence of multiple system atrophy due to widespread degeneration throughout the central nervous system. Respiratory abnormalities in these patients may be due to laryngeal obstruction caused by bilateral abductor paralysis of the vocal cords, or to disorganization of central respiratory control, i.e., functional instabilities inherent in the organization of respiratory rate and rhythm [8]. These may produce episodes of sleep apnea with concomitant hypoxia which may presage death due to cardiorespiratory arrest [21]. Our patient had a tachypnea associated with snoring observed in 100% of the TST. These are compatible with the patophysiologic findings described above.

In chronic obstructive pulmonary disease (COPD), Tobin et al [42] observed an elevated respiratory rate during wakefulness, similar in patients with or without hypercapnia, when compared with normal subjects and symptomatic asthmatic patients. They postulated that, since the severity of resistive loading as reflected by the airway resistance was comparable among the two COPD groups and symptomatic asthmatic patients, the faster respiratory rate in patients with COPD implied a proportionally greater fall in compliance which shortened the time constant of the respiratory system. Compliance of the respiratory system was equivalent to the sum of the reciprocals of the lung and thoracic wall compliances. Dynamic lung compliance probably decreased to approximately the same extent in COPD as in symptomatic asthma and would not account for the more rapid rate in COPD. The chronically hyperinflated thorax in COPD appeared to be less compliant than normal. In their patients, the most specific variability in the components of the breathing pattern appeared to be expiratory timing. This concurs with the hypothesis of Sullivan et al [39] that the mechanism initiating inspiratory burst, rather than the one responsible for terminating the burst, is of fundamental importance in setting up breathing frequency.

A commentary may be made in relation to smokers. Tobin et al [42] observed an increased respiratory rate with heightened respiratory center drive as reflected by elevated mean inspiratory flow (VT/TI) in smokers who had little or no subjective complains. In our series of patients, 6 tachypneic patients and 4 control patients were smokers. This enabled us to exclude the effect of a higher respiratory center set point induced by chronic intermittent stimulation with nicotine with a factor allowing us to differentiate T and C patients.

Conclusion. Our results confirm the data observed in literature for normal subjects in relation to the stability of f within a subject, independent of vigilance states and the inter-individual variability that exists [35,37,38]. We believe that for the majority of our tachypneic patients, the most likely hypothesis that may explain the observed acceleration of breathing frequency during sleep is that this was due to the morbid obesity associated with the diminution of pulmonary volumes (VC and FEV1) and hypercapnia. The reduction in pulmonary volumes may potencialise ventilatory decreases normally observed during sleep, enhancing the development or underscoring and increasing the hypercapnia that already exists. This in turn induces tachypnea and tachycardia (detected as PF) as a compensatory mechanism.

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