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Research Article

IMPACT OF DIURNAL RHYTHM ON PULMONARY FUNCTIONAL STATUS IN NORMAL SUBJECTS

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ABSTRACT

Many physiological functions show day-night fluctuations called circadian rhythm. Day time fluctuation is called diurnal variation which is a part of circadian rhythm. Both are enabled by the biological clock in supra-chiasmatic nucleus (SCN) of hypothalamus. Impact of diurnal oscillations on body temperature and metabolic rate are widely studied. However, its role in modulating the lung functions from morning till evening is less explored. Hence, an attempt had been made in this arena. Respiratory functional status was assessed at 8 AM, 12 noon and 5 PM in 15 normal young individuals in the age group of 17 to 20 years by pulmonary function test (PFT). The values of PFT variables were analysed in SPSS version 17 by using ANOVA. The mean values of FVC, FEV1, FEV1/FVC ratio, FEV25-75% and PEFr were maximum (122.80, 128.20, 121.40 and 107.33) at 5 PM and minimum (105.00, 98.40, 99.53 and 97.80) at 12 noon revealing that lung function was at its best around 5 PM with minimum airway resistance and worst at 12 noon with maximum airway resistance. It is postulated that SCN regulates circadian rhythm through retinal impulses and pineal gland. Pineal gland, in turn, controls circadian rhythm by secreting melatonin which may play a key role in modulating the expression of chemotaxins in airway epithelium. We conclude that the pulmonary functional status is at its best around 5 PM it may be considered in determining the time of treatment to enhance the therapeutic efficacy for the pulmonary disorders.

Keywords: Biological clock, Circadian rhythm, Pulmonary function test, Therapeutic efficacy.

INTRODUCTION

Physiological functions of the living body shows day-night fluctuations around 24 hours, what is called as circadian rhythm or diurnal rhythm. It is modulated by the supra-chiasmatic nucleus which is popularly known as 'biological clock'. It dwells in hypothalamus and operates through the feed-back regulatory mechanism involving hypothalamic-pituitary axis and autonomic nervous system (ANS)^{1,2,3}. The cyclic changes may be noticed as peak or trough depending upon the demand of the biological requirements during activities and awakening in day-time or rest and sleep in night-time^{4,5}. Importance of this regulation is evident from the fact that any deviation in the functional pathway leads to the disturbances in the routine functions ending up with emotional disturbances, gastrointestinal disorders, headache, fatigue and malignancy⁶.

Extensive studies have been done on the impact of circadian rhythm on body temperature, metabolic changes and sleep pattern^{6,7,8} and its role in modulation of pulmonary function is

also an accepted fact^{9, 10}. Further understanding of the impact of different timings in day time on pulmonary functions may throw a brighter light on the knowledge of the causes and symptoms of respiratory diseases and may give a better guidance for proper approach towards therapeutic interventions^{11,12}.

Lot of studies had been done in this regard on both asthmatics and non-asthmatics. Majority of the results showed that the common symptoms of asthma like breathlessness, dyspnea, wheezing, maximum airway resistance and obstruction were predominantly seen during the night time and early mornings and disappeared as the day advanced. This nocturnal and early morning problems in asthmatics were attributed to the reduced serum epinephrine level, increased cholinergic activity with heightened vagal tone, esophageal reflex and increased eosinophil count^{13,14,15}.

However, information regarding the pattern of fluctuations in pulmonary functions during daytime hours (diurnal rhythm) in normal young healthy individuals is scanty and controversial. One of the studies showed the lowest maximal voluntary

ventilation (MVV) at noon and highest flow rates in the afternoon hours (around 4 to 5 PM)¹⁶. According to another group, the airway resistance was at its maximum in early hours of the morning, reaching minimum at noon and again increasing in the afternoon hours in normal subjects as well as the patients with restrictive and obstructive lung diseases¹⁷. These controversial results triggered the interest of evaluating the impact of diurnal variation on the pulmonary functional status in normal healthy individuals.

MATERIALS AND METHODS

The study was conducted in 15 normal healthy male adults in the age group of 17-20 years with matching anthropometric measurements. They were screened for their medical history and physical conditions; the functional status of respiratory system was assessed by pulmonary function test (PFT) using spirometer. Ethical clearance was obtained from the Institutional Human ethical committee and informed consent was obtained from all the subjects after explaining the experimental procedure.

Exclusion criteria: Subjects with obesity, cardiorespiratory problems and those who were on medication for some reason or other were not included in the study.

Prior to the actual procedure, they were trained to do PFT in a proper way. The recording was done in three different timings of the day viz., 8:00 AM, 12 Noon and 5:00 PM. by using a computerized spirometer (MEDSPIROR). The parameters studied were forced vital capacity (FVC), forced expiratory volume in 1st sec. (FEV1), FEV1/FVC ratio, FEV3/FVC ratio, peak expiratory flow rate (PEFR), Forced expiratory flow 25-75 (FEF 25-75) and maximum ventilatory volume (MVV). All these parameters were recorded by single breath technique.

The data were analysed in SPSS version 17. The mean values and standard deviation of the mean (SD) were calculated for all the subjects. One-way analysis of variance (ANOVA) was used to identify statistical differences between the timings of the recording. Tukey’s multiple comparison test was applied to determine the significance between the groups

RESULTS

Overall comparison:

All subjects were with normal height and weight for the age group of 17 to 20 years and none of them were over-weight or obese (Table 1)

Table 1: Demographic characteristics of studied subjects

Variable	Mean ± SD
Age in years	18.53 ± 1.06
Height in cm	171.33 ± 7.49
Weight in kg	64.33 ± 8.99
Body mass index	21.9 ± 2.69

Statistical analysis of FVC, FEV1, FEV1/FVC, FEF 25-75% and PEFR showed highly significant diurnal variation. The highest mean values were seen at 5 PM (mean ± SD: 122.80 ±

14.40, 128.20 ± 18.69, 121.40 ± 8.65, 107.33 ± 4.06) and lowest mean values were observed at 12 noon compared to the values at 8 AM. The difference between the highest and the lowest values of each variable was highly significant (Table 1). The FEV3/FVC ratio and MVV did not show any significant difference between the groups (Table 2).

Table 2: Mean Spirometric values recorded at 8 AM, 12 Noon and 5 PM

Variable	8 AM	12 Noon	5 PM	Sig-between groups
FVC	117.67 ± 15.91	105.00 ± 8.60	122.80 ± 14.50	0.006*
FEV1	119.47 ± 16.55	98.40 ± 10.60	128.20 ± 18.69	0.000*
FEV1/FVC ratio	115.53 ± 6.33	99.53 ± 5.15	121.40 ± 8.65	0.000*
FEV3/FVC ratio	102.47 ± 1.77	101.53 ± 1.46	102.73 ± 2.08	0.168 NS
FEF 25-75%	102.67 ± 4.05	98.13 ± 2.97	102.53 ± 3.74	0.001*
PEFR	102.40 ± 2.20	97.80 ± 5.38	107.33 ± 4.07	0.000*
MVV	102.17 ± 4.09	97.97 ± 5.64	100.18 ± 5.53	0.095 NS

Values are expressed as mean ± SD
Significant level is fixed at p < 0.05
Significance is indicated as *
NS – Not significant

Comparison between different timings:

FVC did not show significant difference between 8 AM and 5 PM but difference between 5 PM and 12 noon was highly significant (p < 0.005) with the peak at 5 PM. In comparison to 12 noon values, FEV1 was significantly higher at 8 AM (p < 0.002) and 5 PM (p < 0.000). FEV1/FVC did not differ statistically between 8 AM and 5 PM (p < 0.061) and was significantly higher at 8 AM (p < 0.000) and 5 PM (0.000) than at 12 noon. FEF25-75% did not show significant difference between 8 AM and 5 PM (p < 0.994) but difference between 8 AM and 12 noon was highly significant (p < 0.004) with the peak at 8 AM. Compared to 12 noon it was significantly more at 5 PM (p < 0.005). PEFR showed significant difference between all the three timings: Compared to 8 AM, it was significantly less at 2 PM (p < 0.008) and more at 5 PM (p > 0.004). Between 8 AM and 5 PM it was significantly more at 5 PM (p < 0.000). FEV3/FVC and MVV did not show any significant difference between the recordings of three timings (Table 3).

Table 3: Comparison of the diurnal variation in the spirometric values

Variable	Comparison between	Mean difference \pm SE	Significance
FVC (L)	8 AM & 12 noon	12.47 \pm 5.30	0.060 NS
	8 AM & 5 PM	- 5.33 \pm 4.20	0.539 NS
	12 noon & 5 PM	-17.80 \pm 5.31	0.005*
FEV1 (L)	8 AM & 12 noon	21.07 \pm 5.72	0.002*
	8 AM & 5 PM	-8.73 \pm 5.72	0.289 NS
	12 noon & 5 PM	-29.80 \pm 5.72	0.000*
FEV1/FVC Ratio	8 AM & 12 noon	16.00 \pm 2.51	0.000*
	8 AM & 5 PM	-5.87 \pm 2.51	0.061 NS
	12 noon & 5 PM	-21.87 \pm 2.51	0.000*
FEV3/FVC Ratio	8 AM & 12 noon	0.93 \pm 0.65	0.336 NS
	8 AM & 5 PM	-0.27 \pm 0.65	0.921 NS
	12 noon & 5 PM	-1.20 \pm 0.65	0.170 NS
FEF25-75%	8 AM & 12 noon	4.53 \pm 1.32	0.004*
	8 AM & 5 PM	0.13 \pm 1.32	0.994 NS
	12 noon & 5 PM	-4.40 \pm 1.32	0.005*
PEFR (L)	8 AM & 12 noon	4.60 \pm 1.46	0.008*
	8 AM & 5 PM	-4.93 \pm 1.46	0.004*
	12 noon & 5 PM	-9.53 \pm 1.46	0.000*
MVV (L)	8 AM & 12 noon	4.18 \pm 1.87	0.077 NS
	8 AM and 5 PM	1.98 \pm 1.87	0.547 NS
	12 noon and 5 PM	-2.21 \pm 1.87	0.473 NS

Significance is shown with*
NS – Not significant

DISCUSSION

The results of the present study are highly informative and take us few steps ahead of understanding the influence of different timings of the day in modulating respiratory functions in normal subjects. Accordingly, the fact that most of the lung function variables (FVC, FEV1, FEV1/FVC, PEFR) were minimum around 12 noon and maximum at 5 PM indicate that the airway resistance was highest at 12 noon and lowest in the evening. This is in accordance with the previous report which states that the airway resistance peaks in the morning, reaches its lowest point at noon and increases in the afternoon^{7,16,17,18}.

These changes seem to be taking place independently, irrespective of the routine day-to-day activities because of the environmental adaptation. However, time and again, some functional systems in the body like respiratory system show less capability in adjusting to the environmental challenges that may lead to the peak and trough of some of the variables round the clock in normal and diseased conditions¹⁹.

The sedidurnal variations are believed to be brought about by SCN in hypothalamus which is aptly named as biological clock^{1,2,3}. The exact mechanism by which SCN does it is yet to be explored. It is postulated that SCN takes information during day and night from the retina, interprets it, and passes it on to the pineal gland. Pineal gland, in turn, regulates the circadian rhythm by secreting melatonin which may play a key role in modulating the expression of chemotaxins in airway epithelium²⁰.

Another report have proposed that these diurnal variations are brought about by the close interrelation with hormonal and autonomic inputs, especially sympathetic input which are concerned with the regulation of smooth muscular activity in the respiratory tract in different timings of the day and night^{12,21}.

Yet another study involving the lung capacity for carbon monoxide diffusion (DLCO) depicted that the diffusing capacity for carbon monoxide (CO) is maximum in morning hours. Increase in morning peak of DLCO of the lung with progressive decrease in the subsequent hours has been found to be in response to alteration in the level of norepinephrine across the day: catecholamine levels were found to be higher in the morning which might contribute to the increased DLCO²². However other reports reveal that diurnal variations are linked with body temperature, oxygen consumption and carbon dioxide production^{7,8}.

Cortisol, a glucocorticoid produced by adrenal cortex shows a circadian rhythm with its peak at about 8.00 AM and fall around 12 noon and midnight with a good improvement by 3 PM²³. The relationship between cortisol levels and FEV1 in children was reported by Anneke et al according to whom these two are directly proportional; higher the serum cortisol level, better the lung function²⁴. These low cortisol levels at night precede the nocturnal fall in FEV1 and may result in less suppression of airway inflammation with subsequent increase in airflow limitation¹⁵.

Blood eosinophil count was also found to be following the path of cortisol: eosinophils in the blood were minimum in the morning and maximum at around noon and 3count that is mediated by SCN via retino-hypothalamic fibers. Diurnal variation in blood eosinophil number (lowest in the morning and highest around noon and midnight) is attributed to the circadian rhythm in cortisol release^{25,26}.

Clinical implications of the study:

The knowledge that diurnal rhythms can modulate human health may help us to determine the administration of medications in asthmatic and hypertensive patients to obtain the optimum benefit. Timing of medical treatment in coordination with the body clock may significantly increase efficacy and reduce drug toxicity or adverse reactions. Many patients with asthma and chronic obstructive pulmonary disease administer bronchodilators around the clock, when

they actually may need less treatments and a different regimen that includes administering the medication at midday when their lung function is at its lowest.

CONCLUSION

Results showed that overall airway resistance of the lung was at its most prominent around 12:00 pm but reached its minimum between 4:00 to 5:00 pm, showing that lung function was at its best in the late afternoon. We often associate the end of the day with being tired and less motivated for physical exertion. However, lung function seems to be at its best during this time. As a result, exercising or engaging in other physical activities in the late afternoon may help us to achieve optimal performance. It also may be better to exudates patients in the late afternoon when their lung function is at its best and breathing on their own is easier. Relaxation techniques or biofeedback may modify the lung-function circadian rhythms, helping to manage a person's low and high lung function throughout the day. But more studies need to be completed in this area.

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