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Circadian Rhythms of the Indices in the Diffusing Function of the Lung in Healthy Men

Naoto Burioka, Hisashi Suyama, Takanori Sako, Eiji Hoshino, Yukio Matsumoto and Takao Sasaki

Third Department of Internal Medicine, Faculty of Medicine, Tottori University, Yonago 683-0826, Japan

Diurnal variation in the lung diffusing function can influence the results of clinical evaluations. We investigated circadian rhythms from diurnal variations of the indices in the diffusing function of the lung. We measured the single breath lung diffusing capacity for carbon monoxide (D_{LCO}) and alveolar volume (V_A) in 13 healthy men, and also measured pulse rate at 7:00, 11:00, 15:00, 19:00 and 23:00. To identify the presence of a circadian rhythm from daily variations, data were analyzed by the group mean cosinor method. Significant circadian rhythms were apparent for D_{LCO}/V_A, V_A and pulse rate. The acrophases for these parameters occurred at 20:15, 5:26 and 18:08, respectively. The double amplitude of D_{LCO}/V_A was statistically 4.72%. Our results suggest that diurnal variations in V_A and pulse rate may contribute to the variation in D_{LCO}/V_A. Although D_{LCO}/V_A showed only a small change throughout the day, our findings suggest that the examination of D_{LCO}/V_A should be performed preferably at the same time of day in an individual.

Key words: alveolar volume; circadian rhythm; cosinor analysis; diurnal variation; lung diffusion capacity

Although the human body maintains homeostasis despite changes in internal and external conditions, diurnal variations may occur in response to those conditions. These variations can be periodic or non-periodic. Periodic phenomena, in particular, are considered to be important for the clarification of morbid states and development of therapeutic methods. A number of indices of respiratory function have been found to show diurnal variations or circadian rhythms (Hetzel and Clark, 1980; Ohga et al., 1992). The lung diffusing capacity for carbon monoxide (D_{LCO}) is widely used as a clinical parameter. It has been found to show diurnal variation in healthy individuals (Cinkotai and Thomson, 1966; Panda and McHardy, 1980; Mahajan et al., 1990), and has not (Frey et al., 1987). Diurnal variations can influence the results of evaluations in routine clinical practice. We examined the time-course of diurnal variations of indices of the diffusing function of the lung in healthy men, and attempted to identify circadian rhythms.

Subjects and Methods

Subjects

We studied 13 healthy men (age: 31.5 ± 4.3 years) without cardiopulmonary diseases. There were 6 nonsmokers and 7 smokers. Smoking was prohibited before and during examinations. The subjects were all doctors in our respiratory laboratory. They were made to get up before 7:00 and ate breakfast between 7:00 and 9:00, lunch between 12:00 and 14:00, and dinner between 19:00 and 21:00. Their working was not regulated during the study.

Abbreviations: D_{LCO}, lung diffusing capacity for carbon monoxide; PR, pulse rate per minute; V_A, alveolar volume

Table 1. Diurnal variations in the indices of lung diffusing function and PR

Index		7:00	11:00	15:00	19:00	23:00
D_{LCO}	(mL/min/mmHg)	25.4 ± 4.1	25.4 ± 4.4	25.1 ± 4.3	26.2 ± 4.3	25.7 ± 3.4
D_{LCO}/V_A	(mL/min/mmHg/L)	4.20 ± 0.71	4.29 ± 0.75	4.33 ± 0.74	4.45 ± 0.73	4.39 ± 0.65
V_A	(L)	6.05 ± 0.56	5.95 ± 0.46	5.81 ± 0.58	5.90 ± 0.44	5.89 ± 0.53
PR	(min^{-1})	69.4 ± 9.5	73.9 ±11.5	76.8 ± 8.8	76.1 ±10.8	76.4 ±10.5

Data are mean ± SD.
D_{LCO}, lung diffusing capacity for carbon monoxide; PR, pulse rate; V_A, alveolar volume.

Measurements

The forced expiratory curve was measured using a Chestac 55V, a rolling seal type spirometer (Chest MI, Tokyo, Japan). The pulse rate per minute (PR) was measured in a sitting position after resting for at least 3-min in 10 of 13 subjects before measuring lung diffusing capacity for carbon monoxide (D_{LCO}) and alveolar volume (V_A) of body temperature ambient pressure, saturated with water vapor, at 7:00, 11:00, 15:00, 19:00 and 23:00. D_{LCO}, V_A and D_{LCO}/V_A were measured at 7:00, 11:00, 15:00, 19:00 and 23:00 with subjects in a sitting position after at least a 3-min rest period. Duplicate analyses were performed at each time point with a Pulmonet III (Gould, Bilthoven, Netherlands) or a Chestac 55V by the single breath diffusing capacity. In the single breath diffusing capacity method, the subject was forced to aspire a gas mixture containing 0.3% CO and 10% He from residual volume up to total lung capacity. After stopping the breath for 10 s, the immediately expired gas was sampled, and D_{LCO}, V_A and D_{LCO}/V_A were analyzed. The same equipment was used for each subject.

Data analysis

Each subject underwent a measurement of 5 points in which measurements were done twice, and measured values were the expressed percentage value from the mean of the daily variation. The relative percentage values of each index were examined by the group mean cosinor analysis, and the presence of circadian rhythm was tested at a significance level of 5% (Nelson et al., 1979). A probability value of less than 0.05 was considered statistically significant.

Results

The predicted average of forced expiratory volume in one second was 82.2 ± 6.2%. In Table 1, D_{LCO}, D_{LCO}/V_A, V_A and PR at each measuring point for subjects are shown. No significant circadian rhythm was observed in D_{LCO}. A significant circadian rhythm was seen in D_{LCO}/V_A, and its acrophase was 20:15 (95% confidence interval: 16:44–0:16) with a %amplitude of 2.36% (0.54–4.21%). In V_A, a significant circadian rhythm was observed, and its acrophase

Table 2. Group mean cosinor analysis of D_{LCO}, D_{LCO}/V_A, V_A and PR in healthy men

n	Index	Acrophase	Percent rhythm (%)	Percent amplitude (%)
13	D_{LCO}	NS	NS	NS
13	D_{LCO}/V_A	20:15 [16:44 – 0:16]	31.1	2.36 [0.54–4.21]
13	V_A	5:26 [3:20 – 8:12]	34.8	1.70 [0.66–2.77]
10	PR	18:08 [16:20 –20:24]	60.9	4.94 [2.50–7.45]

[ ], 95% confidence interval; percent rhythm, $r^2 \times 100$.
D_{LCO}, lung diffusing capacity for carbon monoxide; NS, not significant; PR, pulse rate; V_A, alveolar volume.

was 5:26 (3:20–8:12) with a %amplitude of 1.70% (0.66–2.77%). Regarding the PR, a significant circadian rhythm was also found in the analysis of the group of 10 subjects, and its acrophase was 18:08 (16:20–20:24) with a %amplitude of 4.94% (2.50–7.45%) (Table 2).

Discussion

The diffusing capacity of the lung, particularly that obtained with carbon monoxide (D_{LCO}) has widely been used clinically. The logical basis of the lung diffusing capacity was established and the measuring method of D_{LCO} was developed by Forster and colleagues (1954). The ratio of D_{LCO} to V_A (D_{LCO}/V_A) is also used as an index of the diffusing function of the lung. Lung diffusing capacity is related to gas exchange between alveolar gas and erythrocytes in alveolar capillaries. It is therefore influenced by the diffusion distance (thickness of the membrane), the surface area of the lung, the size of the capillary bed in the lung, the pulmonary capillary blood volume, the hemoglobin content of erythrocytes, and the uneven distribution of the ratio of aeration to blood flow. The subject's posture during evaluation of D_{LCO} can also affect measurements.

In order to clarify the cause of the diurnal variation in detail, the diurnal variation was examined from an aspect of circadian rhythm which has not been performed so far. We used cosinor analysis for the purpose of identifying circadian rhythm (Nelson et al., 1979). The acrophase is the time of the highest point of a cosine curve fitted to a time series while the bathyphase is the time of the lowest point; it differs 180° (12 h) from the acrophase. Although D_{LCO} did not exhibit a circadian rhythm, D_{LCO}/V_A, V_A and PR showed significant circadian rhythms. Studies have shown that V_A peaks in the morning and decreases toward evening (Panda and McHardy, 1980; Frey et al., 1987; Mahajan et al., 1990), which is consistent with the present study. The mechanism of the change in V_A is uncertain, but the decrease of V_A may be related to the decrease of the lung recoil pressure (Saito et al., 1996).

Our results are different from published results (Cinkotai and Thomson, 1966; Panda and McHardy, 1980; Mahajan et al., 1990). We hypothesize that the lack of significant circadian rhythm in D_{LCO} may have been related to the finding that the acrophases of V_A and PR almost occurred at opposite times. V_A was high and PR was low in the morning, and V_A decreased and PR increased toward the evening. D_{LCO} is expected to decrease when V_A decreases because the lung surface area becomes smaller and the gas-exchange area is decreased. It is considered that the pulmonary vascular change is one of the factors to change the magnitude of D_{LCO}. When the PR is increased by a loading exercise test in normal subjects, pulmonary capillary blood volume increases, resulting in an increase in D_{LCO} (Johnson et al., 1960; Rosenberg and Foster, 1960). Changes in PR at rest are linked to the diurnal variation in the plasma level of norepinephrine, suggesting that acceleration of the sympathetic nervous system during the daytime can contribute to an increase in the pulse rate. D_{LCO} has been found to increase in response to norepinephrine, induced an increase in the diffusion capacity of the pulmonary membrane (Lewis et al., 1960). Therefore, although the relation is indirect, D_{LCO} may increase when PR increases. Since both V_A and PR can affect D_{LCO}, the changes in these indices may have canceled out significant changes in D_{LCO}. In

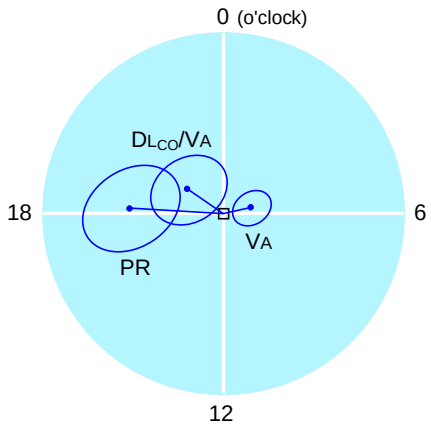

Fig. 1. Group mean cosinor expression on a 24-h clockface. D_{LCO}, lung diffusing capacity for carbon monoxide; PR, pulse rate; V_A, alveolar volume.

previous studies (Cinkotai and Thomson, 1966; Panda and McHardy, 1980; Mahajan et al., 1990), the relative contributions of these 2 factors may have been different from the present study.

Group mean cosinor analysis showed that the 95% confidence interval of the acrophase of D_{LCO}/V_A overlapped with that of the PR and bathyphase of V_A (15:20–20:12) (Fig. 1). Therefore, the increase in D_{LCO}/V_A at 19:00 compared with 7:00 may have been due to the decrease of V_A, and an increase in pulmonary capillary blood volume or an increase in the diffusing capacity on the pulmonary membrane. Although the hemoglobin content of erythrocytes was not measured in the present study, it has been found to decrease from the morning to the evening (Renbourn, 1947) and to affect the magnitude of D_{LCO} (Frey et al., 1987). Daily change in hemoglobin content may also have been involved in the diurnal variations of the indices in the lung diffusing function.

On the basis of group mean cosinor analysis, the maximal amplitude of an index with significant circadian rhythm is double %amplitude at acrophase. Therefore, the maximal amplitude during diurnal variation was 4.72% for D_{LCO}/V_A (95% confidence interval: 1.08–8.42%). Although the variation is small, our findings suggest that D_{LCO}/V_A should be evaluated at the same time of day when monitoring clinical changes in an individual whose work is not regulated.

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