

Synchronization Between Cardiac and Respiratory Rhythms in Healthy Subjects and Patients

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Abstract Synchronization between cardiac and respiratory rhythms may be important for oxygen transport to tissues. The aim of this study was to investigate the synchronization between cardiac and respiratory rhythms. We evaluated the rhythms in 12 healthy males and 24 patients. The incidence rates of heart beats were obtained in each time interval relative to the initiation time point of inspiration. A simple index of timing variability of heart beats was defined. When the variability is large, the link between cardiac and respiratory rhythms was considered to be strong. The variability value of patients with disorder in the autonomic nervous system was larger than that of healthy subjects ($p < 0.05$). The variability of patients on controlled ventilation was lower than that of healthy subjects ($p < 0.01$), whereas the value on cardiac pacemaker did not differ from healthy subjects. In conclusion, the synchronization between cardiac and respiratory rhythms was confirmed, and it is suggested that the synchronization is enhanced when feed-back signals from respiratory movement to respiratory center were decreased.

1 Introduction

Rhythmic phenomena in biological systems often show coordinate regulation that may lead to synchronization among rhythms. In some instances rhythms may be entrained by other strong rhythms, and respiration is an important factor in the rhythm modulation of the cardiovascular system, which is known as respiratory sinus arrhythmia [1]. On the other hand, the cardiovascular system also affects the rhythm control of respiration, *via* right ventricular strain [2], *via* pulmonary J receptor [3], and *via* aortic and carotid bodies [4]. Evidence of these mutual coordinate regulations between the respiratory and

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cardiovascular systems has been accumulating during the past two decades (reviewed by Daly [5]). Although the synchronization between cardiac and respiratory rhythms has been reported [6–11], the synchronization has not yet been investigated in detail, particularly in patients. The aim of this study was to investigate the synchronization between cardiac and respiratory rhythms in healthy subjects and patients with several kinds of disease.

2 Methods

Twelve healthy male subjects, ranging from 21 to 71 years old, and 24 patients, 15 males and 9 females, ranging from 37 to 83 years old, were studied. The lung function of healthy subjects was %VC at $96 \pm 21\%$ (mean \pm SD) and FEV₁% at $77 \pm 11\%$. The patients consisted of 8 patients with chronic obstructive pulmonary disease (COPD) with %VC at $94 \pm 29\%$ and FEV₁% at $41 \pm 13\%$, 5 with fibrosing lung disease (FLD) with %VC at $43 \pm 12\%$ and FEV₁% at $93 \pm 8\%$, 5 with disorders of the autonomic nervous system (ANS) (1 with Shy-Drager syndrome, 1 with multiple sclerosis, 2 with olivo-ponto-cerebellar atrophy, 1 with severe orthostatic hypotension), 3 on ventilator therapy (1 with heart failure, 1 with COPD, 1 with FLD) and 3 with sick sinus syndrome on cardiac pacemaker.

The subjects breathed through a face mask (Survivor Blue, Hans Rudolph, Kansas city, M.O.) installed with a hot-wire flowmeter (ATD280, Minato Medical Science, Osaka, Japan). Electrocardiogram (ECG) was monitored using surface electrodes on the chest. The subjects breathed for 40 min in a quiet room. The continuous signals of mouth-flow and ECG were fed to a computer via a 12-bit AD converter with 100 Hz (10 ms) sampling rate. The signal from the pneumotachograph indicated that there were no superimposed cardiogenic oscillatory waves. Initial unsteady data were discarded. In 5 healthy subjects, we employed an elastic load of 1.8 kgw/cm² by restricting the chest wall movement using a chest band, and abdominal wall was restricted with a corset, or employed an inspiratory resistance of 10 cmH₂O/l/min by adding a flow resistance tube (TV241T, Nihon Koden, Tokyo, Japan) to the inspiratory port of a two-way non-rebreathing valve (1500 series, Hans-Rudolf, Kansas City, M.O.). The dead space was 25 ml. This investigation was performed in accordance with Declaration of Helsinki.

The starting points of inspiration (tr_1 , tr_2 , etc.; Fig. 1a) and R waves (th_1 , th_2 , etc.; Fig. 1b) were identified. Using these time series data, we obtained plots for the incidence rate of cardiac beats relative to the start of inspiration as follows. The incidence of the R waves within a given time window ($\pm \Delta s$) at a given delay time (t s) after or before the start of inspiration (marked as “hit” in Fig. 1c) was identified, and then the incidence rate of R waves was calculated by the number of “hits” divided by the number of breaths. The delay time from the start of inspiration (t) was varied, ranging from $-$ half the mean respiration interval to $+$ half the mean respiration interval (Fig. 1d). We deleted the range over $\pm 2SD$

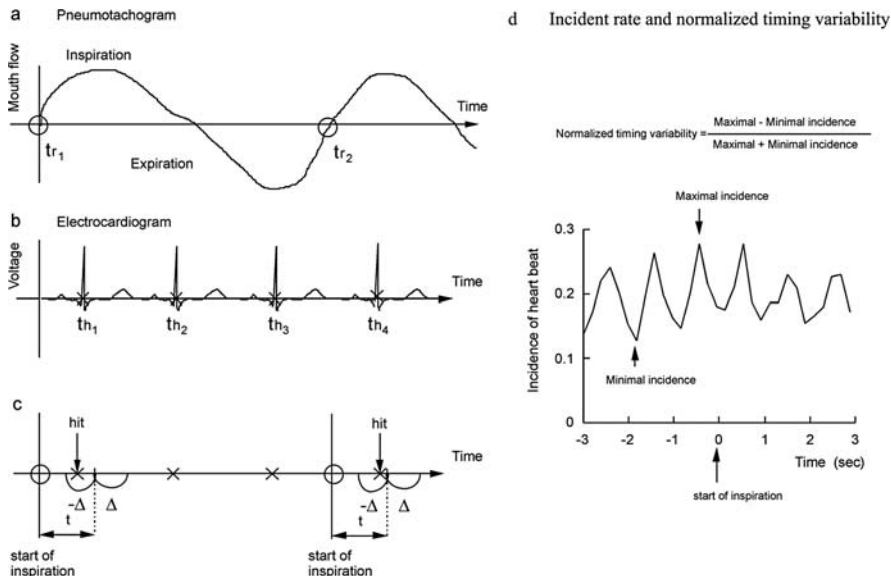


Fig. 1 Data analysis. The start of inspiration (tr_1, tr_2 , etc.; **a**) and R waves (th_1, th_2 , etc.; **b**) were identified. The incidence of R waves within a given time window ($\pm \Delta$ s) at a delay time (t s) from the start of inspiration was identified (marked as “hit” in **c**), and then the incidence rate of R waves relative to the start of inspiration was calculated (**d**). Then the normalized timing variability was obtained

of mean respiration interval on both sides to avoid the effects of breathing fluctuation. The time window of each subject, $\pm \Delta$, was set as mean R-R interval multiplied by 0.1. This constant multiplier was chosen, since the plots of the incidence rate with 0.02 or 0.3 did not substantially differ, but was more stable with 0.1.

A simple index of timing variability of heart beats was defined as the difference between the maximum and the minimum values of the heart-beat incidence rate, and was normalized as (maximal – minimal incidence rate)/(maximal + minimal incidence rate), thereby ranging from 0 to 1 (Fig. 1d). If the timing of heart beat was completely independent of breathing and was observed for a long time, the incidence rate profile becomes even throughout breathing, the normalized timing variability becoming zero (no synchronization). If the timing of heart beat was completely synchronized with breathing, the maximal incidence rate becomes one, the minimal being zero between the peaks, thereby the normalized timing variability being one (full synchronization). In a preliminary study the normalized timing variability value became stable as the number of respirations exceeded 200, and was evaluated by 500 breaths.

Probability histograms of heart-beat and breathing intervals were also obtained to investigate the relationship between heart beat and breathing intervals.

The normalized timing variability values were expressed as means \pm SEM and other values were expressed as means \pm SD. An unpaired Wilcoxon analysis was employed to compare the normalized timing variability of each patient group with that of healthy subjects, and analysis of variance was employed to test the difference in the normalized timing variability values of healthy subjects between loaded and unloaded conditions. $P < 0.05$ was considered as significant.

3 Results

In 12 healthy subjects the normalized timing variability was 0.28 ± 0.03 (mean \pm SEM: larger than 0, $p < 0.001$), and was independent of age which ranged from 21 to 71 years old ($r = 0.03$, *n.s.*). The normalized timing variability of 8 COPD patients at 0.26 ± 0.03 and of 5 patients with FLD at 0.33 ± 0.07 did not differ from healthy subjects. In 5 patients with ANS disorders, it was 0.55 ± 0.10 , and was larger than that of healthy subjects ($p < 0.05$). In 3 patients on controlled ventilation it was 0.12 ± 0.01 , and was lower than healthy subjects ($p < 0.01$), but that of 3 patients on cardiac pacemaker at 0.27 ± 0.05 did not differ from healthy subjects. In 5 healthy subjects, the normalized timing variability was 0.29 ± 0.04 at rest without load, and increased to 0.56 ± 0.12 with elastic load ($p < 0.05$), while the value with resistive load at 0.31 ± 0.03 did not differ from that without load (Fig. 2).

In all subjects, probability histograms of time intervals of heart beats had a single peak (Fig. 3a–c), while the probability histograms of breathing intervals in subjects with larger normalized timing variability had one-to-several peaks at integer multiples of the mean interval of heart beats (Fig. 3a, b). Patients on

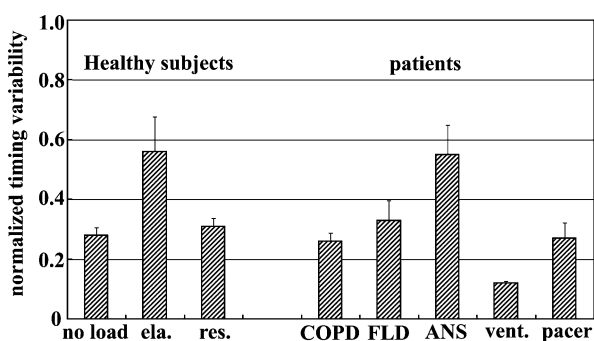


Fig. 2 Normalized timing variability in healthy subjects and patients. no load: without load; ela.: elastic load, res.: resistive load; COPD: chronic obstructive pulmonary em-physema; FLD: fibrosing lung disease; ANS: autonomic nervous system disorder; vent.: on ventilator; pacer: on pace-maker. *: $P < 0.05$; **: $P < 0.01$ compared to healthy subjects with no load ($n = 5$ vs. ela. or res., $n = 12$ vs. patient groups)

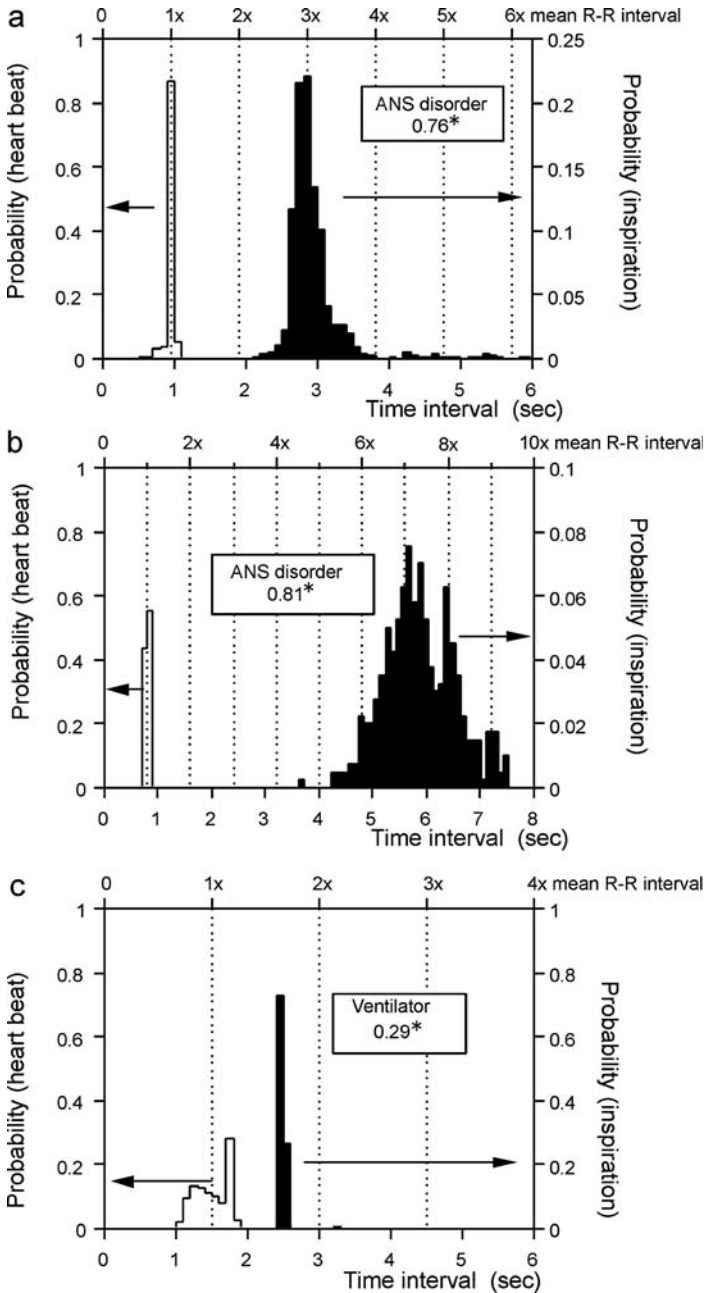


Fig. 3 Probability histogram of heart beats and breathing. The probability histogram of heart-beat intervals had a single peak in all subjects, while the probability histogram of breathing intervals had one (a: a patient with ANS disorder) to several (b: a patient with

controlled ventilation (Fig. 3c) had a single peak for breathing intervals, which did not locate at integer multiples of the mean interval of heart beats.

4 Discussion

Hinderling [12] and Hinderling and Bucher [13] investigated the mutual synchronization of cardiac and respiratory rhythms, by artificially inducing cardiac rhythm by a pacemaker or by employing voluntary hyper- or hypo-ventilation in humans, and found that pacemaker regulation synchronized respiration rate, while voluntary ventilation failed to synchronize heart rate. We have also confirmed that in patients on controlled ventilation the average normalized timing variability was significantly lower than that of healthy subjects, while the average normalized timing variability of patients on cardiac pacemaker regulation did not differ from that of healthy subjects. In contrast to the single-peaked probability histogram of heart beat intervals, the histogram of breathing intervals had one-to-several peaks at integer multiples of the mean interval of heart beats, particularly in the patients with larger normalized timing variability, a finding that also indicated that respiratory rhythm was entrained by the heart rhythm in these cases.

It is likely that cardiac rhythm is influenced by respiratory movement, whereas the respiratory rhythm is influenced and entrained by cardiac rhythm, but is also influenced by a feed-back control of respiration, such as the Hering-Breuer reflex. During quiet breathing with restricted thoracic movement, when the reflex is not activated, respiratory rhythm is considered to be mainly synchronized by cardiac rhythm. However, under conditions that enhance the feed-back signals of respiratory movement, the synchronization of respiratory rhythm to cardiac rhythm would be disturbed. Patients with disorders of the ANS are likely to have defective feed-back control by respiratory movement, while the afferent signals originated from cardiac beats will be transmitted to the central nervous system via several afferent routes, thereby increasing the normalized timing variability.

The physiological significance of the synchronization between respiratory and cardiac rhythm is not obvious. However, since respiratory movement influences the circulation with the change in venous return and blood pressure due to pleural pressure oscillation, it could be speculated that the rhythm synchronization would improve the energy cost for the circulation. It has



Fig. 3 (continued) ANS disorder) peaks at integer multiples of the mean interval of heart beats in the subjects with high normalized timing variability values. A patient on controlled ventilation (c) had a single peak in the probability histogram of breathing intervals, which did not locate at integer multiples of mean interval of heart beats.*: normalized timing variability

been shown that respiratory sinus arrhythmia benefits the pulmonary gas exchange and may improve the energy efficiency of pulmonary circulation by “saving heartbeats” [14, 15].

Another possible physiological significance could be that the possible entrainment of respiratory rhythm to cardiac rhythm might assure the safety of generation of respiratory rhythm. Cardiac rhythm is mainly generated locally in the sinus node. If the sinus node fails, another slower pacemaker in the AV node and/or ventricular branches will assure control of heart rhythm. In contrast, if the rhythm generating system in brain stem is disturbed or damaged, there are no secondary regulatory centers that may assure the control of breathing. The cardiac rhythm is generated in the sinus node even during the apnea for a while, and the respiratory center may incorporate the afferent signal(s) of cardiac rhythm to generate and restart a new respiratory rhythm. This hypothesis should be further investigated.

In conclusion, the synchronization between cardiac and respiratory rhythms was confirmed, and it is likely that the synchronization is enhanced in the situation that feed-back signals from respiratory movement to respiratory center were decreased.

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