Diurnal Change in Heart Rate Variability in Healthy and Diabetic Subjects

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We assessed the hourly coefficient of variance of RR intervals (CVrr) in 29 subjects with non-insulin-dependent diabetes mellitus and 19 age-matched healthy subjects using an ambulatory 24-hour ECG monitoring system. We also evaluated CVrr during 100 beats in both groups in the supine posture at 07:00 and 10:00 in the morning. Hourly CVrr showed an overt diurnal variation in both groups especially in the daytime and at midnight, but was significantly lower (p < 0.05) in diabetic patients. CVrr during resting 100 beats at 07:00 was significantly higher (p < 0.05) than that at 10:00 in both groups. These findings indicate that HRV shows an obvious diurnal variation in both groups. As a steep and marked change occurs in the morning, careful consideration is necessary to assess the test performed for a short time span at random times throughout the day, particularly in the morning. (Internal Medicine 31: 453–456, 1992)

Key words: diabetic autonomic neuropathy, ambulatory 24-hour electrocardiography, coefficient of variance of RR interval, RR interval variation

Introduction

Disorders of the autonomic nervous system are one of the significant complications of diabetes mellitus, therefore various non-invasive tests (1, 2) which evaluate autonomic dysfunction are widely used in clinical situations. Heart rate variability (HRV) is representative of the cardiovascular autonomic function tests performed on diabetic patients; methods of quantifying it have utilized such measures as standard deviation (SDrr) (3–6), mean square successive difference (4, 7) or coefficient of variation (CVrr) of RR intervals (8, 9). HRV has been assessed over a time span as short as 1 to 5 min (1–6, 8, 9). Recently however, analysis of all RR intervals from a 24-hour-ECG recording has become feasible through a sophisticated software which can compensate for such confounding factors as ectopic beats, atrioventricular block, and abrupt changes in body position (10, 11).

It is well known that there exists an overt circadian rhythm in blood pressure or heart rate (HR) (12, 13) which is under the regulation of the autonomic nervous system. No full scale reports, however, are available concerning the diurnal variation of HRV in diabetic subjects. To examine the influence of the diabetic state on diurnal variation, we monitored 24-hour continuous ECG and measured the hourly CVrr in healthy and diabetic subjects. CVrr was reported to be less dependent on the influence of corresponding RR interval length than SDrr (8–10).

The following questions were asked: 1) whether the diurnal variation of CVrr exists in both healthy and diabetic subjects, and 2) whether the measurement of hourly CVrr is more useful as compared with the measurement at random times over a short time span in evaluating the autonomic function in diabetic patients.

Materials and Methods

Subjects

Nineteen healthy subjects (15 men and 4 women; average age: 54.9 ± 3.1 years (X ± SEM) with a range of 16–76 years) and 29 non-insulin-dependent diabetic patients (21 men and 8 women; average age: 57.2 ± 2.4
years (x ± SEM) with a range of 23–73 years) were studied. Twenty-five patients were on insulin treatment and 4 on oral hypoglycemic agents. Patients under treatment with vagolytics, beta-blockers, or drugs known to affect the autonomic nervous system were excluded. None had clinically overt heart diseases or respiratory abnormalities. Both healthy subjects and diabetic patients were advised to continue normal daily activities and to walk at least 8,000 steps using walking step counters during the monitoring period. Review of the daily records indicated that diabetic patients were no more sedentary than healthy subjects. Mealtimes, rising time (06:00–07:00) and bed time (22:00–23:00) also did not differ significantly between the two groups.

Method

1) 24-hour ambulatory ECG: Two channel recordings were obtained using a Marquette 8500 recorder and were analyzed by a Marquette 8000 system which consisted of a computer with manual overread. HRV was measured by the method of Kleiger et al (14), briefly as follows: the arrhythmia analysis algorithms used in the computer systems labeled each QRS complex. QRS complexes with normal morphology and occurring within ± 20% of the preceding interval were measured. A human editor was given an opportunity to review portions of the computer processed ambulatory ECG and to modify any of the computer labels applied. After human overread, QRS data were processed by a microcomputer software program which computed the average and its SDrr of RR interval in the normal cycles. CVrr was calculated by dividing each hourly SDrr by the corresponding mean RR interval.

2) CVrr during 100 beats at rest: ECGs recording over 100 beats were monitored after a 10-minute rest in the supine position at 06:50 and 09:50 and RR intervals were analyzed by an automatic measuring device (Autonomic R-110, Fukuda Denshi Company, Tokyo) which uses a microcomputer to measure the RR interval with an accuracy of 1 m second, excluding premature beats, atrioventricular block and abrupt change in body position.

Statistical analysis

Intra-group data were analyzed by paired Student’s t test and inter-group data were analyzed by unpaired Student’s t test. Values are expressed as mean ± SD.

Results

1. Diurnal change in hourly CVrr

A diurnal variation in hourly CVrr was observed in both healthy and diabetic subjects (Fig. 1). In the healthy subjects, CVrr gradually increased early in the morning and achieved a manifest peak of 13.40 ± 4.08% at 05:00–06:00 before awakening. Thereafter, CVrr decreased and remained stable during the daytime (11:00–17:00), then gradually declined to reach a nadir of 7.43 ± 2.18% at midnight (0:00–01:00). A similar pattern was also observed in the diabetic subjects, but its diurnal variation was less evident in the diabetic patients than in the normal subjects (difference between peak and nadir of the means: 3.7% vs 6.0%). Furthermore, hourly CVrr in the diabetic patients was significantly lower (p < 0.01) than that of the healthy subjects during the daytime (08:00–17:00) and at midnight (20:00–04:00).

2. Diurnal change in hourly HR

Hourly HR over 24 hours in healthy and diabetic subjects is shown in Fig. 2. Here again a diurnal change was observed in both groups. HR started to increase after awakening, remained high during the daytime and gradually decreased after 19:00. No significant differences in hourly HR were observed between healthy and diabetic subjects, except for those during 05:00 and 07:00.

3. Change in CVrr during 100 beats at rest in the morning

CVrr during 100 beats at rest in the diabetic patients was significantly lower (p < 0.05) than that in the healthy subjects.
The variability of intra-individual results has been observed. Sympathetic nervous function of diabetic patients, but (18), and its usefulness remains a matter of debate.

of vagal integrity, and is widely used to evaluate parasympathetic changes, but this technique was reported to be unsuitable for the analysis of full 24-hour recording HRV over a short time span at rest is a simple index for cardiac diseases (10, 11, 14, 15), but few on diabetic neuropathy (7, 16, 17). A number of time domain measures for quantification of HRV have been proposed (11). SDANN measure (standard deviation of all 5-minute mean RR intervals over 24 hours) (14) and SDrr measure (mean of standard deviations of all RR intervals for successive 5-minute periods over 24 hours) (14, 15) have been used most widely in the clinical studies. We measured CVrr which is obtained by dividing each hourly SDrr by the corresponding mean RR interval, since CVrr was reported to be more reproducible, more stable (10) and less dependent on cardiac cycle length (8, 9) than SDANN or SDrr. HRV has also been assessed using frequency domain measures (power spectrum analysis) to provide more specific information concerning the underlying autonomic changes, but this technique was reported to be unsuitable for the analysis of full 24-hour recording (18), and its usefulness remains a matter of debate.

HRV over a short time span at rest is a simple index of vagal integrity, and is widely used to evaluate parasympathetic nervous function of diabetic patients, but variability of intra-individual results has been observed. Since an obvious circadian rhythm is generally seen in the cardiovascular autonomic nerve system (12, 13), HRV would also exhibit the diurnal change. It is important in assessing HRV measurement at random times in a day to elucidate a diurnal variation both in healthy and diabetic subjects.

Hourly CVrr showed the maximal value early in the morning and the minimal value at midnight in both groups, showing an innegligible variation of 7.4 to 13.4% in healthy subjects, and 5.4 to 9.1% in diabetic patients (Fig. 1). This diurnal variation in healthy subjects is consistent with the diurnal variation in SDrr recently reported by Huikuri et al (19). Although the reason for the abrupt increase of HRV early in the morning is unclear, it indicates a dramatic change occurring just before waking in the autonomic nerve function regulating cardiac rhythm.

Each hourly CVrr was significantly lower in the diabetic patients than in the healthy subjects, and the differences were marked especially during the daytime (08:00–17:00) and around the middle of the night (20:00–04:00) (Fig. 1). Although the HR levels (Fig. 2) and daily cards for the ambulatory ECG recordings were similar among each group, the possibility cannot be excluded that the diurnal variation of HRV in both groups and the difference of HRV between the groups were affected by their physical and mental activities. Thus, we also measured CVrr over a short time span at 07:00 and 10:00 in the supine posture after a 10-minute rest. Significant differences in the CVrr were observed between the two time points in each group and between the groups at each time point (Fig. 3). The levels of CVrr during each hour and during 100 beats at rest at 07:00 and 10:00 showed no correlation with the levels of fasting plasma glucose and hemoglobin A1c in the diabetic subjects, but tended to decline along with the progress of autonomic nerve symptoms (data not shown).

It is reported that a stimulation of cardiovascular sympathetic activity and concomitant vagal withdrawal occurs in the morning, even when the subjects are still lying in bed after awakening (20). During the morning hours, the roller of an intrinsic change in the autonomic neural balance is so huge and rapid that the CVrr decreases consistently, even when measured during various daily activities or only for a short time span in the resting state. Thus, it appears unsuitable to assess HRV during that time point. The assessment of the vagal function of diabetic patients may be most appropriately performed at around midnight during sleep, the most basal state of the day, when the sympathetic nerve tone is low and does not affect HRV in the resting supine posture. Since rapid eye movement (REM) sleep is less frequent in diabetic patients (21), the reduction of CVrr would not be caused by the activation of the sympathetic nervous system. HR in the diabetic patients was slightly higher than that in the healthy subjects, but the difference...
was not significant at midnight, although resting tachycardia has been suggested as a marker of diabetic vagal denervation (22).

In conclusion, since there exists a diurnal oscillation in CVrr which can be detected not only during normal daily activities but also at rest both in healthy and diabetic subjects, careful attention should be paid to the timing of cardiovascular autonomic nerve testing, especially in the morning when the change is steep and wide. The mean CVrr over an hour and during sleep late at night obtained by an ambulatory monitoring ECG is an excellent index of diabetic parasympathetic neuropathy.

References