Heart-Rate Variability and Cardiac Autonomic Function in Diabetes

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Cardiac autonomic function was measured in 25 subjects with insulin-dependent diabetes mellitus and 11 control subjects. Autonomic integrity was assessed with standard tests of autonomic function and a new technique of measuring heart-rate variability (HRV) for 24 h. All of the diabetic subjects were selected on the basis of peripheral or autonomic neuropathy or long-term poorly controlled diabetes. They were divided into groups according to presence or absence of vagal neuropathy based on the results of standard tests of autonomic function. Thirteen diabetic subjects had normal autonomic function tests (group 1), and vagal neuropathy was detected in 12 diabetic subjects (group 2). All subjects were monitored by ambulatory electrocardiograph, and the recordings were played back through an analyzer that identified and timed successive pulse (R-R) intervals. HRV was measured from the standard deviation of the successive differences between R-R intervals. HRV was significantly reduced in group 1 (mean ± SE 73 ± 9 ms) and group 2 (65 ± 12 ms) diabetic subjects compared with the control group (138 ± 10 ms). The standard tests of autonomic function did not distinguish the vagal dysfunction noted with HRV monitoring in group 1 diabetic subjects compared with control subjects. Measurement of 24-h HRV can detect small changes in cardiac autonomic function compared with currently available tests. Diabetes 39:1177–81, 1990

With the advent of simple noninvasive cardiovascular reflex tests, it became apparent that autonomic degeneration in diabetes was not only more common than previously thought but also widespread throughout the body (1). Initially, autonomic neuropathy was generally thought to be a late complication, because it was detected in patients with diabetes of long duration (2). As newer techniques to test autonomic function developed, however, it became clear that autonomic nervous dysfunction is present much earlier in the course of diabetes (3,4). There is therefore a need for a sensitive test to detect early neuropathic changes.

Standard tests of cardiac autonomic function (Valsalva maneuver, deep breathing, 30:15 ratio) may reflect abnormalities before the onset of clinical symptoms by observing short-term changes in the cardiac cycle, as a reflection of sympathetic and parasympathetic integrity (5). Initially, these tests were used to classify subjects according to the presence or absence of neuropathy; however, more recent studies attempted to grade the severity of neuropathy (6–8). Measurement of short-term (5-min) heart-rate variability (HRV) has been advocated as an indicator of autonomic neuropathy (9). There is disagreement, however, about whether the recording should be performed standing, sitting, or lying (10) and about the best method for measuring HRV (11). Ambulatory ECG monitoring (Holter monitor), used frequently to identify abnormalities in heart rhythm, has also been used to measure HRV as a test of autonomic function (12). Despite indications for future studies, however, there have been no further investigations with this technique in diabetic subjects. Monitoring for 24 h provides a unique opportunity to examine autonomic function during normal daily activities without interference from investigators. It may enable monitoring disease progression in diabetes. This article examines the hypothesis that measurement of 24-h HRV is an accurate method for assessing changes in cardiac autonomic function occurring in diabetes mellitus.

RESEARCH DESIGN AND METHODS

Twenty-five subjects with insulin-dependent diabetes mellitus (aged 34–60 yr, mean age 46 yr) underwent autonomic assessment by standard autonomic function tests and measurement of 24-h HRV. Subjects were selected by a clinician...
on the basis of signs that may indicate autonomic neuropathy, e.g., duration of diabetes (range 4–39 yr, mean 24 yr), impotence, bladder or bowel disturbances, abnormal sweating, and peripheral neuropathy. None of the subjects had hypertension or clinical evidence of heart disease, and none were taking medication other than insulin. An ECG was taken to exclude subjects with cardiac rhythm abnormalities. Eleven healthy age-matched control subjects were also assessed. The protocol was approved by the Wellington Hospital Ethical Committee (Wellington, NZ), and all participants provided informed written consent.

All subjects underwent several autonomic function tests. Detailed methods were described before (13). An abnormal deep-breathing response was sinus arrhythmia <15 beats/min. The 30:15 ratio of heart-rate response to standing was measured; a ratio of <1.03 was defined as abnormal. The change in blood pressure after standing was also measured, and a fall >10 mmHg diastolic and 20 mmHg systolic indicated sympathetic failure. The Valsalva maneuver ratio of the smallest heartbeat interval during straining to the longest after the release of pressure was calculated; a ratio of <1.21 was defined as abnormal. Carotid baroreceptors were stimulated by applying suction (−50 mmHg) to the neck (14). The suction was applied rapidly (−600 mmHg/s) and held for 3 s. The longest R-R interval during the suction was measured; a failure to prolong the R-R interval by >120 ms was defined as abnormal.

Subjects were fitted with a Holter monitor (MR14, Oxford Medilog), which recorded two channels of ECG onto a standard 60-min cassette tape for 24 h. Subjects kept self-recorded diaries of each day’s events (e.g., mealtimes, exercise, and sleep). Tapes were later played through an analyzer (MA14, Oxford Medilog) at 60 times the recorded speed. Fluctuations in the recording speed were adjusted by a phase-locked loop time signal. Filtered ECG output from the analyzer was fed through a QRS complex detector that incorporated a Schmitt trigger. This generated a pulse corresponding to each R wave. False triggering off the T wave was inhibited by generating a relatively long width (250 ms real time) for the resultant pulse. The time between R waves was counted with a rate-logging device (accuracy ±5 μs). The data were relayed through a parallel interface to a personal computer, where the R-R intervals were added sequentially to a file divided into consecutive segments, reflecting 30 min of real-time recording. QRS intervals outside a preset range (300–1800 ms) were deleted, and recordings containing >5 extrasystoles/h were discarded from further analysis (12). Results for individuals were standardized to a starting time of 0900.

Diabetic subjects were divided into two groups according to the presence or absence of autonomic neuropathy as defined from the standard tests of autonomic function, where two or more abnormal test results indicated autonomic neuropathy (15). The standard deviation of successive differences (SDSD) between R-R intervals was measured as an index of HRV for each 30-min subfile in each individual with a commercially available statistical package (SAS, Cary, NC). Two-way analysis of variance (ANOVA) was used to compare 24-h HRV results in nondiabetic subjects and the two groups of diabetic subjects with the Bonferroni multiple-comparisons procedure (16). There was an 80% power at the 5% level of significance to detect a difference of 50 ms in HRV between control and diabetic groups with the sample size studied. Results are presented as means ± SE. Statistical significance was achieved when P < 0.05.

RESULTS

Thirteen diabetic subjects (group 1) had normal autonomic function test results. Vagal neuropathy was detected in 12 diabetic subjects (group 2). Sympathetic neuropathy was not detected in any subject. Mean responses to standing, the Valsalva maneuver, deep breathing, and neck suction were significantly different between group 2 diabetic subjects and nondiabetic subjects but not between group 1 diabetic subjects and nondiabetic subjects (Table 1). The predominant factor in the selection of diabetic subjects was the duration of diabetes. Forty percent of those selected had few signs of neuropathy but had diabetes of sufficiently long duration to warrant inclusion. There was no significant difference in age or duration of diabetes between the groups.

Examination of the diary cards indicated that diabetic subjects were generally no more sedentary than nondiabetic subjects. Mealtimes and sleep periods did not differ significantly. Sixteen 30-min segments of ECG recordings were discarded from further analysis because of extrasystoles. All subjects exhibited a significant circadian variation in R-R intervals, the slowest heart rate was at 0500 in nondiabetic subjects and at 0530 in both groups of diabetic subjects. There was a tendency for both groups of diabetic subjects to have higher heart rates than the nondiabetic subjects throughout the 24 h (P = 0.067). The mean 24-h R-R interval was 806 ± 38 ms in nondiabetic subjects, 737 ± 21 ms in group 1 diabetic subjects, and 733 ± 21 ms in group 2 diabetic subjects.

Table 1

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Non-diabetic</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing (30:15 ratio)</td>
<td>1.12 ± 0.02</td>
<td>1.19 ± 0.04</td>
<td>1.02 ± 0.02</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.74 ± 0.09</td>
<td>1.61 ± 0.08</td>
<td>1.23 ± 0.08</td>
</tr>
<tr>
<td>Deep breathing (beats/min)</td>
<td>20 ± 2</td>
<td>17 ± 2</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Bradycardia with neck suction (ms)</td>
<td>222 ± 46</td>
<td>201 ± 28</td>
<td>33 ± 17</td>
</tr>
</tbody>
</table>

Values are means ± SE.

*P < 0.05 vs. group 2 diabetic subjects.
HRV was significantly reduced ($P < 0.01$) in both diabetic groups compared with the nondiabetic group at all times during the 24 h; however, the diabetic groups were not significantly different from each other. The HRV did not exhibit the same degree of periodicity for 24 h as the R-R intervals, and no clear rhythm was apparent (Fig. 1). However, averaging of the HRV for the morning, lunch, afternoon, evening, sleep, and waking periods illustrated a significant rise during sleep (Table 2). The increase during sleep was similar in all groups but set at a lower point in the diabetic groups. The mean SDSD for 24 h was $138 \pm 10$ ms in nondiabetic subjects, $73 \pm 9$ ms in group 1 diabetic subjects, and $65 \pm 12$ ms in group 2 diabetic subjects. The 24-h SDSD was not related to age or duration of diabetes. Six nondiabetic subjects repeated the ambulatory monitoring 1–12 wk apart (mean 3 wk), and a reproducibility coefficient for the SDSD of 0.83 was calculated by an ANOVA procedure (17); therefore, the method has acceptable reproducibility. Seven of 13 diabetic subjects in group 1 clearly had a mean 24-h SDSD less than the lowest normal value, and even the maximum individual value in this group was less than the mean for the nondiabetic group (Fig. 2). When the results from all diabetic subjects were considered as a group, 15 of 25 diabetic subjects had Valsalva ratios within the normal range. The proportion for the 30:15 ratio was 15 of 25, for sinus arrhythmia 17 of 25, and for neck suction 14 of 25. The proportion of diabetic subjects with mean HRV values within the normal range was 11 of 25, and it was significantly less than the proportion for autonomic function tests.

**DISCUSSION**

Some studies have examined various techniques for measuring HRV as a means to assess resting autonomic tone
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without the need for more provocative maneuvers (18,19); however, there is little information comparing these techniques with more commonly recognized measures of autonomic tone. Our study indicates an increase in the ability to detect minor changes in cardiac autonomic function with long-term HRV monitoring compared with standard tests of autonomic function. This increase was evidenced by the ability to detect significant reductions in HRV in group 1 diabetic subjects compared with nondiabetic subjects, which would not have been possible with the standard tests of autonomic function. There was no difference in HRV between group 1 and group 2 diabetic subjects; this may initially suggest that HRV was less sensitive than standard autonomic function tests, which easily detected such a difference. Nevertheless, the differences in proportions of diabetic subjects with HRV or autonomic function test results within the normal range indicate that grouping the diabetic subjects according to presence or absence of neuropathy may conceal important information.

Autonomic neuropathy in diabetic subjects is gradual in its onset, with signs often hidden for many years by reflex compensatory mechanisms. The ability to detect early complications of diabetes is important, because such evidence may modify subsequent management. The commonly employed autonomic tests inflect a temporary imbalance on the examined system, do not reflect its steady-state function, and require active participation from the patient. It is unlikely that standard tests of autonomic function have the necessary power for monitoring possible therapeutic interventions or gauging disease progression, and long-term HRV monitoring may provide sufficient sensitivity. This technique is, therefore, a useful guide in longitudinal assessment, e.g., in trials of treatment offering potentially beneficial effects or simply to monitor disease progression.

The measurement of R-R interval variation as an autonomic test in diabetes has been carefully reviewed and fulfills many of the characteristics of an accurate practical test (20). Interest in the study of 24-h HRV in diabetic subjects was initially stimulated by Ewing et al. (12). They noted a reduction in 24-h HRV in diabetic subjects with established vagal neuropathy and a tendency for diabetic subjects with normal cardiovascular reflexes to have HRV at the lower end of the normal range. We examined a similar group of diabetic subjects and noted unequivocal reductions, supporting the proposal of Ewing et al. (12) that this method is accurate in detecting early cardiac parasympathetic damage. Measurement of HRV has also been conducted via spectral analysis techniques in diabetic subjects with and without peripheral neuropathy (18). A decline in HRV in all frequencies was noted in all groups compared with control subjects. Although these results were not compared to a range of standard autonomic function tests, they indicate that autonomic dysfunction could occur in patients without clinically detectable evidence of diabetic neuropathy. Spectral analysis of HRV has provided a quantifiable index of sympathovagal interaction (19), however, the technique is not suitable for analysis of full 24-h recordings (21).

The increased power for 24-h HRV measurement to detect minor alterations in autonomic function was gained through the addition of every R-R interval occurring during 24 h and through the measurement of HRV by the SDSD. The SDSD has been used to measure HRV in newborn infants (22) and subjects with multiple sclerosis and diabetes (23,24), but it has had limited application to 24-h ECG recordings (12). The sensitivity of the SDSD as a measure of HRV has been critically examined (25). It is unaffected by linear trends in the heart rate, acting as a statistical filter in which the low-frequency components (generally not autonomic) are removed. Therefore, the SDSD is an index of beat-to-beat variability determined largely by autonomic influences on the heart.

Ambulatory monitoring comprises records of HRV during many different body positions and activities that cannot be fully annotated. However, measurements are made during sleep, which comprises some of the most basal states of the day. Twenty-four-hour monitoring provides an opportunity to examine cardiac autonomic function during this time. It is likely to be a reflection of natural background stimuli rather than the artificial maneuvers conducted in laboratory-based tests. The rise in HRV during sleep noted in this article was observed before (12). This may confer some extra stability of the sinoatrial axis, because a decrease in arrhythmia has been found during orthodox slow-wave sleep (26).

The development of autonomic neuropathy in diabetic subjects is a significant factor contributing to mortality with a rate of 50% for 3 yr (27). The occurrence of sudden or otherwise unexplained deaths among this group was also described (28). A lowered HRV was demonstrated in patients known to be at risk of sudden death (29). Similarly, patients recovering after myocardial infarction have a risk of death 5.3 times greater if HRV is reduced (30). It has been suggested that autonomic nervous system integrity plays an important role in the prevention, promotion, or precipitation of cardiac arrhythmia and that reduced vagal efferent activity may favor cardiac electrical instability (31). This could have considerable influence on the mortality rate of diabetic subjects, and HRV measurement may help to identify this high-risk group further. In conclusion, 24-h HRV measurement is able to detect small changes in cardiac autonomic function compared with available tests.

ACKNOWLEDGMENTS

Financial support for this research was provided by the Wellington Medical Research Foundation.

We thank Dr. R.B.W. Smith for referring diabetic subjects under his care and G. Purdie for statistical advice.

REFERENCES