A Critical Level of Diabetic Autonomic Neuropathy

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KAGEYAMA, S., TANIGUCHI, I., TANAKA, S., TAJIMA, N., SAITO, N., IKEDA, Y. and ABE, M. A Critical Level of Diabetic Autonomic Neuropathy. Tohoku J. exp. Med., 1983, 141, Suppl., 479-483 — Diabetic autonomic neuropathy was expressed quantitatively using the coefficient of variation of R-R intervals (CV_R-R) in ECG and its critical level where diabetics were plagued with various symptoms was investigated. The subjects were 58 diabetics under the age of 40 years. ECGs were recorded in the resting supine position and the degree of autonomic neuropathy was expressed as CV_R-R by processing 100 consecutive R-R intervals. Symptoms caused by diabetic autonomic neuropathy were determined using a questionnaire. CV_R-R were 1.10±0.34% (mean±SD) and 4.31±2.01% in patients with and without orthostatic hypotension respectively, the former being significantly lower. CV_R-R were 1.30±0.88% and 3.81±1.31% in those with and without impotence respectively, the former being significantly lower. CV_R-R were 0.80±0.14% and 3.85±2.17% in those with and without diabetic diarrhea respectively, the former being significantly lower. Concerning sweating abnormality CV_R-R were significantly reduced in subjects exhibiting gustatory sweating (1.62±0.74%) and hypohidrosis (2.26±1.44%) when compared to those without these symptoms. From the results obtained, a CV_R-R of 2% can be considered as the critical level which determines whether symptoms due to diabetic autonomic neuropathy will appear or not. —— diabetic autonomic neuropathy; R-R interval variation; orthostatic hypotension; impotence; diabetic diarrhea

Diabetic autonomic neuropathy (DNA) is frequently observed in patients with a long duration of diabetes and causes various symptoms once it is advanced. It has often been described by patients but there have been few objective descriptions. In 1973, Wheeler and Watkins reported that R-R interval variation disappears in patients with DNA (Wheeler and Watkins 1973). We have previously reported that autonomic nervous system function can be expressed quantitatively by a coefficient of variation of R-R intervals (CV_R-R) (Kageyama et al. 1980) and its usefulness in DNA (Kageyama et al. 1979). In this report we investigate the relationship between symptoms caused by DNA and CV_R-R.
PATIENTS AND METHODS

Our subjects were 58 diabetics (37 with insulin-dependent diabetes mellitus and 21 with non-insulin-dependent diabetes mellitus, 28 males and 30 females) aged from 15 to 39 years. As reported previously (Kageyama et al. 1979, 1980). ECGs were recorded in the resting supine position and 100 consecutive R-R intervals were processed by computer (Signal processor 7T07, San-Ei Sokki Co.). CVR-R was calculated from the mean and s.d. (s.d./mean × 100 (%). Symptoms caused by DAN, such as diabetic diarrhea, constipation, impotence, sweating abnormalities, sense of residual urine and hypoglycemic unawareness were evaluated from the results of a questionnaire. A fall in systolic blood pressure of more than 30 mmHg on assuming an erect posture was taken as orthostatic hypotension (OH). Concerning impotence, 20 males aged from 20 to 39 years were asked if they ever have a morning penile erection. If they had not had a morning erection for more than 6 months, they were considered impotent.

Data are presented as mean ± s.d. and the Student's t-test was used in statistical analyses.

RESULTS

CVR-R were 1.10 ± 0.34% and 4.31 ± 2.01% in 15 patients with OH and in 41 patients without OH respectively, the former being significantly lower (p < 0.001). The maximum CVR-R in patients with OH was 1.58% and the minimum CVR-R in patients without OH was 1.79%.

CVR-R were 0.80 ± 0.14% and 3.85 ± 2.17% in 7 patients complaining of diabetic diarrhea and in 45 patients without diarrhea, respectively, the former being significantly lower (p < 0.001) The maximum CVR-R in patients with diabetic diarrhea was 1.00%, and the minimum CVR-R in those without diarrhea was 1.02%.

CVR-R were 2.22 ± 1.27% and 3.83 ± 2.32% in patients with and without constipation respectively, the former being significantly lower (p < 0.01). The maximum CVR-R in patients with constipation was 4.49% and the minimum CVR-R in those without constipation was 0.74%, showing a large overlapping of CVR-R values between the 2 groups.

CVR-R were 1.47 ± 0.75% and 4.16 ± 1.52% in patients with and without impotence respectively, the former value being significantly lower (p < 0.001). The maximum CVR-R in subjects with impotence was 1.90% and minimum CVR-R in subjects without impotence was 2.13%.

CVR-R in 6 patients complaining of gustatory sweating was 1.52 ± 0.74% with the maximum of 2.60%. CVR-R in 9 patients complaining of hypohidrosis was 2.26 ± 1.44% with a maximum of 4.43%. CVR-R in patients with hyperhidrosis was 3.60 ± 2.09% with a maximum of 5.98%, and 4.02 ± 1.93% in those without symptoms. The former two values were significantly lower than CVR-R in subjects without symptoms.

CVR-R in 5 patients complaining of a sense of residual urine was 0.98 ± 0.35% with a maximum of 1.58%. CVR-R in subjects not complaining of this symptom
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TABLE 1. Coefficient of variation of R-R intervals (%) in various symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>With symptom</th>
<th>Without symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension</td>
<td>1.10±0.34*</td>
<td>4.31±2.01</td>
</tr>
<tr>
<td>Diabetic diarrhea</td>
<td>0.80±0.14*</td>
<td>3.85±2.17</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.22±1.27†</td>
<td>3.83±2.32</td>
</tr>
<tr>
<td>Impotence</td>
<td>1.47±0.75*</td>
<td>4.16±1.52</td>
</tr>
<tr>
<td>Gustatory sweating</td>
<td>1.52±0.74</td>
<td></td>
</tr>
<tr>
<td>Hypohidrosis</td>
<td>2.26±1.44</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>3.60±2.02</td>
<td></td>
</tr>
<tr>
<td>No sweating abnormality</td>
<td>4.02±1.93</td>
<td></td>
</tr>
<tr>
<td>Sense of residual urine</td>
<td>0.98±0.35*</td>
<td>3.72±2.16</td>
</tr>
<tr>
<td>Hypeglycemic unawareness</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

Data show mean±s.d. ( ) : denotes number of cases.
Asterisks show statistical significance when compared to those without symptoms (*p<0.001, †p<0.01).

was 3.72±2.16%.

There was only one patient who had an episode of coma due to hypoglycemic unawareness and his CVR-R was 0.76%.

DISCUSSION

Variation in R-R intervals in ECGs is abolished by the administration of atropine sulfate, and is therefore considered to be a sign of activity in the cardiac branch of the vagus. As we reported previously2,3, the physiological significance of R-R interval variation is in the efferent respiratory-locked phasic discharge in the cardiac branch of the vagus which plays a major role in eliciting variation in R-R intervals.

In the application of this autonomic function test, the age of the subjects must be taken into consideration. No difference in CVR-R was observed in subjects between their teens and their 30's, but after the age of 40, CVR-R decreased to 2-3%. Therefore, in this study, we limited patients to those under 40 years of age.

Advanced autonomic neuropathy gives rise to various symptoms, for example, in the circulatory system, in the digestive system, etc. Since there has been no way of expressing autonomic function quantitatively, the degree of autonomic neuropathy at the points where symptoms ensue has not been elucidated.

Every patient with OH had CVR-R less than 1.58% and all those without OH had CV-R-R more than 1.79%, showing no overlapping of CVR-R values between the 2 groups. CVR-R of 1.58% to 1.74% is therefore taken as the critical level in the development of OH.

Advanced DAN can sometimes cause intractable diarrhea, which is usually
painless and often occurs at night regardless of whether the patient has eaten or not. The authors studied diarrhea not only during the night but also during the daytime. The CVR-R of patients with diabetic diarrhea was 0.80±0.14% with a maximum of 1.00%. On the other hand none of the patients with a CVR-R of more than 1.02% had this symptom, and therefore a CVR-R of 1% is considered to be the critical level for the occurrence of diabetic diarrhea.

It is not clear whether diabetic diarrhea is caused DAN alone, or whether some other factors such as decreased pancreatic exocrine function or gut hormone abnormality may also be involved. In the present study, there was a strong relationship between diabetic diarrhea and DAN.

The CVR-R of patients complaining of constipation were reduced, but CVR-R values ranged widely and were not necessarily parallel to the degree of autonomic neuropathy.

CVR-R in patients complaining of impotence was 1.47±0.75% and significantly lower than in those without impotence. Penile erection is caused by the vasodilation of the sacral division of the parasympathetic nervous system and there has been no report of variation in neuropathy between the cranial and sacral divisions of the parasympathetic nervous system in DAN. From these results, it is reasonable to assume that CVR-R is a good parameter of impotence.

Concerning sweating abnormalities, CVR-R was 1.52±0.74% in patients with gustatory sweating, 2.26±1.44% in those with hypohidrosis and 3.60±2.09% in those with hyperhidrosis. Although there was a great deal of overlap between CVR-R values among the 3 groups, CVR-R was markedly decreased in those complaining of gustatory sweating with the maximum value being 2.60%. Gustatory sweating is thought to be the result of aberrant nerve regeneration between fibers of the vagus and sympathetic cholinergic sweat fibers at the level of the superior cervical ganglion (Watkins 1973).

Out of the 58 subjects, those with a CVR-R of less than 2% numbered 18, but of these, only 4 manifested none of the symptoms stated above. The CVR-R of these four were all over 1.62%. In cases with a CVR-R of less than 1.5%, some symptoms were invariably present. Although CVR-R reflects efferent activity in the cardiac branch of the vagus, no difference in the degree of disturbance between the sympathetic and parasympathetic nervous system has so far been observed in our investigation. Since there is a strong correlation between CVR-R and clinical symptoms, CVR-R can be used as a standard parameter of DAN and a value for CVR-R of 2% can be considered as the critical level at which symptoms which plague diabetics and even prevent them from returning to work appear.

References


