Autonomic Neuropathy of Heart in Diabetes

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INTRODUCTION

Although the maximal incidence of coronary artery disease in diabetics is well recognized, the other forms of diabetic heart disease have received little attention. Among the latter, one of the major forms is diabetic autonomic cardiac dysfunction.

It was in the last century that Eichorst[1] thought persistent tachycardia to be due to vagal neuropathy and Rundles[2] proposed it as a possible feature of diabetic autonomic neuropathy. However, till quite sometime there were only sporadic references to the abnormal cardiovascular reflexes and cardiac denervation. Advent of newer investigative techniques of continuous heart rate monitoring by Wheeler and Watkins[3] has shown gross abnormalities of cardiac autonomic innervation. This might be responsible for painless myocardial infarction, altered responses to physiological and pathological stress and sudden cardiorespiratory arrest leading to death in a diabetic[4].

MATERIALS AND METHODS

The autonomic function tests were carried out in diabetics by subdividing them into patients with or without peripheral neuropathy. The clinical profile of the diabetics who underwent autonomic function tests is shown in table 1.

Table 1
Clinicopathological profile of diabetic patients who underwent autonomic function tests

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>No of patients with autonomic symptom</th>
<th>Mean±SEM of DM (yrs)</th>
<th>Mean±SEM duration of DM (yrs)</th>
<th>Postural giddiness</th>
<th>Impotence</th>
<th>Diarrhoea gastric fullness</th>
<th>Hypoglycaemic unawareness</th>
<th>Gustatory sweating</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM with peripheral neuropathy</td>
<td>22</td>
<td>15</td>
<td>34.7 ± 2.6</td>
<td>3.9 ± 0.4</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>DM without peripheral neuropathy</td>
<td>23</td>
<td>3</td>
<td>37.0 ± 2.4</td>
<td>3.8 ± 0.6</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The mean age and the duration of DM in both groups were identical. Out of the 22 patients with peripheral neuropathy, 15 (68%) patients showed autonomic symptoms while only 3 out of 23 DM patients (13%) without peripheral neuropathy exhibited the same. The details of the various autonomic symptoms are presented in table 2.

Table 2
Details of autonomic symptoms in both the groups of diabetics

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
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<td>1</td>
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<td>-</td>
</tr>
</tbody>
</table>

Among the various symptoms, postural giddiness was predominant in 15 out of 22 DM patients with neuropathy (68%) and 3 out of 23 DM patients without neuropathy (13%). Other symptoms were minimal.

Cardiovascular Autonomic Function Tests[5]

Valsalva Manoeuvre

The reflex response to the valsalva manoeuvre includes tachycardia and peripheral vasoconstriction during strain, followed after release by an overshoot rise in blood pressure (BP) and bradycardia. Simple measurements of blood pressure and heart rate changes give a valuable and reliable guide to the associated haemodynamic events and have done away with invasive procedures like intra-arterial blood pressure recordings.

The resting values of blood pressure and heart rate were noted with the patient in the supine position. At the outset, the patient was trained to maintain the column of mercury in the standard sphygmomanometer at 40 mm by blowing. After the period of training, the test was performed with continuous heart rate monitoring before, during and after the period of strain. The BP was recorded at a minutes’ interval before (3 readings), during (1 reading) and after the period of strain (3 readings). The entire process was repeated thrice.

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Calculation of Valsalva ratio

The “Valsalva ratio” was calculated from the ratio of the longest R-R interval after the manoeuvre (reflecting over-shoot bradycardia) to the shortest R-R interval during the strain (reflecting tachycardia during the manoeuvre).

Beat-to-beat (R-R interval) variation

Out of several methods currently available to measure beat-to-beat variation, the simplest one namely heart rate variation, during forced deep breathing was adopted here. The subject lies quietly in a supine posture and Lead II of the ECG machine is connected for record the heart rate. After obtaining a stable heart rate record, the patient is instructed to breath deeply at 6-8 breaths/min (for one respiratory cycle, time taken is 10 secs; 5 secs inspiration and 5 secs expiration). This produces the maximum variation in heart rate which is calculated by measuring the differences between minimum heart rate on inspiration and maximum on expiration. Two recent modifications of this technique have been adopted in this study. The first was the measurement of expiration/inspiration ratio - the mean of longest R-R interval during expiration to the mean of shortest R-R interval during inspiration. The second modification is to measure successive maximum and minimum heart rates from an ECG during a period of deep breathing and record the difference.

According to Watkins et al, all normal subjects have a score greater than 9 and the presence of autonomic neuropathy is ruled out if the score is greater than 12.

Postural reflexes

a) Heart rate changes on standing

Change from horizontal to vertical position produces an integrated cardiovascular response including alteration in the heart rate. There is a characteristic and rapid increase in heart rate maximal at about the 15th beat after standing, with a subsequent relative bradycardia, maximal at about 30th beat in normal persons. This reflex is mediated through the vagus nerve. The HR was recorded by the transistorized bedside ECG machine (Siemens) and R-R intervals at beats 15-30 after standing was noted to give the 30/15 rates.

b) BP changes on standing

On standing, there is an immediate fall in BP due to pooling of blood in the legs. In presence of normal baroreflex functions, this is rapidly corrected by peripheral vasoconstriction and tachycardia.

The BP was recorded at 1 minute intervals in the recumbent, sitting and standing position. Three recordings were obtained and the mean value was calculated.

The Atropine Test

This test was done on a different occasion separately on all the patients. Continuous ECG recordings were obtained in the resting state and 3 mins after administration of 1.2 mg of atropine intravenously. HR was again recorded at the 6th and the 10th min. The R-R intervals before and after 3,6 and 10 mins were obtained.

The Nitroglycerine Test

The resting HR and BP was measured initially. Then the patient was administered sublingual tablets of 0.5 mg of nitroglycerine and following complete dissolution, the postural reflexes were repeated as stated above.

Resting Tachycardia

The resting tachycardia was made out by palpatory method while the patient was lying comfortably in a supine postural with complete mental rest. Simultaneous ECG monitoring confirmed the presence of resting tachycardia.

The details of the several autonomic function tests carried out in diabetics (both the groups) are presented in table 3.

Table 3

Autonomic function in diabetic patients with and without peripheral neuropathy (PN)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-diabetic controls (20)</th>
<th>DM with out PN (23)</th>
<th>DM with PN (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beat-to-Beat variation score (no./min.)</td>
<td>19.6±1.9</td>
<td>15.9±1.6</td>
<td>9.4±1.3***</td>
</tr>
<tr>
<td>Postural mean arterial pressure change (mm Hg)</td>
<td>+6.7±0.6</td>
<td>+2.5±0.4**</td>
<td>-5.2±1.0**</td>
</tr>
<tr>
<td>Postural Heart rate change</td>
<td>16.0±1.1</td>
<td>12.2±1.8</td>
<td>7.4±1.2**</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.5±0.06</td>
<td>1.3±0.4</td>
<td>1.2±0.05***</td>
</tr>
<tr>
<td>Atropine Test (rise in heart rate)</td>
<td>25.2±1.2</td>
<td>24.4±1.8</td>
<td>10.1±2.6***</td>
</tr>
</tbody>
</table>

Values are mean ± SEM
Numbers in parentheses indicate the number of patients **P<0.01, ***P<0.001 compared to control
The beat-to-beat variation, HR changes and the
valsalva ratio were significantly reduced in diabetics
with peripheral neuropathy as compared to non-
diabetics (control group), while these parameters
were not significantly altered in diabetics without
peripheral neuropathy. Seventeen out of 22 patients
of DM with peripheral neuropathy (78%) had beat-
to-beat variation in HR below 10, whereas only 3
out of 23 patients of DM without peripheral
neuropathy (13%) had similar variation. When
patients were tested for mean arterial pressure
change, there was a significant fall in diabetics with
peripheral neuropathy in contrast to the rise
observed in non-diabetics. However, in diabetics
without peripheral neuropathy, there was a
significant reduction in the mean arterial pressure
(MAP) rise as compared to non-diabetics.

The atropine test in the diabetics with peripheral
neuropathy produced a significantly less rise in
heart rate compared to that of non-diabetics and
diabetics without neuropathy.

In trinitroglycerine (TNG) test, the vasodilatory
action of the drug results in a fall in mean arterial
pressure to which compensatory tachycardia occurs.

The TNG test revealed that the diabetics without
peripheral neuropathy showed a corresponding fall
in MAP with a concomitant reflex increase in HR
similar to that observed in the non-diabetic control
group. On the contrary, diabetic patients with
peripheral neuropathy failed to show an increase in
the heart rate even though the fall in MAP was
much greater. On repeating the postural reflexes on
standing after TNG in the control group, the mean
arterial pressure fell and was followed by an
appropriate rise in HR. In this group without
peripheral neuropathy(PN), there was a fall in MAP
with an attendant increase in HR. In contrast, in the
group of DM with PN the fall in MAP was
significantly greater than either of the previous
groups and the heart rate increase was much lower
showing loss of the baroreceptor reflex.

SUMMARY AND CONCLUSION

These investigations denote that autonomic cardiac
dysfunction is one of the most important facets in
the genesis of diabetic heart disease. Absence of
several cardiovascular reflexes in a diabetic is
bound to have repercussions in times of stress
during which normal cardiac reserve will not come
into play. As discussed, by using the simple,
reproducible above mentioned tests, it is possible to
detect and quantify autonomic dysfunction. Hence,
it is recommended that each diabetic clinic should
carry out such initial evaluation procedures to
identify these groups of DM patients who warrant
special attention.

Autonomic cardiac denervation is an important
companion of diabetic peripheral neuropathy and
every diabetic clinic should have group of such
patients identified by using simple, non-invasive,
reproducible tests so as to follow its natural
evolution and exercise caution in the management
of such patients.

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