Heart rate variability and diastolic dysfunction in patients with type 2 diabetes mellitus

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Abstract

Background and objective  Cardiovascular autonomic neuropathy is a common form of autonomic dysfunction in diabetes mellitus (DM) and associates abnormalities in heart rate control and in vascular dynamics. This study evaluates the impact of diabetes mellitus on left ventricular diastolic dysfunction (LVDD) and heart rate variability in a group of type 2 diabetes mellitus without signs of cardiovascular disease.

Materials and methods  The study group consisted of 58 patients, aged 61 ± 8 years, diagnosed with type 2 DM. The subjects were selected from a series of 104 consecutive diabetic patients. All the subjects were on oral therapy or on diet for DM and ECG was normal for all the subjects. The control group consisted of 45 healthy subjects, matched for age and sex. Heart rate variability was measured using a 24-hour ECG monitoring system and standard 2D and Doppler echocardiography was performed in all the subjects.

Results  There are significant differences between groups regarding disease duration, longer in patients with impaired relaxation (11.22 ± 9.17 versus 8.31 ± 8.95 years), and disease control, worse in impaired relaxation group. Heart rate in impaired relaxation group is significantly higher than in controls, and higher, but not significantly, as compared with normal group (91 ± 10, versus 88 ± 11 and 71 ± 11, respectively).

Conclusion  Cardiac autonomic neuropathy was associated with LVDD in patients with type 2 DM, but without clinically manifest heart disease. 24-hour ECG monitoring and echocardiography can detect diabetic cardiomyopathy in early stages and should be performed in all subjects.

Keywords: diabetes mellitus, cardiovascular autonomic neuropathy
Introduction

The autonomic nervous system is often imbalanced in patients with type 2 diabetes mellitus (DM) and this neuropathy may be clinically inapparent. Cardiovascular autonomic neuropathy (CAN) is a common form of autonomic dysfunction in DM patients and associates abnormalities in heart rate control and in central and peripheral vascular dynamics [1].

Diabetic cardiomyopathy, on the other hand, is an incompletely defined entity which may be detected in early stages, only by left ventricular diastolic dysfunction (LVDD). The pathophysiology of LVDD in DM includes delayed relaxation, impaired LV filling and increased stiffness. These changes may develop without any evidence of ischemic heart disease, hypertension and/or valvular heart disease [2, 3].

Echocardiography, both classic and pulsed tissue Doppler imaging (TDI), is essential in analyzing the systolic and diastolic function of left ventricle even in pre-clinical stages [4].

The relation between heart rate variability (HRV) and LVDD was discussed in some studies, but is not yet fully understood. Arora et al [5] compared HRV parameters in patients with systolic heart failure and patients with isolated diastolic dysfunction and found that the prognosis was better in the latest. Poirier et al [2] stated that is important to define the stage of diastolic dysfunction, as patients with restrictive LV filling pattern had significantly lower HRV compared with patients with a non-restrictive LV filling pattern. These data have been confirmed by other studies [6, 7].

The objective of this study was to evaluate the impact of diabetes mellitus on LVDD and heart rate variability parameters in a group of type 2 DM without significant cardiovascular disease, including hypertension.

Subjects and methods

Study population

The study group consisted of 58 patients, males and females, aged 61 (±8), diagnosed with type 2 diabetes mellitus and followed up at an outpatient clinic. The subjects were selected from a series of 104 consecutive diabetic patients. The rest of the patients (46) didn’t met the inclusion criteria.

Inclusion criteria: uncomplicated and well-controlled DM, assessed by laboratory findings, including HbA1; age < 65 years; normal chest radiographs and normal left ventricular systolic function at echocardiography. In all cases, rest ECG was normal.
Exclusion criteria: subjects with systolic impairment and with other chronic diseases that could affect the left ventricle function (ischemic heart disease, hypertension, valvular heart disease). None of the subjects had impaired renal function. All the subjects were on oral therapy or on diet. Insulin treated patients were excluded, as insulin may influence the autonomic balance.

We created two study groups of patients, with and without diastolic dysfunction, defined as ejection fraction over 50%, modified E/A ratio (normal value between 1 – 2), abnormal isovolumic relaxation time – IVRT (normal values: 60 – 110 milliseconds) and abnormal deceleration time of E wave – DecT (normal values: 150 – 240 milliseconds).

The control group consisted of 45 healthy subjects who were matched for age and sex. Informed consent was obtained from all patients and the study was conducted according to the Declaration of Helsinki.

Heart rate variability

HRV was measured using a 24-hour ECG monitoring system (Holter Digital recorder AsPEKT 812) in all subjects during normal daily activity. Time domain parameters used are: SDNN expressed in milliseconds (ms) accounts for standard deviation of all NN intervals. SDANN expressed in ms accounts for standard deviation of the averages of NN intervals in all 5 min segments of the entire recording. pNN50 % is the number of pairs of adjacent NN intervals divided by the total number of all NN intervals. Frequency domain parameters used are: low frequency and high frequency components of spectral analysis expressed in squared milliseconds (ms$^2$) or normalized units.

Echocardiography

Standard two dimensional Doppler echocardiography was performed in all the subjects. The standard views and the measurements of heart chambers were performed according to American Society of Echocardiography recommendations [8] and the same clinician performed all the examinations. The following parameters were obtained: left ventricular diastolic diameter, left ventricular systolic diameter, ejection fraction, peak E velocity, peak A velocity, deceleration time in ms (time measured between peak E velocity and the point where the deceleration slope of the E velocity crosses the baseline), isovolumic relaxation time (time elapsed between aortic valve closure and mitral valve opening), and E/A ratio. E/A ratio 1-2 was defined as normal [9].

Statistical analysis

Continuous variables were expressed as mean (SD). Differences were tested for significance by unpaired Student’s $t$ test. Upper and lower 95% confidence limits for each variable were calculated from the two tails of the Student’s $t$ test distribution. We compared the results between the study groups and with control
A p value <0.05 was considered significant. Pearson correlation coefficients were used to explore linear relationships between the study variables. Statistics were performed with SPSS for Windows, version 10.0.

Results

Characteristics of the DM patients are shown in table 1.

Place for Table 1

There are significant differences between groups regarding duration of DM, longer in patients with impaired relaxation; oral treatment and/or diet, the number of patients on diet being significant lower in patients with impaired relaxation; diabetes is better controlled in patients with normal diastolic function, both fasting glucose and HbA1 being significant lower in this group. Heart rate in impaired relaxation group is significantly higher than controls, and higher, but not significantly, as compared with normal group.

Heart rate variability parameters

The results are shown in table 2.

Place for table 2

There are no significant differences between groups regarding time-domain parameters, although SDANN, SDNN and p50NN are lower in diabetic patients and are decreasing with alteration of diastolic function. LF and HF parameters are significantly lower for impaired relaxation group as compared with both normal and control groups, but when analyzing the normalized values, the differences are significant only for HF, which accounts for parasympathetic activity. There is no significant difference for LF/HF ratio among groups.

Echocardiographic measurements

Table 3 summarizes the results from ultrasound-derived parameters of diastolic function, left ventricular dimensions and systolic function. There were no significant differences between groups in aortic root, posterior wall, inter-ventricular septum, right ventricular dimensions.

Place for table 3

There are no differences among groups regarding left ventricle diameters and ejection fraction. The E/A ratio significantly correlate with age (r = 0.51) and HF, expressed both in ms$^2$ and normalized units (r = 0.43 and 0.48 respectively). There is also a negative but not significant correlation between E/A and LF/HF ratios (r = 0.18), and positive but not significant between E/A and LF (r = 0.20).
Discussion

CAN is best evaluated using heart rate variability (HRV) on 24-hours recordings [10]. A reduction in time-domain parameters of heart rate variability seems not only to carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy [10-13]. In diabetic patients without evidence of autonomic neuropathy, reduction of the absolute power of low-frequency (LF) and high-frequency (HF) during controlled conditions was also reported [13, 14]. LF accounts for both sympathetic and parasympathetic dysfunction. Very low frequency (VLF) components account for sympathetic dysfunction and HF component accounts for parasympathetic dysfunction [3].

However, in some studies, when the LF/HF ratio was considered or when LF and HF were analyzed in normalized units, no significant difference in comparison to normal individuals was present [15].

In DM, the first injury of the autonomic system concerns the parasympathetic system (nervus vagus). This impairment is leading to rest tachycardia; after about five years of latency, the damage of sympathetic nerve fibers occurs, with a slight regression in tachycardia [16]. In advanced cardiac autonomic neuropathy all the components of HRV are reduced (both for sympathetic and parasympathetic activity), along with LF/HF ratio [3, 15].

In our group of patients we found decreased values for heart rate variability only for frequency-domain parameters, whilst LF/HF ratio and time-domain parameters were comparable among groups. It is important to underline that LF, HF and HF nu were significantly lower also in impaired relaxation group as compared with normal group, being in concordance with other studies showing a positive correlation between vagal impairment and diastolic dysfunction [2].

LVDD and cardiac dysautonomy can be sought as preclinical manifestation of diabetic cardiomyopathy and should always be looked for and/or diagnosed together [2]. Some studies demonstrated that this association is independent of metabolic control (e.g. the levels of blood sugar or HbA1) [2, 17]. In our study there is a strong correlation between altered heart rate variability parameters, fasting plasma glucose and HbA1 (r = -0.44 and r = 0.53 respectively). This observation is in accordance with a study by Schonauer et al [16], showing that optimizing metabolism is currently the only effective treatment method for CAN.

For assessing diastolic dysfunction it is better to associate classical echocardiography (2-D, pulsed and Doppler) along with pulsed tissue Doppler imaging of lateral mitral annulus excursion. This association may improve the positive diagnosis according to some studies [4], and could be a study limitation in our case.
All the patients in present study were free of coronary ischemic disease, hypertension or other cardiovascular diseases that could change the results, and also they were free of complications such as retinopathy or nephropathy.

Thus, the alterations in heart rate variability and diastolic function should be monitored even in early stage from the onset of DM, even in asymptomatic patients with disease duration longer than 5 years [16]. On the other hand, the natural history of CAN is still under debate, as it can be detected at the time of diagnosis in many cases [3]. This is more reason to perform 24-hour ECG recording for baseline evaluation in all patients with diabetes, along with echocardiographic examination. The reasons are obvious, as is well known that lower HRV is associated with increased cardiovascular risk, and LVDD can lead to heart failure.

**Conclusion**

The present study describes an association between cardiac dysautonomy, analyzed by heart rate variability parameters, and left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus without clinically heart disease. These tools can detect diabetic cardiomyopathy in early stage, not only when the patient eventually became symptomatic, and could therefore improve the prognosis.

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References


**Table 1**: Demographic characteristics of diabetic patients separated on the basis of left ventricle diastolic function, and of control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Impaired relaxation</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>20</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>B: 8 (40%)</td>
<td>B: 24 (63.1%)</td>
<td>B: 25 (55.5%)</td>
</tr>
<tr>
<td></td>
<td>F: 12 (60%)</td>
<td>F: 14 (36.8%)</td>
<td>F: 20 (44.5%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>58 (±9)</td>
<td>62 (±7)</td>
<td>59 (±8)</td>
</tr>
<tr>
<td><strong>Disease duration (years)</strong></td>
<td>8.31 (±8.95)</td>
<td>11.22 (±9.17)*</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>9 (45%)</td>
<td>5 (2.23%)*</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Oral treatment</strong></td>
<td>11 (55%)</td>
<td>33 (86.8%)*</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total-cholesterol (mg%)</strong></td>
<td>236.88 (±66.93) §</td>
<td>256 (±54.19) §</td>
<td>188 (±19.22)</td>
</tr>
<tr>
<td><strong>Tryglicerides (mg%)</strong></td>
<td>193.45 (±93.07) §</td>
<td>223.45 (±73.67) §</td>
<td>153.45 (±84.07)</td>
</tr>
<tr>
<td><strong>Fasting glucose (mg%)</strong></td>
<td>129.35 (±63.13) §</td>
<td>159.42 (±53.63)* §</td>
<td>82.22 (±13.23)</td>
</tr>
<tr>
<td><strong>HbA1 (%)</strong></td>
<td>6.70 (±2.44) §</td>
<td>7.30 (±2.59)*§</td>
<td>4.3 (±1.22)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td>128 (± 9)</td>
<td>130 (± 8)</td>
<td>131 (± 7)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td>81 (± 5)</td>
<td>82 (± 9)</td>
<td>79 (± 6)</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>88 (±11)</td>
<td>91 (± 10) §</td>
<td>71 (±11)</td>
</tr>
</tbody>
</table>

* p<0.05 between normal and impaired relaxation, § p<0.05 between patients and controls
Table 2: Heart rate variability parameters of diabetic patients separated on the basis of left ventricle diastolic function, and of control group

* p<0.05 between normal and impaired relaxation, § p<0.05 between patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Impaired relaxation</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN ms</td>
<td>118.37 (± 35.24)</td>
<td>107.37 (± 37.42)</td>
<td>129.17 (± 45.76)</td>
</tr>
<tr>
<td>SDANN ms</td>
<td>87.54 (± 28.18)</td>
<td>80.34 (± 39.28)</td>
<td>94.64 (± 32.75)</td>
</tr>
<tr>
<td>p50NN %</td>
<td>26.63 (±13.94)</td>
<td>22.53 (±16.85)</td>
<td>28.74 (±14.05)</td>
</tr>
<tr>
<td>LF</td>
<td>626.08 (± 297.15)</td>
<td>564.11 (± 280.75)* §</td>
<td>689.20 (± 301.16)</td>
</tr>
<tr>
<td>HF</td>
<td>545.68 (± 346.17)</td>
<td>445.68 (± 339.13)* §</td>
<td>591.86 (± 296.21)</td>
</tr>
<tr>
<td>LFnu</td>
<td>38.57 (± 11.15)</td>
<td>31.17 (± 19.05)</td>
<td>41.38 (± 9.18)</td>
</tr>
<tr>
<td>HFnu</td>
<td>23.34 (± 7.21)</td>
<td>16.44 (± 6.13)* §</td>
<td>29.45 (± 8.11)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.61 (± 0.43)</td>
<td>1.72 (± 0.51)</td>
<td>1.93 (± 0.13)</td>
</tr>
</tbody>
</table>

Legend: SDNN=standard deviation of all NN intervals; SDANN=standard deviation of the averages of NN intervals in all 5 min segments of the entire recording; p50NN=the number of pairs of adjacent NN intervals divided by the total number of all NN intervals; LF=low frequency; HF=high frequency; nu = normalized units
Table 3: Ultrasound parameters of diabetic patients separated on the basis of left ventricle diastolic function, and of control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Impaired relaxation</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>49.35 (±6.16)</td>
<td>50.24 (±5.27)</td>
<td>44.36 (±7.22)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>36.69 (±6.77)</td>
<td>35.71 (±6.01)</td>
<td>33.89 (±8.11)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>54.13 (±8.82)</td>
<td>56.20 (±6.91)</td>
<td>61.96 (±7.19)</td>
</tr>
<tr>
<td>E/A</td>
<td>1.03 (±0.29) §</td>
<td>0.76 (±0.18)* §</td>
<td>1.51 (±0.26)</td>
</tr>
<tr>
<td>A (m/s)</td>
<td>0.68 (±0.18) §</td>
<td>0.87 (±0.14)* §</td>
<td>0.56 (±0.29)</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.78 (±0.15)</td>
<td>0.57 (±0.11)* §</td>
<td>0.85 (±0.14)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>92 (±16) §</td>
<td>118 (±12) §</td>
<td>82 (±22)</td>
</tr>
<tr>
<td>DecT (ms)</td>
<td>198 (±46)</td>
<td>241 (±57) §</td>
<td>187 (±54)</td>
</tr>
</tbody>
</table>

* p<0.05 between normal and impaired relaxation, § p<0.05 between patients and controls

Legend: LVEDD=left ventricular end diastolic diameter; LVESD=left ventricular end systolic diameter; EF=ejection fraction; IVRT=isovolumic relaxing time; DecT=deceleration time