Association Between Cardiac Autonomic Neuropathy and Echocardiography in Type 2 Diabetes Mellitus

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Abstract
The aim of this study was to determine the association between cardiac autonomic neuropathy and left ventricular systolic and diastolic function of the heart and left ventricular mass index. This study included 103 (56 males and 47 females) pure diabetic patients without hypertension or prediagnosed ischemia. They had attended to the diabetic center in Marjan Medical City in Hilla from March 2013 to February 2014. The patients had undergone thorough assessments that included clinical (history and full examination), cardiac autonomic function test and Echocardiographic assessments. Echocardiography showed that most of the diabetic patients (89.8%) had a left ventricular hypertrophy by measuring the left ventricular mass index. However, there were no significant changes in Echocardiographic results between patients with CAN and those without. Most of the patients in the study group (89.8%) are present with left ventricular hypertrophy and there is no significant changes in Echo result between patients with CAN and those without. Also concludes that there is a perfect direct correlation between waist and BMI with LVMI.

Keywords: Cardiac autonomic neuropathy, Left ventricular mass index

Introduction
Cardiac autonomic neuropathy (CAN) is the most important and Diabetes cardiac myopathy (DC) has been defined as ventricular dysfunction that occurs independently to hypertension and coronary artery disease (CAD) [1]. The existence of a DC was first proposed by Rubler and his co-workers in 1972 on the basis of postmortem findings. In DC, heart failure syndrome is not precisely defined despite...
the usually used definition of DC as a diastolic heart failure with normal ejection fraction [2].

There are many reports about the association between DM and the presence of cardiac hypertrophy and myocardial stiffness, independently to hypertension [3, 4]. Basically there are two pathophysiological processes leading to heart failure in diabetic patients, the first being CAD and the second DC.

**Materials and Methods:**

This cross sectional study included 103 (56 males and 47 females) pure diabetic patients without hypertension or prediagnosed ischemia. They had attended to the diabetic center in Marjan Medical City in Hilla from March 2013 to February 2014. Informed consent was obtained from all patients.

They were divided in to two groups according to the presence of autonomic neuropathy:

**Group I:** Seventy five patients with abnormal cardiac autonomic function test (42 males and 33 females) with a mean age 50.6 ± 7.8 years (mean ± SD).

**Group II:** Twenty eight with normal cardiac autonomic function test (14 males and 14 females) with a mean age of 45 ± 6 years (mean ± SD).

CARTs were performed in a time between (8.00 am – 1.00 pm) by the same operator and were analyzed by one investigator. According to Ewing’s protocol cardiac autonomic neuropathy (CAN) was assessed by the five standard cardiovascular reflex tests; 3 for parasympathetic and 2 for sympathetic divisions [5].

The parasympathetic functions were assessed by heart rate responses to deep breathing (R-R variation), to standing (30:15 ratio) and to Valsalva maneuver assessed automatically by Mortara ECG recordings. On the other hands, the sympathetic functions were mainly assessed by sustained handgrip test and by blood pressure responses to standing.

According to these five tests, cardiac autonomic function were classified into three categories (normal, borderline and abnormal) which were pointed as 0, 0.5 and 1, respectively [6] (Table 1). Cardiac autonomic neuropathy scores were classified as follows: CAN score 0 (total points 0), CAN score 1 (points 0.5-1.5), CAN score 2 (points 2-3), and CAN score 3 (points ≥ 3.5). CAN was considered absent, early, definite, or severe if the CAN scores were 0, 1, 2, or 3, respectively [7].

If two of these five test results were abnormal, the presence of cardiovascular autonomic neuropathy was assumed [8].

<table>
<thead>
<tr>
<th>Tests</th>
<th>Point 0 (normal)</th>
<th>Point 0.5 (borderline)</th>
<th>Point 1 (abnormal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand grip test (DBP)</td>
<td>&gt;16</td>
<td>11-15</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Standing BP (SBP)</td>
<td>&lt;10</td>
<td>11-29</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Standing HR (30/15)</td>
<td>&gt;1.04</td>
<td>1.03-1.01</td>
<td>&lt;1</td>
</tr>
<tr>
<td>HR breathing (I-E)</td>
<td>&gt;15</td>
<td>14-11</td>
<td>&lt;10</td>
</tr>
<tr>
<td>HR valsalva (re/st)</td>
<td>&gt;1.21</td>
<td>1.2-1.11</td>
<td>&lt;1.1</td>
</tr>
</tbody>
</table>

The echocardiograms were obtained on a Vivid 5 GE medical ultrasound machine with a 2.5-MHz transducer and were stored digitally for later blinded analysis. For all Doppler recordings, a horizontal sweep of 100 mm/s was used, and for all Doppler variables, the average of 5 consecutive beats was measured. Subjects were examined in the left lateral decubitus and
supine position using standard parasternal long axis, short axis and apical views. The M-mode echocardiographic measurements of the following left ventricular systolic function parameters were taken:

1. Left ventricular internal dimensions; End diastolic diameter (EDD) and end systolic diameter (ESD) in cm.
2. Interventricular septal thickness in systole and diastole (IVSS and IVSD, respectively) in cm.
3. Left ventricular posterior wall thickness diastole (LVPWS) in cm.
4. Ejection fraction (EF) in %.

The LV dimension were obtained from the parasternal long-axis view. LV mass index was calculated using the formula:

\[
LVMI = (0.8 \times [1.04 \times (LVDd+IVSd+PWd)^3-(LVDd)^3]) + 0.6 \text{ g})
\]

Statistical Analysis
Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Distribution of genotypes and alleles was compared by chi-square test. Clinical data were compared by one-way analysis of variance (ANOVA) and mean ±SD. Correlation between variables was tested by Spearman correlation coefficient. Statistical significance was defined as \( P < 0.05 \).

Results
Cardiac autonomic neuropathy and Echocardiography
Of 103 diabetic patients, 75 patients were presented with abnormal cardiac reflex test and 28 patients had a normal test. The parameter of Echocardiography study were tested and showed no significant changes in Echo result between patients with CAN and those without CAN (p>0.05) (Table 2). Also, there are no differences in the number of patients with diastolic dysfunction between those with CAN and those without it as shown in Figure (1).

Table 2: Comparison of Echocardiographic parameter between patients with CAN and patients without CAN

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with CAN</th>
<th>Without CAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>0.68±0.18</td>
<td>0.69±0.18</td>
</tr>
<tr>
<td>A</td>
<td>0.75±0.16</td>
<td>0.77±0.18</td>
</tr>
<tr>
<td>E/A</td>
<td>0.92±0.25</td>
<td>0.92±0.31</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>48.5±4.2</td>
<td>47.65±5.6</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>10.27±2.5</td>
<td>9.57±3.1</td>
</tr>
<tr>
<td>EF (%)</td>
<td>63.64±6.6</td>
<td>63.71±7.3</td>
</tr>
<tr>
<td>LVMi</td>
<td>62.87±14.38</td>
<td>62.17±12.89</td>
</tr>
</tbody>
</table>

CAN= Cardiac autonomic neuropathy, E= Early velocity, A= Atrial velocity, LVEDD= Left ventricular end diastolic dimension, IVS= Interventricular septum, EF= Ejection fraction, LVMi= Left ventricular mass index, Values are expressed in mean ± standard deviation.
Left ventricular hypertrophy (LVH)
Distribution of left ventricular hypertrophy according to the age and duration of diabetes
Most of the patients in the study group (89.8%) are present with left ventricular hypertrophy according to the left ventricular mass index (LVMI) in which LV mass indexed for height\(^2\) in male and females was \(>49.2\) and \(>46.7\) g/m\(^2\), respectively. In addition to that, The age of the patients in the study group with LVH were more than that the patients without LVH, still is not significant (\(P>0.05\)). Moreover, the patients with LVH have longer duration of diabetes than patients without LVH but these changes was not significant (\(P>0.05\)) (Table 3).

**Table 3:** Effect of age and diabetes duration on the presence or absence of left ventricular hypertrophy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with LVH (89.9%)</th>
<th>without LVH (10.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.9±8.2</td>
<td>44.8± 5.7</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>6.2±6</td>
<td>4.8±3.8</td>
</tr>
</tbody>
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LVH= Left ventricular hypertrophy, Values are expressed in mean ± standard deviation

Correlation between waist circumference and body mass index with the left ventricular mass index
There is a perfect direct correlation between waist and LVMI (\(R= 0.24\)) as shown in figure (2). Also, there is a direct correlation between BMI and LVMI but this correlation is not significant (\(R=0.19\)) as shown in figure (3).
**Discussion**

Table (2) showed no significant changes in Echo results including diastolic dysfunction parameters between patients with CAN and those without CAN. The results regarding early diastolic velocity (E) to late diastolic velocity (A) ratio, left ventricular mass and ejection fraction was agreed with that of Julian and his co-workers in 2010 [9].

These results disagreed with other studies that found that the majority of patients with postural hypotension had diastolic dysfunction that precedes systolic dysfunction [10, 11]. This discrepancy in the results may be due to the selection criteria as the effect of hypertension was excluded in the current study and the selective criteria for diagnosing CAN were also different. Moreover, some studies failed to found significant changes between diastolic dysfunction in patients with

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**Figure (2):** Correlation between waist circumference and left ventricular mass index

**Figure (3):** Correlation between body mass index and left ventricular mass index
diabetes when compared to control people [12, 13]. This might be attributed to other factors such as age that might affect the prevalence of diastolic dysfunction. Figure (1) showed that 48% of the patients in the study group had a diastolic dysfunction and only few of them were free from CAN. About the same percents of high diastolic dysfunction in diabetic patients were showed by other studies [14, 15, 16]. On the other hand, Patricia and his co-workers (2000) found that patients with CAN had a highest percentage of diastolic dysfunction than the patients without CAN [17]. These differences were attributed to the selection criteria which exclude hypertension that affect the structural and function of the heart.

Distribution of left ventricular hypertrophy according to the age and duration of diabetes (Table 3)

In this study, most of the patients with diabetes were presented with LVH determined by left ventricular mass index (LVMI). This increment in the LVMI in diabetic patients could be attributed to the presence of micro angiopathy and the deposition of glycoprotein [18]. Additionally, this LVH in diabetic patients may be due to lack of the parasympathetic dominance over the night which may lead to nocturnal hypertension that eventually results in LVH [19].

Similar results were reported by other studied such as that of Sato and his co-workers (2005) and Sotonye and his co-workers (2013) [16, 20].

Table (3) showed that there no significant effect of the patient age on the presence of LVH (P>0.05). Similarly, there is a non-significant increase in the duration of patients with LVH when compared to those with normal LV.

These results disagreed with other studies that found direct correlations between LVMI with the duration of diabetes. This inconsistency could be attributed to the small sample size of this study [21, 22].

Correlation between waist circumference and body mass index with the left ventricular mass index

When the body weight was increased this lead to increase metabolic demand and thus, both cardiac output and blood volume was increased. These circulatory changes cause cavity dilatation and geometrical changes of the heart and resulted in an increase of LVM [23]. This explains the direct correlation between BMI and waist circumference with the LVMI showed in this study (figures 2 and 3).

Friberg and his co-workers in 2004 reported that increased LVMI in obese adolescents is correlated well with their BMI and systolic blood pressure [24]. The results of many other studies also agreed with such findings [21].

Conclusions

This study tested patients with type 2 diabetes mellitus (T2DM) and it concluded that most of the patients in the study group (89.8%) are present with left ventricular hypertrophy according to the left ventricular mass index (LVMI) and there is no significant changes in Echo result between patients with CAN and those without. Also concludes that there is a perfect direct correlation between waist and BMI with LVMI.

Acknowledgements

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References

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