How Accurate can Electrocardiogram Predict Left Ventricular Diastolic Dysfunction?

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ABSTRACT

Heart failure continues to be a major challenge to healthcare; several resting and exercise electrocardiographic parameters have been investigated to predict the left ventricular diastolic dysfunction (LVDD).

One hundred and forty patients, classified into 2 groups according to LVDD, were assessed by measurement of normal and corrected QT interval, T wave peak to T wave End and P wave dispersion in resting ECG. Exercise stress test looking for Hump sign (upward deflection of the ST-segment) was done. The relationships between these ECG parameters and LVDD were investigated.

The study revealed significant occurrence of hump sign in patients with LVDD, there was a significant difference between both groups regarding QTc and P wave dispersion. P wave dispersion was significantly higher in patients with LVDD. Sensitivity and specificity of the ST hump sign in prediction of LVDD were 86% and 78% respectively. The study also concluded that P wave dispersion at cut off value of about 0.045 msec had the highest sensitivity (sensitivity 98%, specificity 64%) while QTc at cut off value of 0.395 msec had the highest specificity (sensitivity 81%, specificity 79%).

P wave dispersion and hump sign had higher sensitivity while corrected QT interval had higher specificity in prediction of LVDD.

Keywords: Hump sign, diastolic dysfunction, QT interval, TpTe interval, P wave dispersion.
INTRODUCTION
Approximately half of the patients with heart failure (HF) have preserved ejection fraction (HFpEF). Recent studies have shown that the pathophysiology of HFpEF, initially believed to be principally due to diastolic dysfunction, is more complex. Appreciation of this complexity has shed new light onto how HFpEF patients might respond to traditional HF treatments, while also suggesting new applications for novel therapies and strategies.

While inherited long QT syndrome (LQTS) has historically been considered a purely electrical disease, echocardiographic studies over the past two decades have demonstrated a crude but replicable relationship between a prolonged QT interval and abnormal mechanical function.

P wave dispersion (PD) is one of the P-wave indices and it is calculated by subtracting the minimum P-wave duration from the maximum P-wave duration in any of the 12 ECG leads. It describes atrial conduction and not repolarization. It is related to the nonhomogeneous and interrupted conduction of sinus impulses intra and inter-atrially. Currently, PD is described as a non-invasive indicator of atrial fibrillation risk.

The interval between the peak of T wave and its end (TpTe) measures transmural dispersion of ventricular repolarization. Sauer et al., revealed a significant inverse linear association between the TpTe interval and tissue Doppler septal E0 velocity. This association persisted after adjustment for several important potential confounders, including age, QTc interval and left ventricular wall thickness.

The standard interpretation of the exercise stress test includes an evaluation of symptoms, exercise capacity, hemodynamic, and changes in ECG. Although ST depression and elevation are the most important ECG findings, a number of other parameters have been shown to be of diagnostic and prognostic value. Among these is a discrete upward deflection of the ST segment termed the ST hump sign (STHS).

Previous studies have shown that this sign represents atrial repolarization and leads to false positive exercise tests.

STHS has been associated with hypertension, which is characterized by myocardial hypertrophy, diastolic and systolic myocardial dysfunction, fibrosis, and limitation in sub endocardial flow reserve.

AIM OF THE STUDY
In this study, we aimed to study different parameters in resting and exercise stress test and evaluate whether they can predict left ventricular diastolic dysfunction (LVDD) diagnosed by Tissue Doppler Echocardiography.

MATERIALS AND METHODS
This prospective study was carried out in the department of cardiology, El-Minia University hospital during the period from November 2012 to November 2013. Four hundred eighty patients were referred for stress ECG for risk stratification of coronary artery disease. Out of these, 140 consecutive patients (96 males and 44 females) were included in this study by the following inclusion criteria: patients not known to have any history of ischemic heart disease, patients with negative exercise stress test, patients with positive exercise stress test and normal coronary angiography (False positive stress test), Normal resting ECG changes (No LBBB, RBBB or Wolf Parkinson White syndrome), Normal left ventricular systolic function, patients not receiving anti-arrhythmic drugs or any drugs that can affect QT interval.

Exclusion criteria included a true positive stress test.

The cohort of patients included 135 patients with true negative stress test and 5 patients (1 male and 4 females) with false positive stress test. The diagnosis of positive
stress test was based upon the upward sloping ST segment depression more than one and half small square. All patients satisfying the inclusion criteria underwent an echocardiographic estimation of the diastolic function of the left ventricle.

**Resting ECG**

1. **QT interval**: This is measured from the beginning of QRS complex to the end of T wave. QT interval should be measured in the longest interval present in ECG. We also used rate corrected QT or QTc which can be obtained by dividing the actual QT by the square root of RR interval.  

2. **P wave dispersion**: This is calculated by subtracting the minimum P wave duration from the maximum P wave duration. P wave duration is calculated from the beginning of P wave deflection crossed isoelectrical line to the last P wave deflection crossed isoelectrical line.  

3. **TpTe interval**: it is measured from the T wave peak to the T wave end in resting ECG and it represents transmural dispersion of repolarization.  

**Treadmill exercise testing**

All patients performed exercise testing on an exercise stress test (GE Medical System, Milwaukee, WI). Exercise was terminated if there was severe angina, fatigue, dyspnea or severe arrhythmias. In the absence of symptoms, the test was terminated at the occurrence of 2 mm ST-segment depression or 1 mm ST-segment elevation, an increase in systolic blood pressure more than 230 mmHg or a decrease 20 mmHg or more or inability to exercise furthermore.  

ST-segment hump sign was defined as a discrete upward deflection of the ST-segment found in any of the leads of the ECGs received during exercise. It was mostly observed in leads II, III, aVF, V1 to V6. Atrial repolarization is represented by a wave (Ta) with direction opposite to that of P wave that may extend up to ST-T forming hump sign and leading to ST-segment depression without presence of ischemia. As shown in Fig. 1, the combination of atrial (Ta wave) and ventricular (ST segment) electrical activity finally forms a depressed ST-segment. The proximal part of this depressed ST segment is a diphasic recording (in the cycle). The first phase of this diphasic recording is convex like a hump (same polarity/ axis with p wave) and we defined it as hump sign. “Hump sign” as defined in this study, is present in the proximal part of ST segment and not within or after the T wave.  

A particular duration or magnitude is not required (these parameters were neither measured nor used as identifying criteria in the analysis).  

The recognition of the hump sign was based entirely on a visual basis, using magnifying lens, and the investigators were blinded to the results of echocardiography and other patient characteristics.
Echocardiographic measurement

All patients included in our study underwent an echocardiographic study using conventional and Tissue Doppler Imaging (TDI) techniques to estimate the diastolic LV function. Imaging was performed in the left lateral decubitus position using a GE Vivid III expert machine (GE Medical Systems, Waukesha, WI), equipped with 2.5 MHz phase array transducer and Tissue-Doppler Imaging software. Trans-mitral left ventricular filling velocities at the tips of the mitral valve leaflets were obtained from the apical four chamber view using pulsed wave Doppler echocardiography. The trans-mitral left ventricular filling signal was traced manually, and the following variables were derived: peak velocity of early (E) and late (A) filling and E/A ratio.

A Doppler velocity range of _30 to 30 cm/s was selected using the lowest wall filter settings and the minimum optimal gain. Doppler tissue imaging velocities were recorded at a sweep speed of 100 mm/s and stored on S-VHS videotape for later playback and analysis. All measurements were made in 3 cardiac cycles and averaged. Cardiac cycles with extrasystolic, postextrasystolic beats, or any rhythm disturbance were excluded.

The following measurements were made from the TDI recordings: early (E) and late (A) diastolic velocities and the deceleration time derived by linear extrapolation of Ea to baseline. The ratio of trans-mitral early LV filling velocity (E) to early diastolic Doppler tissue imaging velocity of the mitral annulus (transmitral E/E’) was calculated. This ratio has been reported to correlate with LV filling pressure. Echocardiographic analysis was performed by a single experienced investigator, who was blinded to the exercise ECG results. The ratio E/E’ was computed as the most reliable index of diastolic LV dysfunction. It is known that E/E’ has direct correlation with pulmonary capillary wedge pressure (PCWP) and can even be used to compute PCWP (PCWP =1.24 [E/ E’] + 1.9)\(^1\). Values of E/E’ = 8 or less under normal conventional Doppler E/A ratio (N1), in most circumstances, predict normal diastolic myocardial function with normal filling pressures, while values of E/E’ = 15 or more predict impaired diastolic myocardial function with increased filling pressures\(^5\).

Ethical approval

The study was ethically approved by the University’s research ethics committee that conforms to the Declaration of Helsinki. All patients provided a written consent prior to their enrolment in the study.
Statistical analysis
Statistical analysis was performed using SPSS statistical software, version 14.0 (SPSS, Chicago, IL). Sensitivity and specificity for the hump sign were also determined. Significance level was set at p ≤0.05.

RESULTS
This cohort of 140 patients was divided into 2 groups of patients according to the presence or absence of LV diastolic dysfunction: group A, including 56 (40%) patients who had no LV diastolic dysfunction, and group B, including 84 (60%) patients who had LV diastolic dysfunction. The different demographic features were compared between both groups. The demographic features of the study sample are displayed in Table 1. Five patients (1 male and 4 females) with false positive stress test (Normal Coronary Angiography and positive stress test) and 135 patients with true negative stress test were included in the study.

Table 1: Demographic features of the study populations.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=56)</th>
<th>Group A (n=84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.6 ± 8.9</td>
<td>47.7 ± 7.8</td>
<td>NS (0.133)</td>
</tr>
<tr>
<td>Sex</td>
<td>M  38 (67.9%)</td>
<td>58 (69%)</td>
<td>NS (0.882)</td>
</tr>
<tr>
<td></td>
<td>F  18 (32.1%)</td>
<td>26 (31%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.6</td>
<td>21.9</td>
<td>NS (0.835)</td>
</tr>
<tr>
<td>Smoking</td>
<td>36 (69%)</td>
<td>46 (52%)</td>
<td>NS (0.627)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>20 (35.7%)</td>
<td>34 (40.5%)</td>
<td>NS (0.571)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (7%)</td>
<td>8 (9%)</td>
<td>NS (0.752)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>6 (11%)</td>
<td>12 (14%)</td>
<td>NS (0.847)</td>
</tr>
</tbody>
</table>

NS: Not significant.

Resting ECG parameters and diastolic dysfunction
Comparing the resting ECG parameters between both patient groups, it was revealed that TpTe interval had no statistically significant difference between them, in contrast to QT interval, QTc and P wave dispersion which had a statistically significant difference as shown in Table 2.

Table 2: Comparing resting ECG parameters in patients with normal and impaired LV diastolic function.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=56)</th>
<th>Group B (n=84)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TpTe (Mean ± SD)</td>
<td>0.104 ± 0.019</td>
<td>0.1 ± 0.01</td>
<td>0.648</td>
</tr>
<tr>
<td>QT interval (Mean ± SD)</td>
<td>0.333 ± 0.026</td>
<td>0.347 ± 0.031</td>
<td>0.005</td>
</tr>
<tr>
<td>QTc (Mean)</td>
<td>0.388 ± 0.021</td>
<td>0.413 ± 0.021</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>P wave dispersion (Mean ± SD)</td>
<td>0.047 ± 0.010</td>
<td>0.069 ± 0.01</td>
<td>&lt;0.0005*</td>
</tr>
</tbody>
</table>

*Significant difference

Hump sign and diastolic dysfunction
The appearance of the ST hump sign at the peak of exercise testing was observed in 88 patients. In 28 patients, hump sign was present in leads II, III, and aVF; in 20 patients, it was noted in leads V4–V6 and in 40 patients, it was noted in leads II, III, aVFand V1–V6.

We did a correlation between presence of diastolic dysfunction and appearance of hump sign in treadmill test using Chi-square test. The “hump sign” occurred more frequently in patients with diastolic dysfunction than in patients with normal diastolic LV function. This difference reaches statistical significance on the T2 test. This is
shown in Table 3. The “hump sign” was equally observed in patients with and patients without hypertensive history (44 patients each). Eight patients from hypertensive group had left ventricular hypertrophy in the echocardiography, but there was no significant correlation between presence of hypertrophy and development of hump sign in treadmill test in our study. Absence of left ventricular hypertrophy was significantly (p <0.001) more noted in patients without history of hypertension (42 patients) than patients with hypertensive history (10 patients).

Table 3: Distribution of hump sign occurrence in patients with normal and impaired diastolic LV function.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=56)</th>
<th>Group B (n=84)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hump sign:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent:</td>
<td>40 (71%)</td>
<td>12 (14%)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Present:</td>
<td>16 (29%)</td>
<td>72 (86%)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant difference.

Bivariate correlation and multivariate analysis.
There was a strong correlation between each of the P wave dispersion (R= 0.69, p <0.0005), QTc (R= 0.472, p <0.0005), QT (R=0.312, p < 0.0005) and the LV diastolic dysfunction. Similarly, there was a strong correlation between the ST-hump sign and the LV diastolic dysfunction (R= 0.544, p< 0.0005). These correlations were significant at the p= 0.01 level. The TpTe revealed no correlation (TpTe, R= 0.043, p< 0.726) with LV diastolic dysfunction. Multivariate analysis revealed that P wave dispersion has the strongest association with the LV diastolic dysfunction (R= 0.733, R2 = 0.538, p< 0.0005).

Sensitivity and specificity for prediction of LV diastolic dysfunction
The sensitivity and specificity of the resting ECG parameters and the ST-hump sign for prediction of diastolic dysfunction are displayed in Table 4 and Fig. 2. Analysis of sensitivity and specificity of these ECG parameters for prediction of diastolic dysfunction showed that P wave dispersion at cut off value about 0.045 ms had the highest sensitivity (sensitivity 98% and specificity 64%) while QTc at cut off value 0.395 ms had the highest specificity (sensitivity 81% and specificity 79%).

Table 4: Cut off values, sensitivity and specificity of resting ECG parameters & hump sign for the prediction of diastolic dysfunction.

<table>
<thead>
<tr>
<th>ECG parameter</th>
<th>Cutoff value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>0.33</td>
<td>69%</td>
<td>64%</td>
<td>0.039</td>
</tr>
<tr>
<td>TPTE</td>
<td>0.095</td>
<td>76%</td>
<td>29%</td>
<td>0.634</td>
</tr>
<tr>
<td>QTc</td>
<td>0.395</td>
<td>81%</td>
<td>79%</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>P wave dispersion</td>
<td>0.045</td>
<td>98%</td>
<td>64%</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Hump sign</td>
<td>NA</td>
<td>86%</td>
<td>78%</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

NA: Not Applicable.
DISCUSSION

Our results also agree with Gunduz et al. who found no significant differences regarding age and sex in patients with and without diastolic dysfunction. On the other hand, our results disagreed with the results of Namdar et al., regarding the relation between age and diastolic dysfunction but agreed with his results regarding the relation between sex and diastolic dysfunction.

In this study we tried to assess some resting ECG parameters to see whether they correlate with the ST-hump sign in exercise ECG and also to evaluate whether these ECG parameters and the ST-hump sign can predict diastolic dysfunction.

This prospective study included 140 patients who were referred for stress ECG for risk stratification of coronary artery disease. We found a significantly higher occurrence of the ST hump sign during exercise stress test in patients with LV diastolic dysfunction (p< 0.0005).

There was no significant difference regarding age and sex in between patients with and patients without LV diastolic dysfunction; this comes in agreement with Michaelides et al., who revealed a significant correlation between hump sign and diastolic dysfunction in a study that included 237 patients with normal resting electrocardiogram (ECG). These results also agree with another study which found significant correlation between hump sign and diastolic dysfunction in hypertensive patients.

Our results match with the study of Liakos et al., who showed that the improvement of LV diastolic function during a 6-month treatment, leads to a significant reduction in the prevalence of hump sign and a parallel decrease in false-positive exercise stress test results, considering that hump sign is responsible for ischemic-appearing ST response.

Lepeschkin et al., reported that the most plausible mechanism of hump sign is that diastolic dysfunction leads to an increase in the LV diastolic pressure which leads to an increase in the atrial “strain”, which finally leads to abnormal atrial repolarization causing accentuation and/or prolongation of the atrial T wave. This Ta wave combined with ventricular electrical activity forms the hump sign in the early portion of the ST segment.
Our study revealed that there was no significant difference in TpTe while there was a significant difference between both groups regarding QT interval and a strong significant difference between them regarding the QTc and P wave dispersion.

Regarding only corrected QT interval, our results match the results of a study by Wilcox et al. and Namdar et al.\textsuperscript{7,12}

Two other studies revealed a significant correlation between diastolic dysfunction and corrected QT interval\textsuperscript{16}.

The study by Namdar et al included patients with hypertension and LV hypertrophy also found a modest correlation between the traditional Doppler parameters of diastolic dysfunction (E/A ratio and isovolumic relaxation time) and QTc\textsuperscript{12}.

In our study we also concluded that there is no significant correlation between TpTe interval in resting ECG and diastolic dysfunction (p= 0.726). These results did not agree with the results of study of Sauer et al., but agreed with the results of Namdar et al\textsuperscript{4,12}.

Multiple recent studies have demonstrated the role of T wave analysis, and TpTe in particular, as a potential ECG biomarker of dispersion of repolarization. In addition, some experiments have begun to investigate the ability of pharmacologically reversing dispersion of repolarization measured by TpTe as a potential therapeutic mechanism for reducing proarrhythmic substrate.

Nevertheless, transmural dispersion of repolarization has only recently been demonstrated as a potential mechanism contributing to mechanical dysfunction in patients with overt HF.\textsuperscript{5} P wave dispersion is related to the nonhomogeneous and interrupted conduction of sinus impulses intra and inter-atrially. Currently, P wave dispersion is described as a noninvasive indicator of atrial fibrillation risk, which can be calculated easily on a 12-lead surface ECG\textsuperscript{3,17}.

Dogan and colleagues compared hypertensive patients who had LV diastolic dysfunction (LVDD) with hypertensive patients who did not have LVDD and found P wave dispersion to be higher in LVDD patients\textsuperscript{18}.

Our results showed that P wave dispersion was significantly higher in patients with LVDD and was significantly correlated to the diastolic dysfunction. Similarly, multivariate regression analysis revealed that P wave dispersion has the best correlation with diastolic dysfunction (R= 0.69, p value < 0.0005). Our results agree with previous studies done by Gunduz et al., Namdar et al., and Dae-Hyeok et al\textsuperscript{8,12,19}.

This significant correlation between P wave dispersion and diastolic dysfunction can be explained by the fact that left ventricular diastolic dysfunction in a hypertrophic or ischemic ventricle results in an increase in left ventricular end-diastolic (LVED) pressure and in left atrial dimensions. The increase in left atrial dimensions as a result of rising intra-atrial pressure changes the geometry of atrial fibrils; this, in combination with nonhomogeneous fibrosis of the left atrial wall, interrupts the conduction of sinus impulses\textsuperscript{8}.

To the best of our knowledge, no prior studies tried to evaluate ECG parameters for cut off values for prediction of diastolic dysfunction. In this study, we tried to define sensitivity and specificity of some resting ECG parameters as well as the hump sign in exercise stress test for the prediction of diastolic dysfunction. Our results revealed that the sensitivity and specificity of the ST hump sign in prediction of diastolic dysfunction were 86% and 78% respectively. We also concluded that P wave dispersion at cut off value about 0.045 ms had the highest sensitivity (sensitivity 98% and specificity 64%) while QTc at cut off value 0.395 ms had the highest specificity (sensitivity 81% and specificity 79%).

These results suggest that resting ECG can be used as an easy bed-side tool for the prediction of diastolic dysfunction\textsuperscript{5}.
STUDY LIMITATIONS
Our study had some limitations. First, patients with ST hump sign but without echocardiographic criteria for diastolic dysfunction were not followed up. So, we were not able to monitor the possible future development of impaired ventricular function in these patients. Second, the ST hump sign is not a specific finding; as in our population, this sign was affected by the presence of arterial hypertension. The small number of our study patients did not allow any safe conclusion regarding the impact of risk factors on the appearance of this sign such as diabetes, hypercholesterolemia and the obesity. Third, the study population was relatively young, so the results of the study can’t be generalized to whole spectrum of ages.

CONCLUSION
Analysis of certain parameters in resting ECG especially QTc and P wave dispersion can help in prediction of diastolic dysfunction. Also, the appearance of a “hump” at the ST segment during exercise testing is associated with higher incidence of diastolic dysfunction. Therefore, its identification may be useful for stratification of these patients and may provide an additional indication for the close follow up and treatment of these patients.

CONFLICT OF INTEREST
The authors report no conflict of interest.

REFERENCES


