Effects of Spironolactone and Metoprolol on QT Dispersion in Heart Failure

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SUMMARY

The effects of spironolactone or metoprolol added to a conventional treatment protocol on QT dispersion, which is accepted as a sudden cardiac death predictor, were evaluated in heart failure patients.

A total of 105 New York Heart Association class III patients were included in this study. The conventional treatment protocol was standardized by giving ramipril, furosemide, and digoxin to all patients for 3 weeks at the same doses. At the end of this period, the patients were divided into three groups. Conventional treatment was continued in group 1, 25 mg spironolactone was added in group 2, and 12.5 mg metoprolol was added in group 3. Patients were followed for 12 weeks and clinical and laboratory tests were conducted at 3 week intervals.

No significant change in corrected QT dispersion was observed in group 1 at the end of 12 weeks (corrected QT dispersion: 80 ± 2 msc to 79 ± 2 msc, P: 0.22). However, corrected QT dispersion in group 2 was reduced by 32.5% (83 ± 2 msc to 56 ± 1 msc; P: 0.01). A 32.9% reduction in corrected QT dispersion (79 ± 2 msc to 53 ± 2 msc; P: 0.01) was observed in group 3.

In conclusion, the addition of spironolactone or metoprolol to a conventional treatment in heart failure patients resulted in improved clinical conditions and the significant decrease in sudden death predictors corrected QT dispersion. The effects of spironolactone and metoprolol on corrected QT dispersion were similar. (Jpn Heart J 2003; 44: 681-692)

Key words: Spironolactone, Metoprolol, QT dispersion, Heart failure

DESPITE the existence of advanced active medication protocols available at present, the mortality rate among patients with chronic heart failure is still high. Sixty percent of mortality in patients with chronic heart failure is due to pump failure, 30% is a result of sudden cardiac death, and 10% is due to accompanying diseases like pulmonary embolism or pneumonia.1) Mortality resulting from pump failure has decreased significantly following the introduction of angioten-
ión-converting enzyme (ACE) inhibitors into chronic heart failure treatment protocols. However, similar positive changes have not been observed in the case of sudden cardiac deaths.1,2)

Sudden cardiac death occurs as a result of malignant ventricular arrhythmias which appear with the regional variation of repolarization time in the ventricular myocardium.3) Inhomogeneities that appear during ventricular repolarization time can be evaluated by standard 12-lead surface electrocardiography (ECG). The fact that there is a close correlation between epicardial monophasic action potential registers in the repolarization variations and QT dispersion (QTd) indicates that the present electrical inhomogeneities reflect directly on QTd in the electrocardiography.4,5) It has been seen in recent studies aiming to identify high-risk arrhythmic unexpected deaths that QTd has a high predictive value in patients with clinical conditions like ischemic cardiac disease,6-9) hypertrophic cardiomyopathy10) and congenital long-term QT syndrome,11) as well those with chronic heart failure.11-13) Therefore, QTd is highly significant in the follow-up of the clinical results of chronic heart failure patients.

It is known that in heart failure patients, various agents can change the clinical results by directly or indirectly affecting cardiac electrophysiological substrates.14,15) Thus, in this study we investigated the changes in QTd and other clinical results caused by the addition of spironolactone and/or metoprolol to a conventional chronic heart failure treatment (ACE inhibitors, diuretic and digoxin preparations).

**METHODS**

**Study population:** One hundred and five cardiac failure patients were included in the study. Coronary artery disease was verified by angiography, but they were not eligible for invasive or surgical intervention; were in stage III according to New York Heart Association (NYHA), and had an angiographic ejection fraction (EF) ≤ 35%. The basal clinical and laboratory test results were registered. All cases were required to have a serum potassium level < 5.5 mmol/L (normal limit: 3.5-5.5 mmol/L) and a serum creatinine value ≤ 2.0 mg/dL (normal limit: 0.8-2.0 mg/dL). In addition, patients who had 1) marked peripheral vascular disease, 2) valve disease, 3) diabetes mellitus, 4) malignancy, 5) chronic pulmonary, liver or renal disease, 6) thyrotoxicosis or hypothyroidism, 7) hypotension (basal blood pressure < 100/65 mmHg) or hypertension (basal blood pressure ≥ 149/90 mmHg), 8) unstable angina pectoris, 9) myocardial infarction within a period of less than 30 days, 10) a history of using a potassium retaining diuretic within a period of less than 30 days, and 11) cardiac rhythm other than sinus (including branch blocks and permanent artificial pacemaker rhythm) were excluded from the study.
Study protocol: After approval was obtained from the patient in writing, the conventional treatment protocol was standardized by administering all patients an ACE inhibitor (2.5 mg/day ramipril), loop diuretic (40 mg/day furosemide), and digitalis (0.25 mg/day digoxin). The diuretic dose could be increased when necessary, however, we attempted to keep the ACE inhibitor and digitalis doses fixed. Apart from the standard treatment, patients were given oral nitrate and/or acetyl salicylic acid preparations (≤ 325 mg) in accordance with their needs. The standard conventional treatment protocol was implemented for three weeks. At the end of this period, the patients were randomly allocated into three different groups, taking the male-female ratio into consideration. After the groups were formed, the biochemical, echocardiographic, and functional capacities of the patients were investigated once more. The values obtained after the conventional treatment were registered as baseline data. The patients in group 1 (n = 35, 15 females) continued on the conventional treatment protocol without any changes. Group 2 (n = 35, 16 females) was administered 25 mg of oral spironolactone and group 3 (n = 35, 16 females) 12.5 mg of metoprolol in addition to the conventional treatment protocol. The groups were administered these new treatment protocols for 12 weeks, and clinical and laboratory tests were conducted every 3 weeks. At the end of the study (12 weeks), echocardiography, functional capacity, biochemistry tests, and drug side effects were investigated, and QT analyses of all groups were conducted.

QT interval and dispersion analyses: QT analyses were performed by two separate researchers who did not know one another, just upon the completion of conventional treatment standardization and at the end of the 12-week spironolactone-metoprolol treatment program. Twelve-lead high-resolution (Marquette-Mac VU, Ohio, USA) ECG was used for QT interval analyses. The QT interval was measured as the time period from the beginning of a QRS complex to the point where the T wave united with the isoelectric line. In those ECG with a U wave, the end of the T wave was accepted as the point at the bottom of the junction of the T and U waves. Three consecutive QT periods in each deviation were measured in milliseconds (ms) and the mean value was determined. Care was given to measure QT intervals from ≥ 9 measurable ECG leads. The QT intervals obtained were modified according to heart rate using Bazett’s formula (QTc = QT/RR^{1/2}).

QT dispersion (QTd) was found by subtracting the shortest QT interval from the longest QT interval calculated on the 12-lead ECG (QTd = QT_{max} - QT_{min}). Corrected QTd (QTdc) was obtained by subtracting the minimum QTc from the maximum QTc (QTdc = QTc_{max} - QTc_{min}).

Echocardiographic investigations: Echocardiographic investigations were conducted before the conventional treatment, after standardization of that treatment...
(values obtained after the conventional treatment were regarded as baseline data), and at the end of the 12-week period during which the spironolactone-metoprolol treatment was continued. Echocardiographic studies were conducted using an Acuson Sequa 515 (Minnesota, USA) from the standard angle and windows. A modified Simson method was employed in calculating ventricular volume. Ejection fraction, beat volume, and cardiac output were calculated from ventricular volumes.

Functional capacity evaluation studies: Functional capacity studies were performed before the conventional treatment, after the standardization of that treatment (values obtained after the conventional treatment were regarded as baseline data), and at the end of the 12-week period during which the spironolactone-metoprolol treatment continued. In the functional capacity investigations Cardiosis treadmill equipment (Tepa-Medical, Ankara, Turkey) was used together with clinical evaluations when necessary. The patients to whom the treadmill test was applied underwent the Naughton treadmill protocol, with 1-2 minute laps and a 1-MET workload increase between laps.

Statistical analysis: Continuous variables are presented as the mean ± standard deviation and categorical variables as %. The cross-match t test was carried out for changes before and after the spironolactone-metoprolol treatment. For the changes in a categorical variable, the chi-square test was employed. A $P < 0.05$ was regarded as being statistically significant.

**RESULTS**

The patients in the study groups were similar in terms of number, age, gender, and baseline body mass indices and there were no significant differences among the groups with regard to these parameters (Table I).

QT analysis: At the end of the 12-week treatment period that followed conventional treatment, no significant changes were observed in the average QTdc periods of patients in group 1 (from $80 \pm 2$ ms to $79 \pm 2$ ms; $P: 0.22$). However, significant decreases in the QTdc periods in group 2 and group 3 patients were observed as follows: In group 2 the average QTdc period decreased by 32.5% (from $83 \pm 2$ ms to $56 \pm 1$ ms; $P: 0.01$), in group 3 the average QTdc period decreased by 32.9% (from $79 \pm 2$ ms to $53 \pm 2$ ms; $P: 0.01$) (Figure 1).

The decreases in QTdc in group 2 and group 3 were significantly higher than those in group 1 ($P: 0.01$). However, there was no difference between group 2 and group 3 with respect to the QTdc decrease ($P: 0.62$).

Echocardiography: The average echocardiographic EF values measured after the 12-week treatment program increased significantly in comparison to the average baseline echocardiographic EF values in all patients from all three groups
Table I. General Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group1 (n : 35)</th>
<th>Group2 (n : 35)</th>
<th>Group3 (n : 35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.2 ± 5.3</td>
<td>58.9 ± 6.1</td>
<td>59.7 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (57)</td>
<td>19 (54)</td>
<td>19 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>15 (43)</td>
<td>16 (46)</td>
<td>16 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23.7 ± 1</td>
<td>24.2 ± 2</td>
<td>23.9 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>24.1 ± 2</td>
<td>24.5 ± 1</td>
<td>24.3 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>27.9 ± 4</td>
<td>27.2 ± 2</td>
<td>27.6 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA Class III (%)</td>
<td>35 (100)</td>
<td>35 (100)</td>
<td>35 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes</td>
<td>8 (23)</td>
<td>9 (26)</td>
<td>9 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4 (11)</td>
<td>5 (14)</td>
<td>3 (9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Not significant; BMI = Body mass index; EF = Ejection fraction; NYHA = New York Heart Association.

Figure 1. Changes in corrected QT dispersions (QTdc) in the study groups.

(group 1 from 29.1 ± 5.5% to 35.3 ± 6.2%, P: 0.02; group 2 from 28.9 ± 6.1% to 36.3 ± 8.3 %, P: 0.00; group 3 from 29.1 ± 4.2% to 35.4 ± 7.1%; P: 0.01) (Figure 2). Increases in cardiac output (CO) and cardiac index (CI), which were calculated by echocardiography, were parallel to average EF (CO increased from 3.3 ± 0.1 to 3.5 ± 0.7, P: 0.02 in group 1; from 3.2 ± 0.5 to 3.6 ± 0.2, P: 0.01 in group 2; from 3.2 ± 0.9 to 3.5 ± 0.9, P: 0.01 in group 3; CI increased from 1.90 ± 0.2 to 2.05 ± 0.2, P: 0.01 in group 1; from 1.89 ± 0.4 to 2.08 ± 0.4, P: 0.01 in group 2;
from 1.89 ± 0.9 to 2.07 ± 0.1, *P* < 0.01 in group 3). However, increases in average echocardiographic EF, cardiac output, and cardiac index did not reveal statistically significant differences among groups.

**Functional capacity:** Functional capacity data obtained after the 12-week treatment program showed slight improvement compared to baseline data in all patients in all three groups, except for one patient in group 3. Nine patients (25.7%) in group 2 and group 3, who had class III functional capacity (FC) according to NYHA were seen to regress to class II FC after the treatment (In group 1, the rate of class III FC patients decreased from 82.9% to 57.1%, *P* < 0.01; the rate of class II FC patients increased from 17.1% to 42.9%, *P* < 0.001; in group 2, the rate of class III FC patients decreased from 85.7% to 60%, *P* < 0.01; the rate of class-II FC patients increased from 14.3% to 40%, *P* < 0.001). Although in group 3 six (17.1%) class III FC patients retrogressed to class II FC, one patient (2.9%) progressed to class IV FC (The rate of class III FC decreased from 82.9% to 62.9%, *P* < 0.01; the rate of class II FC patients increased from 17.1% to 34.3%, *P* < 0.02; and the rate of class IV patients FC increased from 0% to 2.9%, *P* < 0.055). However, these differences in terms of functional capacity among the groups were not statistically significant (*P* > 0.05).

**Biochemical findings:** The serum biochemical, hematological, and urinary analysis results obtained in groups 1 and 3 after the treatment did not reveal any significant differences in comparison to the values obtained before the treatment. In group 2, however, the average serum potassium (K⁺) - magnesium (Mg²⁺) levels increased (K⁺: from 4.53 ± 0.2 mEq/L to 4.98 ± 0.3 mEq/L, *P* < 0.03; Mg²⁺: from
2.01 ± 0.3 mEq/L to 2.33 ± 0.3 mEq/L, \( P: 0.05 \); urinary sodium excretion was augmented (from 110.6 ± 3 mEq/L to 117.4 ± 3 mEq/L, \( P: 0.01 \)); and potassium excretion decreased significantly (from 50.1 ± 16 mEq/L to 40.3 ± 12 mEq/L, \( P: 0.001 \)).

**Side effects:** The treatment protocols were generally well tolerated by all groups. Although no side effects, clinical or laboratory, were observed in the patients in group 1, the serum potassium level was found to be higher (> 5.5 mmol/L) in one patient in group 2 on the third visit and in two patients (8.57%) in group 2 again on the third visit. One patient in group 3 (2.85%) was seen on the fourth visit to have progressed from class III to class IV in terms of functional capacity according to current NYHA. No deaths were recorded in the three-month follow-up period.

**DISCUSSION**

ACE inhibitors administered to patients with chronic cardiac failure may to a great degree block the renin-angiotensin-aldosterone system (RAAS) which is activated in the initial period.\(^1\,^5\,^6\,^18\,^19\) However, it has been seen that chronic ACE inhibition does not ensure neurohormonal suppression of the RAAS at the desired level.\(^18\,^21\) It has been established that the suppressive effects caused by ACE inhibition on aldosterone are weak, variable, and transient, especially in chronic periods.\(^20\,^21\) The fact that chronic ACE inhibition cannot ensure complete neurohormonal suppression of the RAAS led to the idea that heart failure patients cannot be sufficiently protected against the negative cellular effects of this system.\(^22\,^30\) Although ACE inhibition markedly reduced mortality due to pump insufficiency, particularly in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), SOLVD (Studies of Left Ventricular Dysfunction), and SAVE (Survival and Ventricular Enlargement Study) studies, it is established that the expected effect was not obtained in arrhythmic sudden deaths.\(^1\,^2\) This demonstrates that ACE inhibitors are not sufficient by themselves to prevent the sudden deaths which account for about 30% of deaths due to cardiac failure and that supplementary medication is necessary to regulate the neurohormonal mechanism that cannot be completely suppressed by ACE inhibitors. In the recent randomized studies using metoprolol (Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot trial: RESOLVD)\(^31\) and spironolactone (The Randomized Aldactone Evaluation Study: RALES)\(^32\), promising results have been obtained to ensure the neurohormonal suppression when ACE inhibition does not provide satisfactory results. When metoprolol and spironolactone-like drugs that have a modifying effect on neurohormonal mechanisms are added to ACE inhibitors, a decrease was achieved in mortality due to progressive cardiac
failure and especially arrhythmic sudden deaths.\textsuperscript{33,34} However, it is not known with absolute certainty which agent is more effective at reducing arrhythmic unexpected deaths. Therefore, it is not known which agent is effective on QTd, the predicator of arrhythmic sudden death.

In our study the addition of spironolactone or metoprolol to conventional treatment caused marked decreases in the QTd and QTdc periods ($P: 0.01$), although the decreases were not different. The similar effect of metoprolol and spironolactone on QTd may depend on the autonomic tonus modulation characteristic of beta-blockers and aldosterone antagonist diuretics.\textsuperscript{35,36} However, it should not be forgotten that in addition to a common autonomic tonus modulation effect, these two drugs have agent-specific effects on QTd.

The recent RALES study in which the 30\% survival advantage was derived by adding spironolactone to conventional treatment, reported that in addition to the autonomic tonus modulation characteristic, aldosterone may play the role of preventing potassium/magnesium loss and blocking myocardial fibrosis.\textsuperscript{32} The fact that in our study the group which was given spironolactone (group 2) showed diuresis (an increase in urinary sodium with a decrease in urinary potassium) and significant increases in serum potassium/magnesium levels led us to agree with the aforementioned view. The potassium/magnesium loss induced by aldosterone may increase QT dispersion and this may cause increase the possibility of ventricular arrhythmias.\textsuperscript{37,38} But magnesium replacement shortens the QT interval and has been seen to be highly effective on the termination of the torsadedef pointes. However, the effects of magnesium on QTd are not known.\textsuperscript{37} Potassium is responsible for the outward current during repolarization, one of the main determinants of the QTd interval. As a result of hypokalemia repolarization slows down and the QT intervals become longer.\textsuperscript{38} In their recent study Choy, et al demonstrated that intravenous potassium infusion not only improved the QT interval which had become longer, but also reduced QTd in patients with chronic heart failure.\textsuperscript{39} Yee, et al reported that spironolactone decreased the heart rate in heart failure patients, especially in the morning, and had positive effects on the parasympathetic tone of the heart and QTd.\textsuperscript{34} In these trials, the relations between potassium-QTd\textsuperscript{38,39} or spironolactone-QTd\textsuperscript{34} were strongly correlated with our spironolactone-QTd relation. However, besides the positive impact brought about by the limited increase in the serum potassium level (when serum potassium level is < 5.5 mmol/L) by adding spironolactone to ACE inhibitors, (when serum potassium level is >5.5 mmol/L) the harmful effects of a hyperkalemic state should not be overlooked. Hyperkalemia was seen (when the serum potassium level is > 5.5 mmol/L) in 11.4\% ($n = 4$) of patients in the study group in which spironolactone was added to the conventional treatment (group 2). However, in our study the rate of patients whose serum potassium level increased was less
than the rates in RALES\textsuperscript{32} which investigated the reliability of adding spironolactone to standard conventional treatment (11.4\% versus 15.2-19.5\%). The reason why our rates were lower may be that the spironolactone dose we used was low or that the patients were regularly taking furosemide. Nevertheless, the risk of hyperkalemia should not be overlooked in cases where spironolactone is added to the conventional treatment.

Although it is believed that the nonselective beta-blockers reduce sudden death because of their greater effect on catecholamine discharge and the prevention of hypokalemia,\textsuperscript{40} Fesmire, \textit{et al} found that both selective and nonselective beta-blockers have similar effects on QTd,\textsuperscript{41} which is a sudden death predictor.\textsuperscript{11-13} In addition, a 41\% reduction in sudden death was observed in the MERIT-HF (Metoprolol Randomized Intervention Trial in Heart Failure) study\textsuperscript{42} in chronic heart failure patients and a 44\% reduction was observed in the CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) trial.\textsuperscript{43} These reductions were attributed to specific agent effects rather than a class effect. Currently, it is believed that beta-blockers reduce sudden death by preventing catecholamine-induced myocyte toxicity/apoptosis (by changing the course of ventricular remodeling),\textsuperscript{44} changing the local environment (electrolyte and ion flow),\textsuperscript{40} and preventing arrhythmia by decreasing ischemia\textsuperscript{45} and catecholamine discharge.\textsuperscript{44} In our study, metoprolol reduced the QTdc by 32.9\% when added to conventional treatment, although the exact mechanism is not known. This reduction was higher than the QTdc reduction found by Fesmire, \textit{et al} who administered metoprolol to patients with nonischemic dilated cardiomyopathy.\textsuperscript{41} These differences may be due to the study population. However, our findings correlated with those of Bonnar, \textit{et al} in patients with impaired left ventricular systolic function.\textsuperscript{46} Based on these findings, we believe that beta-blockers have a greater effect on QTd or QTdc in patients with impaired left ventricular systolic function.

In our study, apart from the positive decreases in QTd and QTdc intervals, an overall improvement in the functional capacities of all patients and increases in the average echocardiographic EF, cardiac output, and cardiac index were observed. However, the changes in functional capacity, average echocardiographic EF, cardiac output, and cardiac index parameters were not significant among the groups ($P > 0.05$). The fact that the changes in the parameters were not significant among the groups suggests that the fundamental effect in this respect may belong to ACE inhibitors. The positive improvements in the parameters of functional capacity, average echocardiographic EF, cardiac output, and cardiac index observed after the treatment are consistent with the results of previous studies\textsuperscript{1,19} which investigated the effects of ACE inhibitors on similar parameters, and seem to confirm our opinion.
Study limitations: The most important limitations of our study were the small study population and the short follow-up period. However, mortality evaluation may be conducted in a study population over a longer period by the aid of our findings. Secondly, the effects of the combination of metoprolol (effective on the sympathetic system) and spironolactone (effective on the parasympathetic system) on QTd are not yet known. The combination of these two drugs may be more effective on QTdc than each drug alone. Further, in the subgroup analysis of the RALES study, it was reported that the combination of spironolactone and beta-blockers may act synergistically in reducing mortality.47)

CONCLUSIONS

This study, though not a mortality study, is still important for investigating the effects of spironolactone or metoprolol on the sudden death predictor QTd. The addition of spironolactone or metoprolol to a standard conventional heart failure treatment significantly decreases the QTd or QTdc intervals, which are predictors of sudden death, and improves the clinical state. Spironolactone and metoprolol seem to have similar effects on the QTd and QTdc intervals.

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