Effect of Long-Term Beta-Blocker Therapy on Microvolt-Level T-Wave Alternans in Association With the Improvement of the Cardiac Sympathetic Nervous System and Systolic Function in Patients With Non-Ischemic Heart Disease

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The purpose of this study was to test a hypothesis that T-wave alternans (TWA) is improved in association with an improvement in cardiac sympathetic nervous system and systolic function by oral \( \beta \)-blocker therapy in patients with non-ischemic heart disease (NIHD). TWA testing, \(^{125}\)I-metaiodobenzylguanidine (MIBG) imaging and echocardiography were performed at the baseline and 3 months after \( \beta \)-blocker therapy in 26 patients with NIHD and positive TWA. The alternans voltage (\( V_{alt} \)), the heart-to mediastinal-ratio on the early (e-H/M) and delayed (d-H/M) images, the washout rate (WR), the left ventricular ejection fraction (LVEF), and the calculated rate of change by \( \beta \)-blocker therapy in each parameter (ie, \( \Delta V_{alt} \), \( \Delta e-H/M \), \( \Delta d-H/M \), \( \Delta WR \) and \( \Delta LVEF \)) were measured. After therapy, TWA turned negative in 8 patients (group A) and remained positive in 18 (group B); \( V_{alt} \) was significantly decreased in group B (p<0.001). In group A, e-H/M, d-H/M and LVEF were significantly increased (e-H/M: p<0.05, d-H/M and LVEF: p<0.01), as were e-H/M and LVEF in group B (p<0.05). There were significant correlations between \( \Delta V_{alt} \) and \( \Delta e-H/M \) (r=–0.61, p<0.01), \( \Delta d-H/M \) (r=–0.82, p<0.0001), \( \Delta WR \) (r=0.60, p<0.01) and \( \Delta LVEF \) (r=–0.70, p<0.01). In patients with NIHD, the TWA is improved in association with the improvement in cardiac sympathetic nervous system abnormalities and left ventricular systolic dysfunction by \( \beta \)-blocker therapy. (Circ J 2003; 67: 821–825)

Key Words: \( \beta \)-blocker; Left ventricular systolic function; MIBG; Sympathetic nervous system; T-wave alternans

T-wave alternans (TWA) is defined as the beat-to-beat oscillation of amplitude of the T wave that repeats every other beat and because microvolt-level TWA is detectable during atrial pacing or exercise, TWA testing is now used as a predictor of the development of lethal ventricular arrhythmias. There have been various reports of its clinical usefulness in patients with ischemic heart disease (IHD), long QT syndrome, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), congestive heart failure, and those with hypertension but although there are many hypotheses on the developmental mechanism of TWA, a consistent view has not been established.

With regard to the effect of anti-arrhythmic drugs on TWA, the effect of procainamide injection and oral amiodarone administration have been reported and previous studies have demonstrated that the alternans voltage (\( V_{alt} \)) is decreased by intravenous \( \beta \)-blocker administration in patients with inducible ventricular arrhythmia. However, there has not been a prospective report of the effect of oral \( \beta \)-blocker administration on TWA.

Harada et al reported that TWA was related to cardiac sympathetic nervous system abnormalities because abnormal \(^{125}\)I-metaiodobenzylguanidine (MIBG) images were found in many patients with positive TWA and non-IHD (NIHD). Recently, it was observed that mechanical alternans disappeared with the improvement in left ventricular ejection fraction (LVEF) after \( \beta \)-blocker therapy in patients with DCM. Those findings suggest that TWA improvements accompany the improvement in cardiac sympathetic nervous system abnormalities and left ventricular systolic dysfunction related to \( \beta \)-blocker therapy, and the present study was designed to investigate whether the same situation applies for patients with NIHD.

Methods

Study Population

After informed consent was obtained, TWA testing and MIBG imaging were performed continuously in in-hospital patients with organic heart diseases, other than IHD, from June 2000 to June 2002. The diagnosis of IHD was made...
from the results of exercise stress scintigraphy and/or coronary angiography. The following patients were excluded: (1) contraindication for β-blocker therapy, (2) unable to undergo an ergometer exercise test, and (3) long-term β-blocker therapy prior to being in hospital.

Seventy-one consecutive patients underwent TWA testing and were diagnosed as NIHD. Of these, 32 showed a positive TWA, and then β-blocker therapy was started. Finally, 26 patients who were followed and who received β-blocker therapy for 3 months were enrolled for the study. The other 6 patients comprised 2 who underwent cardiac surgery after registration (aortic regurgitation: 1, tetralogy of Fallot: 1), 1 for whom exercise was difficult because of leg fatigue, 1 who dropped out of this study by choice, 1 for whom β-blocker administration was discontinued because of bradycardia, and 1 whose heart rate did not reach 110 beats/min during TWA testing because of leg fatigue.

There were 18 males and 8 females aged 57±14 years (mean±SD) and the cardiac diseases were dilated cardiomyopathy (n=13), hypertrophic cardiomyopathy (7), hypertensive heart disease (4), mitral regurgitation (1) and aortic regurgitation (1). The β-blockers administered were metoprolol (n=15; mean dose, 26 mg); carvedilol (9; 11 mg); bisoprolol (1; 5 mg); and atenolol (1; 5 mg). Only 3 of the patients had severe ventricular arrhythmia: 2 had sustained ventricular tachycardia and one had non-sustained ventricular tachycardia.

**Study Protocol**

The enrolled patients, who were positive for TWA testing and underwent MIBG myocardial imaging, were started on a low dose of β-blockers, which were then increased slowly according to tolerance, assessed by each patient’s physician on the basis of symptoms and physical examination, chest X-ray, echocardiography. After 3 months, the TWA testing, MIBG myocardial imaging and cardiac echocardiography were repeated.

**Subgroups**

The subjects were divided into 2 groups according to the TWA findings after β-blocker administration: patients in whom the TWA turned negative comprised group A, and those in whom it remained positive were group B. In group B, we investigated the changes in the Valt by β-blocker therapy. The heart-to-mediastinal-ratio on the early (e-H/M) and delayed (d-H/M) images, the washout rate (WR), and the LVEF before and after β-blocker therapy were compared between the 2 groups, and the calculated rate of change by β-blocker therapy in each parameter (ie, ΔValt, Δe-H/M, Δd-H/M, ΔWR and ΔLVEF) were measured in group B.

**Assessment of TWA**

TWA was measured at rest and during exercise on a sitting bicycle ergometer using the CH 2000 system (Cambridge Heart, Inc, Bedford, MA, USA) and was judged according to the positive criteria reported by Gold et al. TWA was defined as positive when it was sustained with an onset heart rate of 110 beats/min with an alternans voltage 1.9 mV and an alternans ratio 3.0 in the vector magnitude lead, any orthogonal lead or 2 adjacent precordial leads. TWA was defined as negative if the artifact-free criteria were met while the heart rate was maintained at a level of 105 beats/min. Otherwise, the test was defined as indeterminate.

The maximum alternans voltage of the vector magnitude lead while the heart rate increased to 110 beats/min during exercise or decreased from 110 beats/min in recovery was defined as $V_{alt}$, and the rate of change in $V_{alt}$ (DValt) induced by β-blocker therapy was calculated as:

$$V_{alt} (%) = \frac{(post V_{alt} - pre V_{alt})}{pre V_{alt}} \times 100$$

where pre is before β-blocker therapy and post is after the therapy.

Patients whose heart rates did not increase up to 110 beats/min were excluded. The TWA recordings were interpreted by one of the authors who was not aware of the results of MIBG myocardial scintigraphy and echocardiography.

**123I-MIBG Myocardial Imaging**

For the MIBG myocardial imaging study, 123I-MIBG (111 MBq; Daiichi Radioisotope Laboratories, Tokyo, Japan) was intravenously injected while the patient was supine. Anterior planar images were obtained 15 min after injection and repeated 210 min later using a rotation-type gamma camera with a low-energy collimator (Toshiba GCA 9300A/PI Medical System).

The mean counts in the heart and upper mediastinum were measured from the anterior planar images, and the
Fig 2. Each patient’s number and diagnosis of non-ischemic heart disease in the 2 subgroups divided according to TWA finding after β-blocker administration. There were no significant differences in sex ratio, age, diseases and left ventricular systolic function between the 2 groups. AR, aortic regurgitation; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; group A, patients whose TWA turned negative; Group B, patients whose TWA remained positive; MR, mitral regurgitation; Pre, before therapy; Post, after therapy; TWA, T-wave alternans.

Results

Representative Case (Fig 1)
The patient was a 67-year-old female with DCM. The TWA turned negative, the e-H/M and d-H/M increased, WR decreased, the left ventricular dimensions decreased, and the LVEF increased after β-blocker therapy, which showed that the parameters of MIBG and echocardiography had improved with the disappearance of TWA.

Table 1 Changes in MIBG Parameters and Ejection Fraction After β-Blocker Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Pre</th>
<th>Post</th>
<th>p valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>e-H/M</td>
<td>A</td>
<td>1.85±0.11 NS*</td>
<td>2.13±0.32 NS*</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.96±0.27</td>
<td>2.08±0.26 NS*</td>
<td>0.036</td>
</tr>
<tr>
<td>d-H/M</td>
<td>A</td>
<td>1.76±0.16</td>
<td>2.13±0.29 NS*</td>
<td>0.0018</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.93±0.29</td>
<td>2.07±0.31 NS*</td>
<td>0.11</td>
</tr>
<tr>
<td>WR (%)</td>
<td>A</td>
<td>29.1±15.6 NS*</td>
<td>21.9±17.4 NS*</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>26.3±12.9</td>
<td>24.5±12.8 NS*</td>
<td>0.64</td>
</tr>
<tr>
<td>EF (%)</td>
<td>A</td>
<td>42±25</td>
<td>50±22</td>
<td>0.0024</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>47±20</td>
<td>51±17 NS*</td>
<td>0.021</td>
</tr>
</tbody>
</table>

The measured values are presented as the means ± standard deviation.

MIBG parameters and EF between the 2 groups were analyzed using unpaired t-tests.

The comparisons of the values of e-H/M, d-H/M, WR and EF before and after medication were analyzed using paired t-tests.

The relationships between ∆Walt and ∆e-H/M, ∆d-H/M, ∆WR, or ∆LVEF were investigated using simple regression analysis. A p-value <0.05 was defined as statistically significant.

Results of TWA Assessment

Among 26 patients with a positive TWA at baseline, the TWA turned negative in 8 (31%) and remained positive in 18 (69%) after β-blocker therapy (Fig 2). There were no significant differences in sex ratio, age, or diseases between the 2 groups. Furthermore, there were 2 patients with a LVEF >50% (25%) in group A and 6 (33%) in group B. There was no significant difference in the LVEF before β-blocker therapy between the 2 groups. On the other hand, Walt was significantly decreased by β-blocker therapy in group B (Fig 3). These findings showed that oral β-blocker therapy had a significant effect on TWA and LVEF.
therapy improves TWA.

Changes in the MIBG Parameters and LVEF After β-Blocker Therapy in Groups A and B

There was no significant difference between the 2 groups in any of the MIBG parameter or LVEF at baseline. In group A, after β-blocker therapy the e-H/M, d-H/M and LVEF were significantly increased and WR tended to be decreased, although the change was not significant (Table 1). In group B, only the e-H/M and LVEF were increased (Table 1). In group B, although the Valt decreased in the overall analysis, it did not decrease in some patients. Therefore, we investigated the relationship between ∆Valt and ∆e-H/M, ∆d-H/M, ∆WR or ∆LVEF. Negative correlations were demonstrated between ∆Valt and ∆e-H/M, ∆d-H/M or ∆LVEF (Δe-H/M: r=−0.61, p<0.01, Δd-H/M: r=−0.82, p<0.0001, ∆LVEF: r=−0.70, p<0.01), whereas a positive correlation was found between ∆Valt and ∆WR (r=0.60, p<0.01) (Fig 4).

Discussion

Changes in the Cardiac Sympathetic Nervous System and Left Ventricular Systolic Function after Oral β-Blocker Therapy

Generally, when abnormalities of the cardiac sympathetic nervous system become severe, the H/M ratio, which reflects global myocardial uptake of MIBG, is decreased, and the WR, which reflects sympathetic nervous activity, is increased25,26. Conversely, when β-blocker therapy is effective for chronic heart failure, the H/M ratio is increased and the WR is decreased27. However, because it has been demonstrated in those patients that these parameters improve with effective β-blocker therapy, we examined whether the TWA findings also improve with the improvements in the cardiac sympathetic nervous system and left ventricular systolic function induced by oral β-blocker therapy. In our study, β-blocker therapy improved all the MIBG parameters and the LVEF in groups A and B (Table 1). The TWA turned negative in group A and the Valt significantly decreased in group B (Fig 3), which suggests that the TWA findings improved together with the improvements in the cardiac sympathetic nervous system abnormalities and left ventricular systolic dysfunction because of oral β-blocker therapy. However, we do not think that the TWA is caused only by abnormalities of the cardiac sympathetic nervous system and left ventricular systolic dysfunction, because some patients have a positive TWA without these abnormalities.

Relationship Between TWA and Cardiac Sympathetic Nervous System Abnormalities

Schwartz et al reported that there was a close relationship between TWA and the cardiac sympathetic nervous system, and that the appearance of TWA with syncope could be repeated with effort and fright stimuli in patients with long QT syndrome28. There are reports that cardiac sympathetic denervation causes heterogeneity in the refractory period of the ventricular myocardium, which contributes to the development of lethal ventricular arrhythmia29,30. Mitani et al reported that a MIBG defect, which reflects regional sympathetic denervation, occurs frequently in patients with ventricular tachycardia caused by NiH31 and Harada et al reported that patients with a positive TWA in NIH had low H/M ratios and high WR, and that cardiac sympathetic denervation and accelerated sympathetic nervous activity both play a role in the development of microvolt-level TWA in these patients22.

Mechanism of the Improvement in TWA After Oral β-Blocker Therapy

Shimizu et al suggested that TWA is related to mechanical alternans, and that Ca2+ release from the sarcoplasmic reticulum plays a pivotal role in the maintenance of these alternans16. A recent stated that mechanical alternans disappears with an improvement in LVEF after oral β-blocker therapy in patients with DCM23 and so it is assumed that the mechanical and T-wave alternans disappear because of the improved Ca2+ handling induced by β-blocker therapy.

Study Limitations

The clinical usefulness of the qualitative evaluation of microvolt-level TWA as a predictor of lethal arrhythmia, has already been demonstrated2,13,10,14 but it has never been established that a quantitative evaluation, such as the alternans voltage, reflects prognosis in patients with lethal arrhythmia. Because this study was based on the premise that TWA is a predictor of lethal arrhythmia, a prognostic evaluation of lethal arrhythmia was not done and furthermore, the different effects on TWA β1 selective and non-selective β-blocker was not investigated.
Conclusion

TWA is improved, in association with the improvements in the abnormalities of the cardiac sympathetic nervous system and/or left ventricular systolic dysfunction, by oral ß-blocker therapy in patients with NHHD.

References