Defibrillator Electrogram T Wave Alternans as a Predictor of Spontaneous Ventricular Tachyarrhythmias in Defibrillator Recipients

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Background Although T wave alternans (TWA) and the T wave peak-to-end (Tpte) interval are associated with vulnerability to ventricular tachyarrhythmia (VT), no previous reports have demonstrated that TWA immediately precedes spontaneous VT in the human ambulatory setting.

Methods and Results Stored electrograms from the implantable cardioverter defibrillators (ICD) of 74 patients (59 males, 55.3±12.2 years) were analyzed. TWA (ΔT amplitude), Tpte interval, QT interval, and RR intervals were measured from magnified digital images immediately before spontaneous VT (VTClinical; n=73), or immediately after ICD shocks during artificially-induced VT (VTInduced; n=74) or inappropriate shocks (ShockInduced; n=6). (1) TWA was significantly greater in VTClinical than VTInduced (P<0.01) or ShockInduced (P<0.001), but Tpte was not (P=NS). (2) In the VTClinical group, TWA was significantly greater in patients with ischemic VT than in those with non-ischemic cardiomyopathy or idiopathic VF (P<0.05). (3) In the same patient, the TWA for VT Clinical was significantly greater than that for VTInduced (P<0.01).

Conclusion TWA measured from ICD electrograms is significantly greater immediately before spontaneous VT than immediately after inappropriate shocks or shocks during induced VT. These findings indicate that repolarization alternans plays an important role in the induction of VT in humans. (Circ J 2009; 73: 55–62)

Key Words: Implantable cardioverter defibrillator; T wave alternans; Ventricular tachycardia

T wave alternans (TWA), which is characterized by changes in the contour, amplitude or polarity of the T wave with regular rhythmicity, represents a temporal dispersion of repolarization. Previous studies show that TWA is a marker of electrical instability in humans and is associated with life-threatening ventricular tachyarrhythmias (VTs). TWA is known to be associated with various conditions, such as long QT syndrome, Prinzmetal angina, acute ischemia, marked electrolyte abnormalities, and hypertrophic cardiomyopathy. The duration from the peak of the T wave to the end of the T wave (Tpte) is associated with transmural dispersion of repolarization, which is also related to the vulnerability to ventricular arrhythmias. Tsai et al reported that TWA was a predictor of VT in a canine model of sudden cardiac death using intracardiac electrograms obtained from an implantable cardioverter defibrillator (ICD). However, no one has previously investigated whether TWA and Tpte immediately precede or follow spontaneous VT in the human ambulatory setting. We hypothesized that TWA and the Tpte interval measured from the stored electrograms of ICD recipients would become prominent immediately before the spontaneous onset of clinical VTs. The purpose of this study was to determine whether TWA and the Tpte interval were measurable in the electrograms from ICD recipients, and if they were closely related to clinical VT.

Methods

This study was approved by the Institutional Review Board of Korea University Anam Hospital, and informed consent was given by each patient.

Patient Enrollment

We included 74 patients (age 55.3±12.2 years, males 79.7%) who had implanted ICDs. All patients had the transvenous-type ICD, and 5 of them underwent cardiac resynchronization therapy with a defibrillator. The ICD profiles were as follows: VENTAK MINI (Guidant Inc, Indianapolis, IN, USA), PRISM2 (Guidant Inc), GEM 7227 (Medtronic Inc, Minneapolis, MN, USA), GEM DR 7271 (Medtronic Inc), and Profile MD (St Jude Inc, Saint Paul, MN, USA). At a mean follow-up duration of 32.2±18.6 months, 17 patients had experienced 161 appropriate ICD therapies, and 5 patients received 6 inappropriate ICD shocks. Four patients with appropriate ICD therapies experienced ICD storms (>20 episodes per day).

Classification of ICD Electrograms

The total number of acquired stored ICD electrograms with tachycardia events was 167 (161 appropriate therapies, 6 inappropriate therapies). Taken together with 205 episodes of ICD shocks recorded during the measurement of

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defibrillation threshold (DFT), we collected 372 ICD electrograms. All electrograms were recorded from shock channel strip pseudo-electrocardiograms (ECGs, right ventricular apical anode to superior vena caval cathode), and printed by an ICD programmer. The sweep speed of the ICD programmer was set at 25 mm/s and the bandpass filtering range was 10–10,000 Hz, regardless of manufacturer. Among these electrograms, we excluded the following data: multiple repetitive ICD therapies during electrical storms (n=110 in 5 patients) except for 6 representative electrograms; multiple ICD shock electrograms recorded during DFT measurement (n=205 in 74 patients), except for a representative electrogram; ICD electrograms with a T wave amplitude <10μV or ambiguous ending of the T wave (n=12 after excluding criteria 1 and 2); cardiac resynchroni-

zation therapy defibrillator or ICD with high ventricular pacing rate (n=10 in 1 patient), except for the electrograms taken at the time of DFT test; Medtronic ICD electrograms, except for those recorded at the time of DFT test (n=2 in 2 patients), because of battery longevity problems with monitoring mode. Therefore, a total of 153 ICD electrograms were included in the T-wave analysis, and classified into 3 groups (Table 1): (1) clinical VT (VTClinic; electrograms immediately before VT/ventricular fibrillation (VF) requiring ICD therapy; n=73, Fig 1); (2) induced VT (VTInduced; electrograms immediately after ICD therapy during DFT measurement; n=74, Figs 2A,B), and (3) inappropriate shocks (ShockInapp; electrograms immediately after an inappropriate ICD discharge; n=6, Figs 2C,D). The data were collected for 6 consecutive beats from electrograms of sinus

### Table 1 Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>VTClinic (n=73)</th>
<th>VTInduced (n=74)</th>
<th>ShockInapp (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>74</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.3±14.8</td>
<td>55.2±15.1</td>
<td>49.8±19.0</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>87.5</td>
<td>81.1</td>
<td>100</td>
</tr>
<tr>
<td>EF (%)</td>
<td>45.3±19.6</td>
<td>49.6±22.1</td>
<td>44.4±23.7</td>
</tr>
<tr>
<td>Medications (patients%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>10 (62.5%)</td>
<td>43 (58.1%)</td>
<td>3 (60.0%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3 (18.8%)</td>
<td>27 (36.5%)</td>
<td>1 (20.0%)</td>
</tr>
<tr>
<td>CRT-D</td>
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<td>5</td>
<td>0</td>
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<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic disease</td>
<td>5</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic VF</td>
<td>1</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic VT</td>
<td>5</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Non-ischemic VT</td>
<td>6</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>No of ICD Ts per patient (ICD shock/ATP)</td>
<td>3.1±7.8/24.8±18.1</td>
<td>2.8±1.2/0.0±0.0</td>
<td>1.2±0.5/0.0±0.0</td>
</tr>
<tr>
<td>Total no. of ICD Ts (ICD shock/ATP)</td>
<td>161 (48/113)</td>
<td>205 (205/0)</td>
<td>6 (6/0)</td>
</tr>
<tr>
<td>No. of EGM analyses Total (ICD shock/ATP)</td>
<td>73 (28/45)</td>
<td>74 (74/0)</td>
<td>0 (0)</td>
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<td>No. of electrical storms</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>No. of RFCA</td>
<td>4</td>
<td>8</td>
<td>0</td>
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</tbody>
</table>

Genetic disease includes long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and hypertrophic cardiomyopathy.

VT, ventricular tachyarrhythmia; EF, ejection fraction; CRT-D, cardiac resynchronization therapy with a defibrillator; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; Ts, treatment; ATP, anti-tachycardia pacing; EGM, electrogram; RFCA, radiofrequency catheter ablation.

![Fig1](image1.png) Electrograms from the VTClinical group. (A) Spontaneously induced fast VT in a patient with ischemic VT. (B) Electrogram during sinus rhythm immediately before the induction of VT, which corresponds to the electrogram in the gray box of (A), shows significant alternans of the T-wave amplitude. VT, ventricular tachyarrhythmia.
rhythm or atrial fibrillation with relatively regular RR intervals immediately before (VTClinic) or after (VTInduced and ShockInapp) the event. Because of the limited duration of ICD electrogram recordings, we evaluated ≥4 beats when the printed electrogram contained <6 beats of measurable T waves in the VTClinic group, and 6 beats of electrograms immediately after ICD shock in the VTInduced and ShockInapp groups, in order to have a longer period of T waves.

Data Analyses
To detect the subtle changes in T-wave amplitude or QT interval in the ICD electrograms, all the printed electrograms were scanned and converted to digital image files with a 300 dpi resolution. Those files were magnified using a regular ratio of 200% and analyzed by customized image software (Image-Pro). The digital measurements of the ICD electrograms were performed using a consistent method by a single student (J-H Park) who was unaware of the clinical information. The exact size of the T wave or QT interval was adjusted by the background scale grid of the electrogram. TWA, Tpte interval, and corrected QT interval (QTc) were measured on the magnified images. TWA was computed as the maximum difference in amplitude between the odd-beat and even-beat complexes of 6 beats on the electrogram from the highest point of the T wave to the lowest point of the same T wave and expressed as $\Delta T_{amp}$ (Fig 1). If the printed electrogram showed <6 beats of measurable TWA in the VTClinic group, at least 4 beats were measured. The Tpte interval was defined as the interval between the peak and end of the T wave (Fig 3). In the case of a biphasic T wave, the first peak was regarded as the T peak. The T wave end was defined as the intersection of the tangent of the T wave downslope with the baseline. The QT interval was defined as the time interval between the initial deflection of the QRS and the point at which a tangent drawn to the steepest portion of the terminal part of the T wave crossed the isoelectric line. To minimize the influence of heart rate on the parameters, we measured the RR interval from each of the episodes and calculated the corrected QT interval (QTc) with Bazett’s formula ($QTc = QT/RR$).

Statistical Analysis
Continuous data are expressed as the mean±SD. The $\Delta T_{amp}$, Tpte interval and QTc interval among the 3 groups (VTClinic, VTInduced, and ShockInapp), were compared by ANOVA. The differences between ischemic VT and non-ischemic VT in each group were compared using the Mann-Whitney rank-sum test. For the evaluation of the TWA and Tpte interval between VTClinic and VTInduced in the same patient, a Wilcoxon signed-rank test was used. Comparisons between clinical variables were made using chi-square analysis; P<0.05 was accepted as statistically significant.

Results
Patients Characteristics
Of the 74 patients, 24 had ventricular arrhythmias with a genetic basis (10 with Brugada syndrome, 7 with long QT syndrome, 6 with hypertrophic cardiomyopathy, and 1 with arrhythmogenic right ventricular cardiomyopathy), 13 were diagnosed with idiopathic VF, 16 had ischemic VT (13 with previous myocardial infarction, 3 with ischemic cardiomyopathy and 3-vessel coronary artery disease), and 21 had non-ischemic cardiomyopathy (Table 1). None of the ICD had been implanted for primary prevention purposes, except for the 3 patients with asymptomatic Brugada syndrome who had a type I Brugada ECG, family history of sudden cardiac death, and inducible VF by programmed
ventricular stimulation. The other 71 patients underwent ICD implantations for secondary prevention purposes. The left ventricular ejection fraction measured by transthoracic echocardiography was 48.1±22.6%. As summarized in Table 1, 73 episodes of VT were analyzed for T-wave changes. In VT Clinic, 15 VT/VF episodes occurred in 5 patients with ischemic VT, and 32 in 6 patients with non-ischemic heart failure. Electrical storms occurred in 1 patient in the ischemic VT group, 3 in the non-ischemic cardiomyopathy group, and none in the structurally normal heart group. All 26 episodes of VF were terminated successfully by the first shock. The mean age, left ventricular ejection fraction and left ventricular end-diastolic diameter did not significantly differ among VT Clinic, VT Induced, and Shock Inapp (Table 1).

TWA Immediately Before Clinical VT
Fig 4 shows representative examples of the TWA and Tpte interval measurements in the 3 groups. The TWA measured by the Δ Tamp of VT Clinic (61.1±26.3 μV) was significantly higher than that of VT Induced (36.2±27.5 μV, P<0.01) or Shock Inapp (34.7±19.3 μV, P<0.001; Fig 5A). However, the Tpte intervals were not significantly different among VT Clinic (89.8±29.4 ms), VT Induced (86.5±22.1 ms, P=NS), and Shock Inapp (79.4±20.9 ms, P=NS; Fig 5B). With respect to the QTc interval, there were no significant differences among VT Clinic (482.4±116.1 ms), VT Induced (468.6±83.1 ms, p

Fig 3. Measurement of the electrogram parameters. The ICD electrogram was magnified by customized software and the RR, QT, and Tpte intervals, and amplitude of the T waves were measured in 4 consecutive regular beats. ICD, implantable cardioverter defibrillator; Tpte, T wave peak-to-end interval.
Comparison of Clinical VT and Induced VT in the Same Patient

In 17 patients who experienced spontaneous VT/VF episodes, the ICD parameters of VT\textsubscript{Clinical} (n=73) were compared with those of VT\textsubscript{Induced} (n=17) in the same patient. Consistent with the analyses from the entire patient group, the $\Delta$Tamp was significantly greater in VT\textsubscript{Clinical} (57.7±27.0 $\mu$V) than VT\textsubscript{Induced} (40.5±23.8 $\mu$V, P<0.01; Fig 6A) in the same patient. The Tpte intervals were not different significantly in VT\textsubscript{Clinical} (81.7±30.2 ms) and VT\textsubscript{Induced} (77.3±22.6 ms, P=NS; Fig 6B) in the same patient.

TWA in Ischemic VT

In the VT\textsubscript{Clinical} group, 15 episodes (1 electrical storm) from 5 patients with ischemic VT, 32 episodes (4 electrical storms) from 6 patients with non-ischemic cardiomyopathy, and 26 episodes from 6 patients with channelopathy or idiopathic VF were compared. In the VT\textsubscript{Induced} group, the DFT measurements from the ICD electrograms in 16 patients with ischemic VT, 21 patients with non-ischemic cardiomyopathy, and 37 patients with channelopathy or idiopathic VF were compared. In the Shock\textsubscript{Inapp} group, a single episode of inappropriate shock in a patient with ischemic VT, 2 episodes in patients with non-ischemic cardiomyopathy, and 2 episodes in patients with channelopathy or idiopathic VF were analyzed and compared. The $\Delta$Tamp was significantly greater in the episodes of ischemic VT (70.5±27.4 $\mu$V) than in those of non-ischemic VT (51.3±19.6 $\mu$V, P<0.05) or channelopathy/idiopathic VF (46.6±27.4 $\mu$V, P<0.05) in the VT\textsubscript{Clinical} group (Fig 6C). However, the magnitude of $\Delta$Tamp in patients with organic heart disease (ischemic VT and non-ischemic VT) was not different when compared with those patients with channelopathy/idiopathic VF. In the VT\textsubscript{Induced} (37.2±26.1 $\mu$V vs 36.8±19.6 $\mu$V or 35.1±22.0 $\mu$V, P=NS) and Shock\textsubscript{Inapp} (32.7 $\mu$V vs 34.4±20.6 $\mu$V or 31.0±34.7 $\mu$V, P=NS) groups, there was no difference between ischemic VT and non-ischemic VT/channelopathy/idiopathic VF (Fig 6C). The Tpte interval did not differ between
the ischemic and non-ischemic VTs/channelopathy/idiopathic VF in the VT\text{Clinic} (91.0±23.8 ms vs 88.4±37.4 ms or 83.6±28.4 ms, P=NS), VT\text{Induced} (85.2±22.9 ms vs 83.4±29.5 ms or 85.2±18.7 ms, P=NS), and Shock\text{Inapp} (68.3 ms vs 76.6±13.5 ms or 71.1±22.6 ms, P=NS) groups (Fig 6D).

**Discussion**

We are the first to provide clinical evidence that TWA immediately before the spontaneous onset of VT/VF is greater than that after an ICD shock for induced VF or inappropriate shocks, by analyzing the stored electrograms from ICDs in humans. Additionally, the change in TWA was more prominent in patients with ischemic VT than in those with non-ischemic VT or channelopathy/idiopathic VF in the VT\text{Clinic} group. These findings suggest that the alternans of the repolarization plays an important role in the induction of VT in humans.

**Mechanisms of TWA and the Tpte Interval**

It has been reported that the beat-to-beat alterations in the duration and amplitude of the action potentials are a consistent precursor to VF in optical mapping studies using detailed measurements of conduction and refractoriness\(^1,11,19\) and simulation modeling studies.\(^{15}\) This phenomenon presents on the surface ECG as TWA,\(^{13,14}\) and has been extrapolated to the clinical setting as a microvolt TWA.\(^{15,16}\)

TWA results from action potential alternans at the cellular level. Several explanations of the mechanism of TWA have been proposed, such as sarcoplasmic reticulum calcium cycling\(^11,17\) and action potential duration restitution.\(^{11,18,19}\) However, VF never occurs without discordant alternans, which is a spatiotemporally discordant action potential duration with an opposite phase between neighboring cells. This phenomenon occurs because of the spatial heterogeneity of calcium cycling, intercellular uncoupling,\(^{20}\) and conduction velocity restitution.\(^{21}\) Therefore, the rapid rate of the action potential enhances the discordant alternans,\(^1\) provoking TWA. It has been reported that the onset heart rate of microvolt TWA provides clinical and prognostic value in cases of heart failure.\(^{12}\)

Various electrophysiologic profiles of the epicardium, endocardium, and mid-myocardial M cells have been reported,\(^2\) and full repolarization of the epicardium appears to coincide with the peak of the T wave and that of the M cells, with the end of the T wave.\(^{24}\) Therefore, a prolonged Tpte interval caused by an increased transmural dispersion of the repolarization might be arrhythmogenic.\(^{25-26}\) The T-wave vector is also generated by locally varying levels of repolarization in the heart.\(^{27}\) Although a prolonged Tpte interval has potential arrhythmogenic effects and is related to the TWA in some pathologic conditions,\(^{28}\) there are reports that the Tpte interval represents the total dispersion of the repolarization time of the entire heart rather than transmural dispersion.\(^{29}\) In this study, the Tpte of the ICD local electrogram was not significantly different in the VT\text{Clinic} group compared with the VT\text{Induced} or Shock\text{Inapp} groups.

**Characteristics of TWA on ICD Electrograms**

In this study, we measured the TWA and Tpte interval on ICD electrograms, and demonstrated that TWA immediately before the spontaneous onset of VT/VF is greater than that after induced VF or inappropriate ICD shocks. It has been reported that the maximum value of TWA is at least 10-fold greater on ICD electrograms than on surface eECG\(^{30}\) and based on human\(^2,30\) and animal studies,\(^3,31\) it has been proposed that analysis of ICD electrograms might be useful for determining TWA, and has potential as a clinically useful short-term predictor of VT/VF. By analyzing the electrograms obtained from an ICD in an ambulatory canine model of spontaneous VT and sudden death, Tsai et al.\(^3\) demonstrated that TWA was a useful predictor of impending VT, with a high specificity (95.3%) and positive predictive value (90.3%); however, that canine model had complete AV block. To the best of our knowledge, ours is the first study to analyze the TWA and Tpte intervals of ICD electrograms and correlate them to spontaneous clinical VT/VF in the clinical ambulatory setting. Although the microvolt TWA of a surface ECG requires an increasing heart rate to provoke TWA,\(^{2,22}\) the TWA of an ICD electrogram is easily recorded during a slow heart rate. TWA is known to be a precursor of VF, but the TWA of the ICD electrogram preceded not only spontaneous VF, but also clinical VT. However, it is unclear why TWA, a precursor of VF, was prominent immediately before monomorphic VT terminated by anti-tachycardia pacing.

**Clinical Implications**

Because TWA is caused by cellular repolarization alternans, which can cause dynamic instability of cardiac repolarization and predispose to VF, microvolt TWA on the surface ECG has been used clinically for stratification of patients at risk of sudden cardiac death. Microvolt TWA may detect high-risk patients for sudden death,\(^3\) and can be used to identify a subgroup of primary prevention ICD candidates who would not benefit from this procedure,\(^3,35\) which would improve the cost-effectiveness of ICD therapy. In contrast, there have been many arguments over the current evidence regarding the negative predictive value of microvolt TWA.\(^16,33\) Microvolt TWA is a subtle change on the surface ECG, and is hard to differentiate with the naked eye at low heart rates. In contrast, ICD electrograms can detect TWA at a voltage amplitude more than 10-fold higher than the surface ECG, even at low heart rates.\(^3\) Therefore, TWA analyzed on the ICD electrograms might be a useful parameter for the early detection of clinical VT/VF.

In the present study, the changes in TWA were more predominant immediately before the induction of ischemic VT than non-ischemic VT or channelopathy/idiopathic VF. These findings suggest a potential difference in the induction mechanism between ischemic and non-ischemic VTs/channelopathy/idiopathic VF. Compared with ischemic VT, the extent and distribution of the abnormal endocardial electrogram appear to be less in non-ischemic VT.\(^3\) In contrast, patch fibrosis, fractionated electrograms, and abnormal conduction patterns in the epicardium and a non-reentrant mechanism of VF are more common in patients with non-ischemic VT compared with ischemic VT.\(^3\) Therefore, the changes in TWA were more prominent in the ischemic VT group of the present study because we analyzed the ICD electrograms recorded from the right ventricular endocardial side.

We also found spontaneous variability in the magnitude of TWA; namely, differences in the TWA measurement in the same patient, when measured at a different times. Therefore, the development of an ICD algorithm that monitors the magnitude of TWA might be warranted for detecting the high-risk condition of VT/VF and to evaluate the effects of antiarrhythmic drugs in patients with ICD storms.\(^38-40\)

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**Study Limitations**

The classical definition of TWA is a T-wave change on every other beat in at least 6 consecutive beats. Because of the limited duration of ICD electrogram recordings, in the VTcinc group we evaluated ≥4 beats when the printed electrogram contained <6 beats with measurable T waves, and 6 beats on electrograms immediately after ICD shock in the VTInduced and Shocknapp groups, in order to have a longer period of T waves. Because we analyzed the local electrograms for the voltage difference from the right ventricular apex to the superior vena cava, it is uncertain whether TWA and the Tpte interval on the ICD electrograms represent the restitution properties and total dispersion of repolarization time of the entire heart. The effects of the cardiac autonomic nervous system could not be excluded in the VTcinc group, because the stored electrograms were recorded while ambulatory. In the VTInduced and Shocknapp groups, the post-shock calcium and membrane potential changes might have exaggerated the TWA or Tpte intervals but not in the VTcinc group. The small, limited amount of data warrants further study of ICD electrogram analysis.

**Conclusion**

The TWA from ICD electrograms was significantly greater immediately before the development of spontaneous VT, which indicates that alternans of repolarization plays an important role in the induction of VT in humans.

**Acknowledgements**

This work was supported by a 21C Frontier R&D Grant #SC1340 to Dr H-N Pak. We thank Mr John Martin for his linguistic assistance.

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