TRIPHASIC TIME DEPENDENCE OF PROGNOSTIC MARKERS
IN PATIENTS WITH SUSTAINED VENTRICULAR TACHYARRHYTHMIAS
AND CORONARY ARTERY DISEASE

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ARTHUR J. GOSSelin, M.D., AND JOHN W. LISTER, M.D.

To characterize the time dependence of prognostic markers for arrhythmia recurrence and arrhythmic death, 81 consecutive patients with documented sustained ventricular tachycardia (VT) or fibrillation (VF) and coronary artery disease (CAD) were analyzed. During follow-up, 28 patients had arrhythmia recurrence and 15 patients had sudden or arrhythmic death. Three different hazard phases were identified by fitting piece-wise exponential function curves to the distribution of both arrhythmia recurrence and sudden/arrhythmic death. An initial phase (0 to 6 months) had an arrhythmia recurrence rate of 2.1% per month; a second low-risk phase (6 to 38 months) had a rate of 0.88%; and a late high-risk phase (>38 months) had a rate of 2.2%. Sudden/arrhythmic death rates in each phase were 1.1%, 0.41%, and 1.7% per month, respectively. Separate Cox regression analyses within each phase identified the following independent predictors of arrhythmia recurrence: in the early phase, ejection fraction (EF) \( p = 0.033 \) and VT inducibility rank \( p = 0.048 \); and in the late phase, VT inducibility rank only \( p = 0.003 \). Likewise, independent predictors of sudden/arrhythmic death were: in the early phase, EF \( p = 0.049 \); and in the late phase, VT inducibility rank \( p = 0.008 \) and previous history of congestive heart failure \( p = 0.032 \).

In CAD patients with documented sustained VT/VF, the probabilities of arrhythmia recurrence and sudden/arrhythmic death each followed a similar triphasic hazard function. Highest risk occurred in the late phase and the VT inducibility rank was predictive of late phase events, while EF was a predictor of early phase events.

REDUCED left ventricular (LV) function and inducibility of ventricular tachycardia (VT) during electrophysiology study are strong predictors of a poor clinical outcome in patients with VT or ventricular fibrillation (VF).1–9 However, the changing influence, over time, of these and other markers predictive of arrhythmia recurrence and death has not been fully characterized. The purpose of this study was to examine the time dependence of various prognostic markers during long term follow-up in patients who have had documented spontaneous sustained VT or VF with underlying chronic coronary artery disease (CAD).

**METHODS**

**Study patients:** Electrophysiologic studies were performed in 81 consecutive patients who

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**Key words:**
- Ventricular tachycardia
- Programmed ventricular stimulation
- Prognostic marker
- Sudden death

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TABLE I  CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>81</td>
</tr>
<tr>
<td>Male / female</td>
<td>72 / 9</td>
</tr>
<tr>
<td>Age (years) Mean ± SD</td>
<td>65.2 ± 8.3</td>
</tr>
<tr>
<td>Range</td>
<td>37.9 – 81.6</td>
</tr>
<tr>
<td>Clinical documented ventricular arrhythmias:</td>
<td></td>
</tr>
<tr>
<td>Sustained VT</td>
<td>56</td>
</tr>
<tr>
<td>with hemodynamic compromise</td>
<td>35</td>
</tr>
<tr>
<td>without hemodynamic compromise</td>
<td>21</td>
</tr>
<tr>
<td>VF</td>
<td>25</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
</tr>
<tr>
<td>1-vessel coronary artery disease</td>
<td>33</td>
</tr>
<tr>
<td>2-vessel coronary artery disease</td>
<td>29</td>
</tr>
<tr>
<td>3-vessel coronary artery disease</td>
<td>19</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>68</td>
</tr>
<tr>
<td>History of more than 1 myocardial infarction</td>
<td>18</td>
</tr>
</tbody>
</table>

SD = standard deviation

TABLE II  VARIABLES ANALYZED

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex, family history of sudden death, clinically documented ventricular tachyarrhythmia, duration between ventricular tachyarrhythmia and EP testing, history of congestive heart failure, history of myocardial infarction, angina.</td>
<td></td>
</tr>
<tr>
<td>QRS duration, QT interval, QTc, A-H interval, H-V interval, ERP of RV, bundle branch block or intraventricular conduction defect.</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, LV aneurysm, number of diseased coronary arteries, LV end-diastolic pressure, LV end-systolic volume, LV end-diastolic volume.</td>
<td></td>
</tr>
<tr>
<td>Holter Lown grade in the control state, predischarge Holter Lown grade</td>
<td></td>
</tr>
<tr>
<td>Inducibility of VT in the control state, inducibility of VT after therapy, cycle length of induced VT.</td>
<td></td>
</tr>
<tr>
<td>Coronary bypass surgery, pacemaker, beta adrenergic blocker, digitalis.</td>
<td></td>
</tr>
</tbody>
</table>

EP = electrophysiology; ERP = effective refractory period; LV = left ventricle; RV = right ventricle.

had clinically documented sustained VT or VF, with underlying chronic CAD. The clinical characteristics of the patients are summarized in Table I. In all cases tachyarrhythmias were unassociated with acute infarction (<6 weeks), electrolyte abnormality, or other reversible causes. Cardiac catheterization was performed in 80 patients. Previous myocardial infarction had occurred in 68 patients with 18 having had more than one infarction. Significant coronary lesions were defined as >70% reduction of the luminal diameter. Presence of a LV aneurysm was determined angiographically according to the criteria of the Coronary Artery Surgery Study. The LV ejection fraction (EF) was calculated angiographically in 72 patients and by radio-nuclide-gated scan in 9. Baseline 24-hour Holter recordings were performed in all patients at least 5 half-lives after antiarrhythmic medication had been discontinued. Predischarge Holter recordings were obtained in 77 patients. Ventricular arrhythmias were classified according to the method of Lown and Wolf11 but grade 5 was excluded. Thirty clinical, electrophysiologic, and angiographic variables were analyzed and are listed in Table II.

Electrophysiologic testing: After informed consent, an initial electrophysiology study was carried out using standard techniques in the fasting non-sedated state. 5 half-lives after antiarrhythmic medication had been discontinued. The electrophysiology study was performed at a mean of 20.7 ± 9.9 (range 3 to 57) days after clinical documentation of sustained VT or VF.

### TABLE III  PREDICTORS OF ARRHYTHMIA RECURRENCE AND SUDDEN/ARRHYTHMIC DEATH FOR THE ENTIRE FOLLOW-UP PERIOD (COX REGRESSION ANALYSIS)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Arrhythmia recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inducibility rank*</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EF (%)*</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>More than 1 MI</td>
<td>0.019</td>
<td>0.010</td>
</tr>
<tr>
<td>Holter grade 4b</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Sudden/arrhythmic death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)*</td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>Inducibility rank*</td>
<td>0.036</td>
<td>0.015</td>
</tr>
<tr>
<td>Three-vessel CAD</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>Previous CHF</td>
<td>0.049</td>
<td>0.039</td>
</tr>
<tr>
<td>Holter grade 4b</td>
<td>0.031</td>
<td>0.031</td>
</tr>
</tbody>
</table>

*CAD = coronary artery disease; CHF = congestive heart failure; Coeff = coefficient; EF = ejection fraction; Exp = exponential; MI = myocardial infarction.

*Data analyzed using VT inducibility rank 0, 1 and 2.

*Data analyzed using continuous values.

The protocol used in our laboratory has been previously reported.\(^{12-14}\) Up to 3 ventricular extrastimuli at twice diastolic threshold were introduced during ventricular pacing at cycle lengths of 600 msec and 400 msec. For each extrastimulus, diastole was scanned to the point of ventricular refractoriness. Upon completion of the protocol, if VT or VF had not been induced, the stimulation protocol was repeated at a second right ventricular site. Responses to ventricular stimulation were defined as: sustained VT = tachycardia lasting longer than 30 seconds or requiring termination because of hemodynamic decompensation; nonsustained VT = 10 or more VT complexes that terminated spontaneously in less than 30 seconds. In patients who had inducible VT, serial electropharmacologic testing was carried out. According to the response in the control state and after therapy, VT inducibility was classified into 1 of 3 ranks: 0 = monomorphic VT was not inducible in the control state; 1 = monomorphic VT was inducible in the control state, but was not inducible after therapy; 2 = monomorphic VT was inducible both in the control state and after therapy. Patients were considered responders at the time of the electrophysiologic study if at least one type of therapy was effective.

**Treatment:** Clinical antiarrhythmic therapy was based on the results of electrophysiology studies. Patients who were noninducible in the control study were not treated with antiarrhythmic drugs, and all the patients in whom no conventional drug was effective during pharmacoelectrophysiologic studies received amiodarone.

**Follow-up:** Follow-up data were obtained at 3- to 6-month intervals via office visits, telephone calls, or letters. The follow-up period began on the day of the electrophysiologic study and ended on the date of last contact or death. In arrhythmia-free survival analysis, the follow-up period for the patients with an arrhythmia recurrence ended on the date of the first recurrence. Arrhythmia recurrence was defined as an electrocardiographically documented recurrence of either sustained VT or VF. Holter monitor recordings were repeatedly performed every 3 to 6 months. Nonsustained VT less than 30 seconds was not considered as an arrhythmia recurrence. Cause of death was classified as sudden/arrhythmic, non-arrhythmic cardiac, and non-cardiac. Sudden/arrhythmic death was defined as death within 1 hour from onset of symptoms, or death resulting as a consequence of electrocardiographically registered ventricular arrhythmias without myocardial infarction.

**Statistics:** Continuous values were expressed as mean ± 1 standard deviation. Stepwise logistic regression analysis\(^{15}\) was performed to analyze

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variables predictive of VT inducibility. Survival curves were calculated using the Kaplan-Meier product-limit method.\textsuperscript{16} Actuarial probabilities of survival and freedom from arrhythmias were expressed as a value $\pm$ 1 standard error. Multivariate analyses of variables for arrhythmia recurrence and sudden/arrhythmic death were performed by the Cox method\textsuperscript{17} for the entire follow-up period as well as for the 3 individually identified hazard phases. A probability (p) value $< 0.05$ was accepted as significant.

**RESULTS**

*Induced ventricular arrhythmias:* In the control state, sustained monomorphic VT was induced in 50 patients (62%), nonsustained monomorphic VT in 8 patients (10%), nonsustained polymorphic VT in 7 patients (9%), VF in 1 patient (1%), and a negative response was obtained in 15 patients (18%). Polymorphic VT and VF were considered as nonclinical responses. Logistic regression analysis of 21 clinical, electrophysiologic, and angiographic variables revealed the following to be significant in predicting inducibility of sustained monomorphic VT in the control state: EF, QRS interval, and documentation of sustained VT (EF and the QRS interval were analyzed using continuous values). Multivariate analysis revealed only EF (p = 0.039) to be an independent variable predictive of inducibility of sustained monomorphic VT (appendix).

Of 58 patients who had inducible monomorphic VT in the control state, 23 patients (40%) were noninducible after drug therapy. No clinical or laboratory variable was predictive by logistic regression analysis of inducibility or noninducibility after therapy.

*Treatment:* The 23 patients in whom monomorphic VT was not inducible in the control state were not treated with any antiarrhythmic
agent. Twenty-two patients in whom any given conventional drug was effective during pharmacoelectrophysiologic studies were treated with the same drug. The remaining 35 patients in whom no conventional drug was effective received oral amiodarone.

Clinical follow-up: The mean follow-up period was 28 ± 17 months (up to 63 months). The mean follow-up period for survivors was 31 ± 15 months, and for patients who died 22 ± 18 months. Twenty-two patients (27%) had recurrence of sustained ventricular tachyarrhythmias in the follow-up period. Of these, 9 patients died during their first recurrence (arrhythmic deaths), and 6 patients died suddenly (sudden deaths); thus the total number of sudden/arrhythmic deaths was 15 (19%). Ten patients (12%) died from non-arrhythmic cardiac causes, and 4 patients (5%) died from non-cardiac causes. The probability of freedom from arrhythmia recurrence after 4 years, follow-up for the study population was 49.7 ± 8.5%, and the probability of survival from sudden/arrhythmic death at this time was 65.4 ± 9.2%.

Analysis of predictors for the entire follow-up period (Table III): Univariate analysis revealed the following variables to be predictive of arrhythmia recurrence: EF (analyzed using continuous values), increased rank of VT inducibility (see Methods), previous history of more than one myocardial infarction, and Holter monitor grade 4b in the control state. None of the remaining variables were significantly related to arrhythmia recurrence, including type of clinical ventricular tachyarrhythmias, LV aneurysm, QT interval, predisharge Holter monitor grade, or coronary bypass surgery. Multivariate analysis showed that an increased VT inducibility rank (p < 0.001) and Holter monitor grade 4b in the control state (p = 0.010) were the only independent variables predictive of arrhythmia recurrence. Patients with rank 1 inducibility had a 2.4 fold higher risk of arrhythmia recurrence than patients with rank 0, and patients with rank...
2 inducibility had a 5.9 fold higher risk of arrhythmia recurrence than patients with rank 0 (coefficient = 0.89). Multivariate relative risk of Holter monitor grade 4b in the control state was 2.8.

Univariate analysis revealed the following variables to be predictive of sudden/arrhythmic death: EF, increased VT inducibility rank 3-vessel CAD, previous history of congestive heart failure, and Holter monitor grade 4b in the control state. Multivariate analysis revealed that increased VT inducibility rank (p = 0.015), previous history of congestive heart failure (p = 0.039), and Holter monitor grade 4b in the control state (p = 0.031) were the only independent variables predictive of sudden/arrhythmic death. Patients with rank 1 inducibility had a 2.2-fold higher risk of arrhythmic death than patients with rank 0, and patients with rank 2 inducibility had a 4.8-fold higher risk of arrhythmic death than patients with rank 0 (coefficient = 0.78). Multivariate relative risks for a previous history of congestive heart failure and Holter monitor grade 4b in the control state were 3.2 and 3.6, respectively.

Characterization of 3 different hazard phases: During arrhythmia free survival analysis, 3 different hazard phases were identified (Fig. 1): an early phase (0 to 6 months) in which the mortality slope was steep, an intermediate phase (6 to 38 months) in which the mortality rate became less steep, and a late phase (after 38 months) in which the mortality rate again increased (steeper slope). The individually fitted exponential curves for each of these 3 phases had a better fit than that obtained by a single curve plotted for the entire follow-up period. The residual mean square error (an indicator of accuracy of fit) total for the 3 curves was greatly reduced (=0.0015) compared with that of a single fit curve (=0.0345). The arrhythmia recurrence rate (% per month) during the early phase was 2.13 ± 0.24%; that during the intermediate phase was 0.88 ± 0.15%; and that during

the late phase was $2.24 \pm 0.60\%$. Sudden/arrhythmic death survival analysis also revealed 3 different hazard phases (Fig. 2). The residual mean square error total for these 3 curves was 0.00026, while that of a single fitted curve was 0.0126. The mortality rate (\% per month) during the early phase was $1.08 \pm 0.12\%$; that during the intermediate phase was $0.41 \pm 0.07\%$; and that during the late phase was $1.63 \pm 0.41\%$. The exact change points of the different hazard phases (cross points of the curves) were 6.1 and 38.2 months for arrhythmia-free survival analysis and 6.9 and 38.3 months for survival analysis.

Three hazard phases in subgroup: Triphasic arrhythmia-free curves were also identified in a subgroup of 22 patients treated with conventional antiarrhythmic drugs (Fig. 3), and in a subgroup of 35 patients treated with amiodarone (Fig. 4). In the 22 patients with noninducible VT in the control study, no analysis for hazard phases could be done because only 1 patient had VT recurrence, and only one died suddenly. The change points for the different hazard phases in the two subgroups were similar to those in the entire population. The subgroup receiving amiodarone treatment showed a lower hazard intermediate phase and a higher hazard late phase compared with the subgroup receiving conventional drugs.

Time-dependent analysis of predictors: Since the hazard rates differed markedly in the 3 phases, Cox regression analyses were performed separately for these 3 phases (Table IV). The variables predictive of arrhythmia recurrence during each phase were different. During the early phase (0 to 6 months), the independent predictors were EF ($p = 0.033$) and increased VT inducibility rank ($p = 0.048$). During the intermediate low-risk phase (6 to 38 months), no significant predictor of arrhythmia recurrence was
found. During the late high risk phase (>38 months), an increased VT inducibility rank (p = 0.003) was the only predictor of arrhythmia recurrence.

Analysis of predictors of sudden/arrhythmic death showed that EF (p = 0.049) was the only independent predictor during the early phase. During the intermediate low-risk phase, no predictor could be found. During the late high risk phase, an increased VT inducibility rank (p = 0.008) was the strongest predictor. A previous history of congestive heart failure (p = 0.032) was a second independent predictor.

DISCUSSION

New non-pharmacologic modes of therapy for life-threatening ventricular tachyarrhythmias, such as electronic devices,19-23 surgical,24-28 and non-surgical29 ablation, are rapidly being developed. The first generation of electronic devices, the implantable automatic cardioverter defibrillator, has proven itself to be highly successful in prolonging life in certain patients21-23. As treatment methods improve and become more widely available, selection of appropriate candidates for each of the specific treatments will depend upon an accurate stratification of each individual patient’s risks at the time of initial evaluation. Such risk stratification requires an in-depth analysis of predictors of arrhythmia recurrence and death, including how these predictors vary over time. The present study shows that the risk itself as well as the predictors of sudden/arrhythmic death may all vary over time during long-term follow-up.

Time-varying hazard phases: Death and other time-related events following an acute illness or a major surgical intervention are often distributed in a highly structured, time-varying pattern.30 Typically, risk is high immediately, falls rapidly to a much lower level, and later rises again. Recently such time-varying analysis has been applied to survival after acute myocardial infarction31,32 and after coronary bypass surgery.33 Waters et al.32 reported biphasic patient survival, with a high initial mortality rate which decreased after 1 year. Kirklin et al.33 found that the risk of dying after coronary bypass surgery followed 3 different hazard phases: an early phase of rapidly declining hazard which extended to about 6 months, an intermediate phase of low constant hazard, and a late phase of gradually increased hazard beginning about 3.5 years after surgery. In the present study, triphasic hazard functions were found both for arrhythmia recurrence and occurrence of sudden/arrhythmic death. The time of change between phases was virtually the same for arrhythmia recurrence and for sudden/arrhythmic death; namely, at 6 and 38 months. These change points are quite similar to those for patients in the post-coronary bypass surgery study.33 However, there was a marked difference in the mortality rate in the late phase, our study having a much higher rate. Whether this high risk late phase was due to the natural

history of this population or to the effects of therapy can not be answered in the present study.

**Time dependence of predictive markers:** The time-dependent hazard concept is useful because the risk itself, as well as the associated risk factors, might differ dramatically in each phase. During the early hazard phase (0 to 6 months), the strongest predictor of arrhythmia recurrence was EF as a continuous variable, and the only independent predictor of sudden/arrhythmic death was also EF. During the intermediate low risk phase (6 to 38 months), no variables predictive of arrhythmia recurrence or sudden/arrhythmic death could be found. Possible explanations for this are that the number of events (arrhythmia recurrence or death) might be small relative to the sample size or follow-up time, or alternatively the Cox model might be insensitive in detecting covariate effects in this particular phase. During the late phase (after 38 months), the only independent predictor of arrhythmia recurrence was an increased VT inducibility rank. The strongest predictor of sudden/arrhythmic death was also an increased VT inducibility rank. These observations suggest that patients with poor LV function and inducible VT are at high risk of dying from their arrhythmia in the early phase. Patients with inducible tachycardia also have a second high risk phase after 38 months irrespective of LV function. Bigger et al. studied patients after myocardial infarction and suggested that a low EF predicted early mortality (0 to 6 months), and a high grade of spontaneous ventricular arrhythmias predicted late mortality (after 6 months).

**Predictive markers for the entire follow-up period:** In contrast to the large number of studies concerned with overall survival, there have been relatively few analyses of factors predictive of arrhythmia recurrence. Denniss et al. reported inducibility of VT and pulmonary congestion as independent predictors of arrhythmia recurrence in patients after myocardial infarction. Freedman et al. found inducibility of VT and New York Heart Association functional class as predictors in their patients' post-cardiac arrest. In the present study, independent predictors of arrhythmia recurrence over the entire follow-up period (all 3 phases) were an increased VT inducibility rank and Holter monitor grade 4b in the control state. Independent predictors of sudden/arrhythmic death were an increased VT inducibility rank, Holter monitor grade 4b in the control state, and previous history of congestive heart failure. According to univariate analyses EF was a predictor of arrhythmia recurrence as well as sudden/arrhythmic death. However, by multivariate analysis EF was not an independent predictor over the entire follow-up period. One explanation is that there was a strong correlation between EF and inducibility of VT. Thus while EF was not an independent predictor over the follow-up period as a whole, it was the strongest independent predictor of arrhythmia recurrence and sudden/arrhythmic death during the early phase (<6 months). This time-dependent change in the risk factors themselves illustrates the importance of time phase analysis when comparing one study with another.

**Limitations:** In the present study, the follow-up period began on the day of the electrophysiologic study. The reason for selection of this time is that medical intervention was given from this date. Even if the onset time were set on the first date of clinically documented sustained VT or VF, the time-varying hazard phases would be almost the same since the variation in intervals between arrhythmia and the of study was small (mean time interval 20.7 ± 9.9 days).

Response to drug therapy in the electrophysiologic study did not include responses to amiodarone. Although the proper timing of the electrophysiologic study after amiodarone therapy is still uncertain, recent reports have indicated that it would be useful in evaluating amiodarone's antiarrhythmic efficacy. If the subgroup of patients still inducible after therapy had been divided into amiodarone responders and non-responders by a follow-up electrophysiology study, the VT inducibility rank might have been a more significant predictor of clinical outcome.

**Conclusions:** In a group of patients presenting with documented spontaneous sustained VT or VF with underlying chronic coronary artery disease, 3 different hazard phases were identified: an early high risk phase (0 to 6 months), an intermediate lower risk phase (6 to 38 months), and a late high risk phase (>38 months). The change-over points were virtually identical for arrhythmia recurrence and for sudden/arrhythmic death. Highest risks occurred in the late phase for both curves. Independent predictors of arrhythmia recurrence were: in the early phase EF and increased VT inducibility.
rank, and in the late phase only increased VT inducibility rank. Independent predictors of sudden/ arrhythmic death were, in the early phase EF, and in the late phase increased VT inducibility rank and previous history of congestive heart failure. These data suggest that patients with poor LV function and increased VT inducibility rank have a high risk of dying in the early phase from arrhythmia. Patients with increased VT inducibility rank also have a second very high risk phase after 38 months irrespective of LV function.

Acknowledgment

We wish to acknowledge the assistance of Minor Duggan, M.D., Robert Chen, Ph. D., and Mrs. Hazel Yon in the preparation of the manuscript.

Appendix

Model for determination of probability of inducible sustained monomorphic VT in the control state (Stepwise logistic regression analysis). Probability = (1 + exp(x))^−1
x = −1.83 + 0.04 (EF)
in which
EF is expressed as a continuous value (%)

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