Fragmented QRS as a Marker of Conduction Abnormality and a Predictor of Prognosis of Brugada Syndrome

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Background—Conduction abnormalities serve as a substrate for ventricular fibrillation (VF) in patients with Brugada syndrome (BS). Signal-averaged electrograms can detect late potentials, but the significance of conduction abnormalities within the QRS complex is still unknown. The latter can present as multiple spikes within the QRS complex (fragmented QRS [f-QRS]). We hypothesized that f-QRS could indicate a substrate for VF and might predict a high risk of VF for patients with BS.

Methods and Results—In study 1, we analyzed the incidence of f-QRS in 115 patients with BS (13 resuscitated from VF, 28 with syncope, and 74 asymptomatic). f-QRS was observed in 43% of patients, more often in the VF group (incidence of f-QRS: VF 85%, syncope 50%, and asymptomatic 34%, $P<0.01$). SCN5A mutations occurred more often in patients with f-QRS (33%) than in patients without f-QRS (5%). In patients with syncope or VF, only 6% without f-QRS experienced VF during follow-up (43±25 months), but 58% of patients with f-QRS had recurrent syncope due to VF ($P<0.01$). In study 2, to investigate the mechanism of f-QRS, we studied in vitro models of BS in canine right ventricular tissues ($n=4$) and optically mapped multisite action potentials. In the experimental model of BS, ST elevation resulted from a large phase 1 notch of the action potential in the epicardium, and local epicardial activation delay reproduced f-QRS in the transmural ECG.

Conclusions—f-QRS appears to be a marker for the substrate for spontaneous VF in BS and predicts patients at high risk of syncope. (Circulation. 2008;118:1697-1704.)

Key Words: death, sudden | arrhythmia | electrocardiography | genes | tachyarrhythmias

Clinical observations have shown that conduction abnormalities contribute to the occurrence of ventricular fibrillation (VF) in Brugada syndrome,1–3 possibly by providing a proarrhythmic substrate.4–7 The existence of late potentials (LPs) in the signal-averaged ECG suggests the presence of regions undergoing depolarization later than most of the ventricle and thus is a useful marker of conduction abnormalities.8 LPs have been reported to occur frequently in patients with Brugada-type ECG,2,3,6,7 although VF can also occur in patients without LPs.5 In addition to LPs, conduction abnormalities can exist within the QRS complex, manifested as a fragmented QRS (f-QRS). In patients with coronary artery disease, f-QRS can be caused by zigzag conduction in the infarcted myocardium, which results in multiple spikes within the QRS complex, and has been used as an indicator of non–Q-wave myocardial infarction and as a predictor of ventricular arrhythmia.9–11 We hypothesized that f-QRS can detect conduction abnormalities within the QRS complex in Brugada syndrome and can be used to identify high-risk patients. To evaluate the effects of the local epicardial conduction delay on the generation of f-QRS, we studied both patients with Brugada syndrome and in vitro canine right ventricular (RV) tissue preparations with drug-induced Brugada syndrome.

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Methods

Clinical Studies

The subjects of the present study were 113 male and 2 female patients with Brugada-type ECGs (mean age 48±12 years). A spontaneous type 1 ECG as detailed in the consensus report on Brugada syndrome12 was detected in all patients without drug provocation. We classified these patients into 3 groups: (1) VF group, for patients with VF at admission or within 24 hours after syncopal episodes; (2) syncope group, for patients who had syncope without detected VF; and (3) asymptomatic group, for patients who...
had only mild symptoms (such as palpitations or chest pain) or who were symptomless. No patients were from the same family. Echo-

cardiography and chest roentgenograms were performed in all patients, and no abnormalities were found.

Standard 12-lead ECGs (with 0- to 150-Hz filters) and additional V1 through V3 leads at the 3rd intercostal space were recorded simultaneously. ECGs acquired before initiation of drug therapy were used for analysis. We evaluated the RR interval, PQ interval, QRS width, QT interval, ST level at the J point, and number of spikes within the QRS complex in leads V1 through V3. ECGs were reviewed blindly by 3 authors (HM, SN, KN).

The presence of LPs was evaluated with a signal-averaged ECG (ART 1200EPX, noise level <0.3 μV, and high-pass filtering of 40 Hz with a bidirectional 4-pole Butterworth). The filtered QRS duration, root-mean-square voltage of the terminal 40 ms in the filtered QRS complex (RMS40), and duration of low-amplitude signals <40 μV in the terminal filtered QRS complex (LAS40) were measured by signal-averaged ECG. LPs were considered to be positive when 2 criteria were met: RMS40 <20 μV and LAS40 >38 ms.3

The risks of the electrophysiological study were explained to each patient, and written informed consent was obtained from all patients. The electrophysiological study was performed in 85 patients as reported previously.15,14 Coronary angiography was performed in all 85 patients and showed no sign of coronary artery disease. Induction of ventricular arrhythmia was initially attempted without the use of any antiarrhythmic drugs. The criterion for the induction of ventricular tachycardia or VF by programmed electrical stimulation from the RV apex, RV outflow tract (RVOT), or left ventricle (LV) with a maximum of 2 extrastimuli at 2 cycle lengths.

The gene analysis of SCN5A was performed in compliance with guidelines for human genome studies of the Ethics Committee of Okayama University. Informed consent was obtained from all patients. Analysis of SCN5A mutation was performed as reported previously.15 Twenty-seven exons and a portion of the introns 20 base pairs before and after exons of the SCN5A gene were amplified with previously reported intronic primers.19 SCN5A gene exon 1 is a noncoding region, and this region was not analyzed in the present study. Mutations were analyzed at least 3 times by independent polymerase chain reaction amplification and sequencing. Polymerase chain reaction products were subjected to single-strand conformation polymorphism analysis followed by direct sequence analysis.

Control Subjects
To exclude right bundle-branch block (RBBB) from the definition of f-QRS, we evaluated the ECGs of 80 control subjects who had RBBB but did not have Brugada-type ST elevation (64 males and 16 females, age 63 ± 15 years). The control group included 53 patients with complete RBBB and 27 with incomplete RBBB without obvious heart disease. The control group consisted of patients who were admitted to Okayama University for noncardiac disease and referred to our department because of the presence of RBBB noted during their ECGs. A physical examination, chest roentgenogram, and echocardiogram were performed in control patients and excluded the presence of heart disease. Standard 12-lead ECGs were recorded in the same way as in the Brugada patients and were evaluated for RR interval, PQ interval, QRS width, QT interval, ST level at J point, and number of positive spikes within QRS complex in leads V1 through V3.

In Vitro Studies
The investigation conforms to the “Guide for the Care and Use of Laboratory Animals” published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996). We prepared tissues with procedures similar to those used previously.16,17

Our previous clinical finding6 suggested the presence of a disturbance in local activation within the epicardium of the RVOT in Brugada syndrome. We isolated 4 neighboring pairs of transmural tissue preparations from the RV free wall of 4 male canine hearts and investigated the mechanism of f-QRS in drug-induced Brugada syndrome. The close anatomic relationship of the tissues in each pair minimized their differences in action potential (AP). Each tissue included a branch of the right coronary artery for perfusion. In each pair of tissues from the same heart, 1 tissue (the epicardial tissue) had only a 2- to 3-mm-thick epicardial layer (with the midwall and endocardium removed), and the other tissue (the transmural tissue) had an intact transmural wall. The prepared tissues were mounted parallel to one another in a warmed chamber with the epicardial tissue placed at the epicardial side of the transmural tissue and their cut-exposed transmural surfaces facing a mapping camera. We paced the endocardium of the transmural tissue and the epicardium of the epicardial tissue. Two silver electrodes were placed in the bath, 5 mm away from the epicardium of the epicardial tissue (anode) and from the endocardium of the transmural tissue (cathode), to register the compound transmural ECG of the tissue pair. Epi indicates epicardial; Endo, endocardial.

As we have done before,16,17 we induced a Brugada-type transmural ECG at 36.5 ± 0.5°C with pilsicainide (2.5 to 12.5 mmol/L, Dai-Ichi Suntory Pharma, Tokyo, Japan), pinacidil (1.25 to 12.5 mmol/L, Sigma Chemical, St. Louis, Mo), and terfenadine (2.0 mmol/L, Sigma Chemical). The doses of drugs were increased progressively and simultaneously in each pair of tissue preparations until both tissues developed the characteristic epicardial AP of Brugada syndrome, as reported previously.16,17,20 We also checked tissue healthiness by direct observations of tissue perfusion and of the amplitude, duration, and signal-to-noise ratio of the fluorescence signals during experiments. As noted previously,16-20 these procedures produced stable tissues during an experimental period of ~2 hours.
We statistically analyzed APDs at the recording sites along the epicardial and endocardial layers in the transmural preparations. Transmural dispersion of APD was calculated as the difference between the endocardial and epicardial APDs. The depth of the phase 1 notch of the AP relative to the height of phase 0 depolarization was used as a surrogate indicator of the effects of $I_{to}^{16,17,21,22}$

Statistical Analysis
Continuous data were expressed as mean±SD values. Comparisons among means were performed with 2-way ANOVA coupled with Scheffé’s test. Comparisons of 2 groups were made with Student’s $t$ test for unpaired data (patient data) and paired data (longitudinal experiment data), as appropriate. Fisher’s exact test was performed for the comparison of proportions among groups. A Mann-Whitney $U$ test was performed to compare the number of spikes within the QRS complex. Survival and event rates were determined with the Kaplan-Meier method and compared between groups with a 2-sample log-rank test. Significance was defined as $P<0.05$.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

ECG Characteristics of Control Subjects With RBBB

Most (64%) of the 80 control subjects with RBBB but without known heart disease had 2 to 3 spikes within the QRS complex in each of the right precordial leads (leads $V_1$ through $V_3$) and a sum of $5.9±1.0$ (median 6, range 4 to 8) spikes in all $V_1$ through $V_3$ (Table 1). To exclude these control subjects, we defined abnormal fragmentation within the QRS complex as $\geq4$ spikes in 1 or $\geq8$ spikes in all of the leads $V_1$, $V_2$, and $V_3$. Two control subjects (2.5%) were regarded as having f-QRS by these criteria.

f-QRS in Patients With Brugada Syndrome

With the above criteria, f-QRS was identified in 43% (50 of 115) of patients with Brugada syndrome, more frequently in the VF group than in the other groups ($P=0.0069$; VF group 85% [11/13], syncope group 50% [14/28], and asymptomatic group 34% [25/74]; Figure 2). In 11 patients (22%), f-QRS appeared in leads $V_1$ through $V_3$ in the 3rd intercostal space but not in the 4th intercostal space (Figure 3A). Therefore, f-QRS occurred preferably in the right precordial leads within
the high (3rd) intercostal space. Multiple spikes were observed in the mid QRS (12%), the upstroke part of the S wave (28%), and the late part of the QRS complex (60%; Figure 2). Spontaneous variations of f-QRS (changing magnitude or altering appearance and disappearance of multiple spikes) were observed in 72% of patients with f-QRS (VF group 91% [10/11], syncope group 57% [8/14], and asymptomatic group 72% [18/25]; Figure 4). f-QRS was detected on the first ECG recording in 43 patients (86%) and was detected for the first time on later recordings of the ECG in 2 patients with VF (0.5 months after the first ECG recording), 2 patients with syncope (0.5 to 1.5 months), and 3 patients in the asymptomatic group (0.2 months to 5 years). Reducing the low-pass filter frequency from 150 to 25 Hz masked the existence of f-QRS in all patients and eliminated f-QRS completely in 37 patients.

Compared with patients without f-QRS, patients with f-QRS had a longer RR interval (899±125 versus 986±226 ms, P=0.0087, respectively), a similar PQ interval (174±25 versus 174±23 ms, P=0.93), a longer QRS width and QT interval (Figure 5), and a longer HV interval (39±7 versus 44±7 ms, P=0.0015). LPs were common in patients with Brugada syndrome (overall group 71%, VF group 83%, syncope group 57%, and asymptomatic group 70%), with no statistical association with f-QRS [incidence of LP: f-QRS(+) 73%, versus f-QRS(−) 69%, P=0.68; Figure 6]. Programmed electrical stimulation frequently induced VF in patients with Brugada syndrome (VF group 67%, syncope group 48%, and asymptomatic group 52%). The existence of f-QRS was not associated with the incidence of VF induction [f-QRS(+) 58% versus f-QRS(−) 49%, P=0.56]. Among a total of 66 patients (26 with f-QRS and 40 without) screened, an SCN5A mutation was identified in 11 (17%; incidence of SCN5A mutations 22% in the VF group, 28% in the syncope group, and 10% in the asymptomatic group). An SCN5A mutation was strongly associated with f-QRS [incidence of SCN5A mutation: f-QRS(+) 34%, f-QRS(−) 5%, P=0.0027].

Eleven patients in the VF group, 12 in the syncope group, and 16 in the asymptomatic group received ICD therapy. During follow-up (43±25 months, range 0.5 to 161 months, median 25 months), 8 of the 28 patients in the syncope group and 8 of the 13 patients in the VF group experienced recurrent syncope due to VF, and each case was defibrillated successfully by the ICD or an external defibrillator; however, 1 patient died of brain damage and recurrent VF. Neither LPs, inducibility of VF by programmed electrical stimulation, nor mutation of SCN5A predicted recurrent syncope due to VF in the syncope and VF groups. Patients who had f-QRS often experienced recurrence of syncope due to VF within 4 years of the first episode of syncope or VF (Table 2; Figure 7). In contrast, the recurrence of syncope was rare in patients without f-QRS.

**In Vitro Model of f-QRS in Brugada Syndrome**

In controls, the transmural tissue had a normal APD gradient (epicardial APD 280±42 ms, endocardial APD 297±41 ms,
and a small phase 1 notch in the epicardial AP (depth of phase 1 notch 11±3% with a small J wave and a positive T wave in the transmural ECG). Delayed pacing in the epicardial tissue resulted in a bundle-branch block type of wide QRS complex in the transmural ECG (epicardial activation time in epicardial tissues: no delay 25±5 ms, delay 56±9 ms, \( P < 0.01 \); QRS width: no delay 35±9 ms, delay 78±12 ms, \( P = 0.0007 \)) but had no effect on the J wave (J-wave width: no delay 32±3 ms, delay 32±4 ms, \( P = 1.00 \); Figure 8A). There were no differences in the epicardial AP between the epicardial and transmural tissues.

The combination of pinacidil (10.0±2.0 \( \mu \)mol/L), pilsicainide (10.0±2.0 \( \mu \)mol/L), and terfenadine (2.0 \( \mu \)mol/L) induced Brugada-type ECGs with large J-ST elevation and a negative T wave, deepened the phase 1 notch of the epicardial AP (to 17±5% from 11±3%), and produced longer APDs in the epicardium than in the endocardium, which resulted in reversal of the transmural APD gradient (epicardial APD 292±52 ms, endocardial APD 269±52 ms, \( P = 0.039 \)). Delayed pacing of the epicardial tissue widened the QRS and induced multiple spikes during the late phase of the QRS complex in the transmural ECG (epicardial activation time in the epicardial tissues: no delay 32±3 ms, delay 32±4 ms, \( P = 1.00 \); Figure 8B).

### Discussion

#### New Observations

In the present study, we updated the definition of f-QRS to exclude control subjects who had RBBB without obvious heart disease. This definition differed from the previous definition of f-QRS, which was created for the diagnosis of

| Table 2. Clinical Characteristics and Outcomes of the f-QRS(+) and f-QRS(−) Groups |
|---------------------------------|---------------------|---------------------|--------|
| **f-QRS(+) (n=50)** | **f-QRS(−) (n=65)** | **P**     |
| Male/female, n | 50/0 | 63/2 | 0.222 |
| Age, y | 49±12 | 47±12 | 0.370 |
| Family history, n (%) | 18 (36) | 21 (32) | 0.680 |
| Therapy,* n (%) | | | |
| ICD | 28 (56) | 12 (18) | 0.006 |
| Ablation | 1 (2) | 1 (2) | 0.852 |
| Drugs | 11 (22) | 0 | <0.001 |
| Disopyramide | 2 | 0 |
| Quinidine | 4 | 0 |
| Bepridil | 5 | 0 |
| Outcome, n (%) | | | |
| SD | 1 (2) | 0 | 0.254 |
| Recurrent VF | 15 (30) | 1 (2) | <0.001 |
| New-onset VF | 1 (2) | 0 | 0.254 |
| Noncardiac death | 1 (2) | 0 | 0.254 |

*ICD indicates implantable cardioverter-defibrillator; SD, sudden death. *Therapy during follow-up.

Figure 7. Recurrence of syncope due to ventricular arrhythmia. A, Freedom from events for patients with and without f-QRS. Patients with f-QRS often experienced recurrent syncope due to VF within 4 years from the first episode. The existence of LPs (B), mutation of SCN5A (C), and VF induced by programmed electrical stimulation (PES; D) did not predict the recurrence of syncope.
myocardial infarction without consideration of bundle-branch block.\(^9\)–\(^11\) We demonstrated that the existence of f-QRS was associated with the prognosis of high-risk patients with Brugada syndrome who had experienced syncope or VF. Although LPs, induced VF, and gene mutation could not predict prognosis, f-QRS was statistically associated with the recurrence of syncope caused by malignant ventricular arrhythmia in patients with Brugada syndrome. Using an isolated canine RV tissue model of Brugada syndrome, we demonstrated that activation delay in the epicardium could reproduce similar f-QRS in the transmural ECG and thus provided a possible mechanism for our clinical observations.

**Conduction Delay in Brugada Syndrome**

The most important characteristic of Brugada syndrome is repolarization abnormality detected as ST elevation in the right precordial leads,\(^1\)–\(^12\) which correspond to the RVOT. Repolarization heterogeneity within the epicardium of the RVOT has been identified as the origin of ventricular arrhythmia (by phase 2 reentry) in Brugada syndrome.\(^16\)–\(^17\),\(^20\)–\(^22\) In addition to the repolarization abnormality, Brugada syndrome is associated with conduction disturbances.\(^2\)–\(^7\),\(^23\) Mutations of the sodium channel gene, \(SCN5A\), which are observed in 20% to 30% of patients with Brugada syndrome,\(^23\)–\(^25\) reduce the cardiac \(Na^+\) current.\(^24\),\(^25\) A reduced \(Na^+\) current not only deepens the phase 1 notch of the AP but also slows the conduction velocity and reduces the safety factor of conduction, which results in conduction abnormalities (with regional delay or block of conduction). It has been demonstrated in a model of Brugada syndrome that conduction abnormalities provide a substrate for the degeneration of polymorphic ventricular tachycardia into VF.\(^5\),\(^23\) Previously, intraventricular conduction abnormalities were observed and reported as RBBB and a prolonged HV interval in patients with Brugada syndrome.\(^1\)–\(^12\) Conduction delays and delayed epicardial activation were observed to cause LPs, especially during VF induction by programmed stimulation\(^2\)–\(^4\) and in the RVOT\(^6\)–\(^7\) in patients with Brugada syndrome. Although delayed activation within a small mass of ventricular tissue could produce LPs without having significant effects on the QRS complex, delayed activation in a larger ventricular mass can cause multiple spikes within the QRS complex, resulting in f-QRS.\(^9\)–\(^11\) The presence of f-QRS can be a predictor of prognosis for patients with a typical Brugada-type ECG.

**Characteristics and Interpretation of f-QRS in Brugada Syndrome**

f-QRS existed in \(\sim 40\%\) of patients with Brugada syndrome and was often observed in patients who had VF episodes. The preferential occurrence of f-QRS in the right precordial leads, especially in the higher intercostal spaces, suggests a localized conduction abnormality within the RVOT area. Because f-QRS consists of multiple small spikes, successful recording of f-QRS requires a low-noise amplifier that has a low-pass filter with a relatively high cutoff frequency (150 Hz). The use of a low-pass filter with a low cutoff frequency (>25 Hz), as has commonly been done to remove the electromyogram signal, can eliminate the f-QRS, underestimate the existence of the f-QRS, and cause pseudo day-by-day variation of the f-QRS.

The present observations of longer QRS width, QT interval, and HV interval in patients with f-QRS than in those without f-QRS suggest that Brugada patients with f-QRS had both prominent depolarization and repolarization abnormalities. Although local conduction slowing can be caused by myocardial fibrosis secondary to myocardial degeneration or myocarditis in addition to \(Na^+\) channel mutation, the present observation of dynamic and spontaneous changes in f-QRS suggests the presence of functional modulation of conduction rather than modulation by a fixed scarred myocardium, eg, by autonomic nerve activity, aging, temperature, or heart rate, in f-QRS.

The occurrence of LPs does not predict the recurrence of syncope, although it suggests the presence of excessive conduction delay (which lasts longer than the QRS) within a small tissue mass that produces the LP but does not affect the QRS complex. In contrast, multiple spikes within the f-QRS complex suggest the presence of an arrhythmogenic substrate that has multiple areas of conduction slowing (within the QRS complex) in a relatively large tissue mass (which affects...
the QRS). Thus, f-QRS suggests an increased probability of spontaneous VF and predicts a high risk of sudden cardiac death in patients.

Although SCN5A mutation is a clearly identified cause of conduction disease and Brugada syndrome,23,25 SCN5A mutation was identified in only 22% of the VF group and 33% of the patients with f-QRS in the present study. In contrast, f-QRS was identified in 85% of the Brugada patients in the VF group.

Effects of Activation Delay in Experimental Model of Brugada Syndrome

We studied 4 pairs of tissue preparations in the experiment study. To create local epicardial activation delay, we changed the timing of pacing in the thin epicardial tissue and recorded the transmural tissue. Therefore, the experiments represented activation delay, which may affect the ECG differently from the conduction delay in patients with Brugada syndrome.

Previous tissue models of Brugada syndrome (mostly single pieces of isolated RVOT tissues5,16,17,20–22) demonstrated the following mechanism of arrhythmogenesis: A reduced membrane Na+ current in combination with a prominent phase 1 notch of the AP causes the simultaneous presence of APs with and without a phase 2 dome within the epicardium of the RVOT, which leads to phase 2 reentry. In contrast, the present study created a new experimental model of Brugada syndrome with regional epicardial activation delay by the addition of a piece of thin epicardium to an intact transmural tissue, along with delayed stimulation of the thin epicardial tissue. The present model demonstrated that regional epicardial activation delay could cause f-QRS in Brugada syndrome similar to clinical observations. On the basis of the results of the present study, we conclude that f-QRS and the underlying conduction disturbance play an important role in the spontaneous occurrence of VF and that f-QRS is a simple and powerful indicator of prognosis of high-risk patients with Brugada syndrome.

Study Limitation

We defined f-QRS based on data from the control subjects with RBBB but without obvious heart disease. The incidence of f-QRS at the 4th intercostal space was high in patients with Brugada syndrome (39 patients). We only recorded the standard 12-lead ECG with V1 through V3 in the 4th intercostal space, not in the 3rd intercostal space, in control subjects. Therefore, the presence of f-QRS in the V1 through V3 in the 3rd intercostal space in control patients is unknown.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Brugada syndrome is characterized by coved-type ST elevation (type I ECG described in the consensus report on Brugada syndrome) in the right precordial leads, which represents abnormal repolarization in the right ventricle. Spontaneous type I ECGs and a history of syncope have been reported as prognostic indicators. Patients with Brugada syndrome also have a depolarization abnormality that can be detected as right bundle-branch block, HV-interval prolongation, late potentials by signal-averaged electrogram, and delayed potentials at the epicardium. The contribution of these abnormal depolarization indices to prognosis is controversial, and indeed, the existence of late potentials did not predict prognosis in the present study. We focused on a new marker of depolarization abnormality, fragmented QRS (f-QRS), which is the presence of multiple spikes within the QRS complex. f-QRS has been reported in patients with myocardial infarction and can detect myocardial damage and arrhythmia occurrence. Of 115 patients with Brugada syndrome, f-QRS existed in 43%, more frequently in patients with prior ventricular fibrillation (VF) than in patients with syncope or asymptomatic patients. Patients with f-QRS who had prior episodes of VF or syncope without detected VF often experienced recurrent VF within 4 years. These results suggest that patients who experienced syncope without detected VF who had f-QRS were at increased risk for a subsequent arrhythmic event and should be considered for an implantable cardioverter defibrillator. In patients with prior VF, the existence of f-QRS also indicates a risk of recurrent VF, including arrhythmic storm.
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