Right Bundle Branch Block, Right Precordial ST-Segment Elevation, and Sudden Death in Young People

Domenico Corrado, MD; Cristina Basso, MD, PhD; Gianfranco Buja, MD; Andrea Nava, MD; Lino Rossi, MD; Gaetano Thiene, MD

Background—Patients with the ECG pattern of right bundle branch block and right precordial ST-segment elevation may experience sudden death in the setting of either arrhythmogenic right ventricular cardiomyopathy (ARVC) or a functional electrical disorder such as Brugada syndrome.

Methods and Results—Among a series of 273 young (≤35 years) victims of cardiovascular sudden death who were prospectively studied from 1979 to 1998 in the Veneto Region of Italy, 12-lead ECG was available in 96 cases. Thirteen (14%; 12 males and 1 female aged 24±8 years) had right precordial ST-segment elevation, either isolated (9 cases) or associated with right bundle branch block (4 cases). At autopsy, all patients had ARVC (92%) except one, who had no evidence of structural heart disease. Compared with the 19 young sudden death victims with ARVC and no ST-segment abnormalities from the same series, those with ARVC and right precordial ST-segment elevation included fewer competitive athletes (17% versus 58%; \( P = 0.03 \)), more often died suddenly at rest or during sleep (83% versus 26%; \( P = 0.003 \)), and showed serial ECG changes over time (83% versus 0; \( P = 0.015 \)), polymorphic ventricular tachycardia (33% versus 0; \( P = 0.016 \)), and predominant fatty replacement of the right ventricular anterior wall (58% versus 21%; \( P = 0.05 \)).

Conclusions—Right precordial ST-segment elevation was found in 14% of young sudden death victims with available ECG. It mostly reflected underlying ARVC with predominant right ventricular anterior wall involvement and characterized a subgroup of patients who share with Brugada patients the propensity to die from non–exercise-related cardiac arrest and to exhibit dynamic ECG changes and polymorphic ventricular tachycardia. (Circulation. 2001;103:710-717.)

Key Words: arrhythmogenic right ventricular dysplasia n fibrillation n death, sudden

Ventricular fibrillation and sudden death may occur in patients with the ECG pattern of right bundle branch block (RBBB) and right precordial ST segment elevation.1-5 The etiopathogenesis of these ECG abnormalities and the pathophysiology of the ventricular arrhythmias leading to the cardiac arrest are still under investigation. The ECG pattern was first described in young patients with clinical and pathological evidence of arrhythmogenic right ventricular cardiomyopathy (ARVC),1 with or without involvement of the specialized conduction system.1,2 More recently, a series of conditions in which ventricular fibrillation occurred without clinically demonstrable organic heart disease were reported to share the same ECG pattern. These primary electrical heart diseases include Brugada syndrome,2 vagally induced idiopathic ventricular fibrillation,4 and sudden unexplained death syndrome of young Southeastern Asians.5 There are still many unanswered questions regarding the epidemiological relevance of this ECG pattern on the risk of sudden death in young people, as well as on the relationship between the underlying conditions.

The aim of the present study was to assess the prevalence of this ECG marker for sudden death in young people, to investigate the underlying substrates, and to define the clinical profile of the sudden death victims in a large consecutive series of young people who died suddenly in the Veneto Region of Italy from 1979 to 1998.

Methods
A clinicopathological study on sudden death in young people was performed in the Veneto Region of Italy from 1979 to 1998. Sudden death in young people was defined as unexpected death as a result of natural causes in which loss of all functions occurred instantaneously or within 1 hour of the onset of collapse symptoms in a person aged 35 years or younger; cases of sudden infant death syndrome were ruled out. The study protocol has been reported in detail elsewhere.5,6

Morphological Protocol
Macroscopic examination included measurements of heart weight, chamber size, and wall thickness and inspection of the coronary arteries (patency, origin, and course) and valves. The following ventricular regions were systematically examined: inflow tract, outflow tract, apex, posterolateral and anterolateral walls of both ventricles, and the interventricular septum. Several coronary arterial

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segments and full-thickness blocks of myocardium were removed for histological examination from each ventricular region in a plan parallel to the short and long axis of the ventricles. All sections (5 to 7 μm thick) were stained with hematoxylin and eosin, Weigert-van Gieson, and trichrome Heidenhain (azan) techniques. The specialized conduction system was studied by serial sections, as previously reported.8

ARVC
ARVC was diagnosed in the presence of gross and/or histological evidence of regional or diffuse fatty or fibrofatty replacement of the myocardium of the RV free wall reaching the endocardium (ie, transmural) in the absence of other known cardiac or noncardiac causes of death.9 Pathological findings were classified according the following 2 morphological patterns6,9: the “fatty” variant was characterized by fatty replacement of the myocardium, with or without tiny interstitial fibrosis, predominantly in the RV anterior wall from the apex to the outflow tract, and the “fibrofatty” pattern was characterized by fatty tissue and replacement-type fibrosis, with involvement of the RV posteroinferior wall.

Mechanism of Sudden Death
Sudden death was considered cardiovascular in origin when the primary cause leading to cardiac arrest was found in the heart or great vessel or other noncardiac causes were excluded. In the absence of mechanical causes of cardiac arrest, such as rupture of the heart or aorta or pulmonary thromboembolism, the mechanism of cardiovascular sudden death was presumed to be arrhythmic.

ECG Analysis
For the purposes of the present study, the analysis of 12-lead ECG focused on heart rate; duration of PR and QT intervals; duration, axis, and morphology of the QRS complex; epsilon waves; degree and pattern of ST-segment displacement; T-wave configuration; and ventricular arrhythmias. Duration of both QRS complex and QT interval was measured in lead II. A normal QT interval was defined as a rate-corrected (QTc by Bazett’s formula) interval ≤440 ms.9 Serial analysis of ECG changes over time was performed in sudden death victims with ≥2 available ECG tracings.

Right precordial ST-segment elevation was defined as a ST-segment that originated from a late R wave and was displaced upward ≥0.1 mV from the isoelectric line in leads V1 to V2/V3. T-wave configuration was classified according to the direction of the deflection as positive, negative, or biphasic. The diagnosis of RBBB and left axis deviation was made according to the criteria of the World Health Organization/International Society of Cardiology Task Force.10

Clinicopathological Correlations
Patients with the ECG pattern of right precordial ST-segment elevation, with or without RBBB aberrancy, in the absence of coronary artery disease were selected for clinicopathological correlation and compared with the group of ARVC patients without right precordial ST-segment elevation from the same series, with respect to a series of clinical and morphological variables.

Statistical Analysis
Continuous variables were expressed as mean±SD. Fisher’s exact test was used to assess the significance of differences between subgroups. A 2-tailed P<0.05 was considered statistically significant.

Results
From January 1979 to June 1998, 273 consecutive cases of cardiovascular sudden death in young people that occurred in the Veneto Region of Italy were investigated. The mechanism of sudden cardiac arrest was arrhythmic in 236 cases (86%), mechanical in 19 (7%), and unexplained in 18 (7%; Table 1). A basal 12-lead ECG was available in 96 of the 273 sudden death victims (36%).

Clinico-ECG Characteristics of Victims With Right Precordial ST-Segment Elevation
Thirteen of the 96 patients with available ECGs (14%), 12 males and 1 female aged 10 to 35 years (mean, 24±8 years), had nonischemic ECG changes that manifested as ST-segment elevation in leads V1 to V2/V3. All patients had sinus rhythm with a rate-corrected QT interval within normal limits; 2 patients had first-degree atroventricular (AV) block. A true RBBB was documented in 4 patients (33%), and it was associated with left axis deviation in 2 (Figure 1A); the other 9 patients had a RBBB-like pattern that was limited to the right precordial leads and was associated with a high takeoff ST-segment elevation (Figure 2A). The mean QRS duration was 95±8 ms in patients with isolated ST-segment elevation and 115±8 ms in those with associated RBBB.

Sudden death was unrelated to physical exercise in all but 2 victims (who were competitive athletes), and it occurred at rest in 9 patients or during sleep in 2. Five patients had a familial history of premature sudden death. Twelve-lead ECG was obtained after episodes of syncope (5 patients) or aborted sudden death (1 patient); in 5 of these patients, ventricular fibrillation (1 case) and nonsustained polymorphic ventricular tachycardia, which occurred at rest with a mean cycle length of 238±14 ms (4 cases), were documented at the time of aborted sudden death or by Holter monitoring after syncopal episodes, respectively. Seven sudden death victims were previously asymptomatic and the ECG was recorded during routine or screening cardiovascular evaluation. No patients were taking antiarrhythmic drugs when the ECG was recorded.

Dynamic changes over time of ST-segment elevation, up to nearly complete ECG normalization, were observed in 5 of

### Table 1. Cardiovascular Causes of Sudden Death in 273 Young Victims

<table>
<thead>
<tr>
<th>Causes</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmic sudden death</td>
<td>236</td>
<td>86</td>
</tr>
<tr>
<td>Obstructive coronary artery disease</td>
<td>54</td>
<td>20</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>26</td>
<td>9.5</td>
</tr>
<tr>
<td>Conduction system disease</td>
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<td>8</td>
</tr>
<tr>
<td>Congenital coronary anomalies</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>18</td>
<td>6.5</td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Acquired nonatherosclerotic coronary artery disease</td>
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<td>3</td>
</tr>
<tr>
<td>Postoperative congenital heart disease</td>
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<td>2</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
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<td>1</td>
</tr>
<tr>
<td>Mechanical sudden death</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Aortic rupture</td>
<td>15</td>
<td>5.5</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Unexplained sudden death</td>
<td>18</td>
<td>7</td>
</tr>
</tbody>
</table>
Figure 1. A 35-year-old man who died suddenly at rest. A, Baseline 12-lead ECG showing first degree AV block, left axis deviation, high takeoff ST-segment elevation in V1 to V3, and true RBBB, as indicated by a widened S-wave in left lateral leads. B, Serial changes over years of right precordial repolarization abnormalities with transient near-normalization unmasking an epsilon wave in lead V1 on
the 6 patients in whom ≥2 recordings were available (Figures 1B and 2B); these changes were recorded at similar heart rates, and no rate-dependent changes were observed. Ventricular arrhythmias with a left bundle branch block pattern had been documented on basal ECG, Holter monitoring, or exercise testing in 7 cases, and they consisted of isolated premature ventricular contractions (3 patients) and episodes of nonsustained (2 patients) or sustained (2 patients) ventricular tachycardia, all of which occurred at rest with a mean cycle length of 327 ± 4 ms. Among 5 patients (all symptomatic) who underwent angiography and/or echocardiography, RV abnormalities were detected in 3.

Pathological Findings in Victims With Right Precordial ST-Segment Elevation
Post-mortem investigation showed an organic heart disease in all but 1 subject, who had a morphologically normal heart. The structural changes in the remaining hearts were consistent with ARVC. The heart weight ranged from 310 to 580 g (mean, 390 ± 15 g). Mild to moderate RV dilatation was seen in 7 of 12 hearts. Ventricular bulgings were identified in 7 hearts at ≥1 of the following RV locations: outflow tract (7 cases), posteroinferior wall (beneath the posterior leaflet of the tricuspid valve; 3 cases), and apex (3 cases). Nine bulgings had a translucent wall. Seven heart specimens

Figure 2. A 27-year-old man who died suddenly while sleeping. A, Baseline 12-lead ECG showing right precordial ST-segment elevation with high takeoff from a late R wave. B, Day-to-day changes of right precordial ST-segment pattern, which exhibits maximum displacement upward on March 22, 1996. The patient died 1 week later. C, Panoramic histological view of RV myocardium disclosing full-thickness fibrofatty infiltration. Myocardial atrophy is predominantly located in subepicardial and midmural layers; subendocardium and trabeculae show areas of residual myocardium with focal spots of replacement-type fibrosis. Trichromic Heidenhain stain was used at magnification of 3×.
showed a fatty morphological pattern characterized by myocardial replacement predominantly located in the RV anterior wall, and 5 had a fibrofatty variant with involvement of the posteroinferior wall. In all cases, histological examination showed a full-thickness involvement of the RV free wall (Figures 1C and 2C). The replacement of the myocardium was predominantly located in the subepicardial and midmural layers, where islands of residual myocardium appeared interspersed with fatty or fibrofatty tissue; the subendocardium and the trabeculae showed a greater amount of surviving myocardium with degenerative changes of myocytes and increased interstitial or replacement-type fibrosis (Figures 1C, 1D, and 2C). The left ventricular myocardium was substantially spared and only exhibited occasional focal spots of fatty and/or fibrous tissue, mostly in the subepicardial layer, in 5 cases. Multifocal inflammatory infiltrates consisting of interstitial collections of lymphocytes and/or macrophages associated with myocyte necrosis were seen in 8 hearts.

At the histological examination of the conduction system, the sinus node and sinus node approaches were normal except in 2 cases with mild fibrosis. The AV node and atrionodal approaches were normal. In 3 of 4 cases with ECG evidence of true RBBB, there was moderate to severe fibrosis of the branching bundle and proximal right bundle branch (Figures 1E and 1F), which appeared interrupted in one. In this latter case, there was a slight fibrous atrophy of the proximal tract of the left bundle branch.

Comparison Between ARVC Victims With and Without ST- Segment Elevation
Among 36 young patients who died suddenly from ARVC (see Table 1), 12-lead ECG was available in 31 (86%). Twelve patients had right precordial ST-segment elevation (see above); in the other 19, the ECG either showed inverted T waves from V1 to V2/V3 without ST-segment elevation (n=15) or was normal (n=4). Tables 2 and 3 show the correlation between ARVC victims with and without ST- segment elevation in right precordial leads with respect to a series of clinical, morphological, and ECG findings. ECG were examined serially in 6 patients with ST-segment elevation and in 5 patients without ST-segment elevation who had a mean of 5±2 and 6.0±2 ECG recordings, respectively. The time interval over which the serial ECGs were examined was 23±17 and 25±15 months, respectively. The ARVC victims with right precordial ST-segment elevation included fewer competitive athletes (17% versus 58%; P=0.03), more often experienced sudden death unrelated to physical exercise (83% versus 26%; P=0.003), showed dynamic changes in right precordial ventricular repolarization (83% versus 0; P=0.015) and polymorphic ventricular tachycardia (33% versus 0; P=0.016), and had a fatty morphological pattern with prevalent myocardial replacement of RV anterior wall (58% versus 21%; P=0.05) compared with the remaining ARVC victims with available ECGs that did not show ST-segment changes.

Discussion
Major Findings of the Present Study
In this study, the pattern of RBBB and/or right precordial ST-segment was found in 14% of young sudden death victims with available ECG. The ECG abnormalities more often reflected a structural RV muscle disease consistent with ARVC (92%) with predominant RV anterior wall involvement than a morphologically normal heart. The distinctive repolarization changes characterized a subgroup of patients with ARVC who peculiarly died of non–exercise-related cardiac arrest and had previously exhibited dynamic ECG changes and polymorphic ventricular tachycardia, which are all clinical and ECG features typically observed in Brugada and related syndromes. These findings show an overlap in clinical manifestation and mechanisms of ventricular arrhythmias between patients with ARVC and Brugada syndrome.

ECG Abnormalities
Most of the patients with the syndrome of RBBB and right precordial ST-segment elevation described in the literature were of South Asian origin.5 The present study provides a prevalence of 14% of the pattern of RBBB and/or right precordial ST-segment among the ECG recordings obtained from a homogeneous series of young sudden death victims from the Veneto Region of Italy, suggesting that this ECG abnormality is not rare in Western countries and should be considered a worldwide marker of arrhythmic sudden death.

A widened S-wave in left lateral leads, which is typical for RBBB,10 was observed in only 4 of the patients with right precordial ST-segment elevation (28%). This indicates that although the QRS complex/ST segment morphology in V1 to V2/V3 mimics RBBB, this pattern is limited to right precordial leads reflecting either a localized RV parietal (rather than a septal) block1 or a J-point elevation associated with a high takeoff ST segment elevation.11 Serial changes of the ST-segment elevation over time, up to transient normalization of the tracing, were noted in >80% of cases. Therefore, the previous concept that dynamic ECG changes are the proof against an underlying structural substrate12–14 is not in keeping with the present findings showing that ECG variations over time occur even in patients with organic heart disease, namely ARVC proven at autopsy. The variability of the autonomic nervous system activity modulating a conduction defect or a repolarization abnormality in the setting of a structural RV myocardial disease is the most likely explanation for these transient ECG changes.14 Of note, dynamic changes of repolarization were never observed in ARVC patients without ST-segment elevation. Although statistically significant, this difference may have been overestimated because of the small number of both patients with serial ECG and ECG serially examined in each patient from both subgroups.

Peters et al15 recently reported that right precordial ST- segment elevation was not a risk factor for sudden death in patients with ARVC. However, in contrast to the present study, their analysis did not focus on high takeoff ST-segment elevation and included any nonspecific upward displacement
of the ST-segment accompanying right precordial T-wave inversion.

**Pathological Substrates**

Morphological studies in sudden death victims with the ECG pattern of RBBB and right precordial ST-segment elevation are rare and limited to case reports.\(^1\,^{3}\,^{16}\,^{17}\) However, when available, autopsy findings consistently show fibrofatty replacement of RV myocardium, frequently associated with a conduction system pathology.\(^1\,^{3}\,^{16}\,^{17}\) We previously studied 16 members of an affected family and demonstrated that structural abnormalities of both the RV myocardium and the specialized conduction system may present clinically as RBBB, right precordial ST-segment elevation, and sudden death.\(^3\) The present study extended our earlier observations and showed that a structural heart disease, namely ARVC, was the most prevalent substrate underlying the above ECG abnormalities in a homogeneous series of young sudden death victims. A functional electrical disease (like Brugada syndrome) could have accounted for ECG abnormalities and arrhythmic cardiac arrest in the only heart that did not exhibit any structural abnormality. These findings may be reasonably explained by the accurate morphological protocol for investigation of the RV in the present study.

In patients with transient right precordial ST-segment elevation and vagal-induced ventricular fibrillation, Kansamuki et al.\(^2\) used body-surface mapping to demonstrate conduction abnormalities that were predominantly localized to the RV.
between the anterior RV wall and the outflow tract; they advanced the hypothesis that this clinical condition may reflect an early subclinical stage of ARVC characterized by a segmental lesion. The pathological findings in our sudden death victims with right precordial ST-segment were all consistent with a widespread form of ARVC that did not differ, in terms of cardiomegaly and extent of myocardial atrophy with fibrofatty replacement, from that without ST-segment abnormalities. However, ARVC patients with right precordial ST segment elevation did tend to have a fatty morphological pattern, characterized by myocardial replacement predominantly located in the RV anterior wall. This pathological finding may account for the clinical, ECG, and pathophysiological differences among the 2 patient subgroups.

Kirschner et al\textsuperscript{18} performed autopsy studies in South Asian victims of sudden unexplained death syndrome in 1986 when the morphological features of ARVC were still incompletely known and found structural changes in the specialized conduction system in 14 of the 18 hearts. In the present study, the histological examination of the conduction system showed the involvement of the branching bundle and proximal right bundle branch, ranging from mild fibrous atrophy to interruption, in 3 of 4 patients with the ECG pattern of true RBBB. These findings confirm that a structural His-Purkinje system rupture, in 3 of 4 patients with the ECG pattern of true RBBB.

Mechanisms of ST-Segment Elevation and Ventricular Arrhythmias

The ventricular arrhythmogenicity of ARVC is traditionally explained by the existence of islands of surviving myocardium surrounded by fibrofatty tissue, which acts as a substrate for an inhomogeneous intraventricular conduction predisposing to re-entrant ventricular arrhythmias.\textsuperscript{19} These depolarization abnormalities are mediated by a sympathetic mechanism that distinctively predispose to sudden death during enhanced adrenergic drive, such as that during physical activity.\textsuperscript{5,7,19} Instead, in the majority of patients with Brugada and related syndromes, the malignant ventricular arrhythmias occur at rest and, in many cases, at night\textsuperscript{2,4,5,13,20}; a sudden rise of vagal activity reportedly occurs just before ventricular fibrillation episodes.\textsuperscript{4} The results of the present study suggest that increased vagal activity and/or withdrawal of sympathetic activity may even play a significant arrhythmogenic role in the subset of ARVC patients with right precordial ST segment elevation who show a propensity to die suddenly at rest or during sleep. Like patients with Brugada syndrome, the presumed arrhythmogenic mechanisms in this group of patients is a vagal-induced ventricular fibrillation originating in the setting of a dispersion of RV repolarization.

Studies by Antzelevitch and others\textsuperscript{11,21,22} provided experimental evidence that a heterogeneous distribution of action potential duration across the RV wall may be the basis for both a right precordial ST segment elevation and rapid ventricular arrhythmias (polymorphic ventricular tachycardia or ventricular fibrillation), which may be precipitated by enhanced parasympathetic activity. A series of pathological conditions or pharmacological interventions, such as sodium channel blockade, may result in the loss of the action potential dome in the epicardium (but not in the endocardium) and provoke a transmural current flow from epicardium to endocardium, which accounts for ST-segment elevation. Moreover, propagation of the action potential dome from sites at which it is maintained to sites at which it is abolished may result in local reexcitation (phase 2 reentry), and this may induce very rapid ventricular arrhythmias in the form of polymorphic ventricular tachycardia or ventricular fibrillation. Litovsky and Antzelevitch\textsuperscript{23} demonstrated that acetylcholine facilitates the loss of the action potential dome and accentuates both ST-segment elevation and dishomogeneity of ventricular repolarization by suppressing the calcium current and/or augmenting the potassium current.

In Brugada syndrome, a genetically induced sodium channel dysfunction resulting in reduced current density is the most likely mechanism of the loss of the epicardial action potential dome with transmural dispersion of repolarization, which in turn may predispose to the development of ventricular fibrillation.\textsuperscript{24} In the present study, the ARVC lesions predominantly involved the epicardial and midmural layers and created a transmural gradient of myocyte degeneration and death in the setting of fibrofatty replacement. This pathological substrate potentially accounted for a “structural” epicardial-endocardial heterogeneity of repolarization in the RV wall predisposing to phase 2 reentry. Accordingly, experimental damage of canine ventricular epicardium secondary to metabolic inhibition and simulated ischemia provoked electrical inhomogeneity and local reexcitation.\textsuperscript{11,25} In addition, Krishan and Antzelevitch\textsuperscript{26} showed a synergism between heterogeneous repolarization and delayed conduction in giving rise to arrhythmic activity in canine ventricular epicardium. In our sudden death victims, therefore, a delayed intraventricular conduction caused by the disarrangement of surviving myocardium in islands interspersed with fibrofatty tissue may have contributed to the induction and maintenance of reentrant activity, in association with the dispersion of repolarization.

Study Limitations

No patients in this study underwent pharmacological testing with sodium-channel blockers designed to induce or enhance ST-segment elevation in right precordial leads, which is a typical finding in Brugada syndrome, because they were generally asymptomatic before death.

ECG monitoring of ST-segment elevation to predict a higher risk of sudden death or to identify a group with a different genetic background cannot be inferred from this retrospective analysis of sudden death victims and should be tested in prospective studies in living ARVC patients.

Acknowledgments

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References


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