Inferior and Lateral Electrocardiographic Repolarization Abnormalities in Brugada Syndrome

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Background—Repolarization abnormalities in the inferior-lateral leads in Brugada syndrome (BS) have not been systematically investigated.

Methods and Results—280 patients (age, 41±18 years; 168 males) with BS were screened for inferior-lateral repolarization abnormalities. The repolarization abnormalities were classified either as early repolarization pattern or coved 2-mm Brugada pattern and as spontaneous or class I antiarrhythmic drug (AAD) induced. Thirty-two patients (11%) had inferior-lateral spontaneous early repolarization pattern. These patients were less likely to be asymptomatic at first presentation (13 of 32 versus 156 of 248 patients, \( P = 0.02 \)), and spontaneous type I ECG was more frequent among them (38% versus 21%, \( P = 0.05 \)). The spontaneous early repolarization pattern occurred more frequently among patients with BS than in 283 family members not having BS (11% versus 6%, \( P = 0.03 \)). Class I AAD administration provoked inferior-lateral coved Brugada pattern in 13 patients with BS. These patients had longer baseline PR intervals (206±48 versus 172±31 ms, \( P < 0.001 \)) and class I AAD–induced QRS interval prolongation (108 to 178 versus 102 ms to 131 ms, \( P < 0.001 \)). In 3 patients, the class I AAD–provoked coved Brugada pattern was only present in the inferior leads.

Conclusions—Inferior-lateral early repolarization pattern occurs spontaneously relatively frequently in BS. These patients have a more severe phenotype. Class I AAD administration provokes inferior-lateral coved Brugada pattern in 4.6% of patients. We report for the first time 3 patients in whom the class I AAD–provoked coved Brugada pattern was only observed in the inferior leads. (Circ Arrhythmia Electrophysiol. 2009;2:154-161.)

Key Words: electrocardiography ▪ death, sudden ▪ Brugada syndrome

Brugada syndrome (BS) is characterized by ST elevation in the right precordial leads (V1 to V3) and an increased risk of arrhythmic sudden death.1 In 2002, a consensus report defined the diagnostic ECG abnormality as a coved-type ST elevation in the presence of at least a 2-mm J wave (type I ECG pattern) in the right precordial leads (V1 to V3), either occurring spontaneously or after a class I antiarrhythmic drug (AAD) challenge.2,3 However, sporadic cases have been reported in which the coved-type Brugada ECG pattern was also observed in the inferior or lateral ECG leads.4–7 The majority of these patients presented with the same clinical characteristics as patients with the typical form of BS. All these findings suggest that BS has a phenotype variant in which the coved-type Brugada pattern manifests not only in the right precordial but also in the inferior-lateral leads. The incidence and the clinical characteristics of this inferior-lateral Brugada phenotype variant have not yet been investigated.

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Additionally, several case reports8–11 and recently a multicenter study12 described patients with idiopathic ventricular fibrillation and accentuated J wave or early repolarization pattern in the inferior-lateral leads. The incidence of early repolarization pattern in the inferior-lateral leads in BS has not yet been investigated.

In the current study, we aimed to determine the incidence and characteristics of spontaneous or class I AAD test–induced inferior-lateral repolarization abnormalities in a large unselected population of patients with BS.

Methods

Patient Population

Since 1992, all patients diagnosed with BS and their relatives tested for the syndrome are included in a registry at our center and followed-up in a prospective fashion. All patients included gave

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ECG Definitions

The diagnosis of BS was based on the presence of spontaneous or class I AAD–induced coved type I Brugada ECG pattern in at least 1 right precordial lead in the index patient or in a first degree relative; and (2) ≥1-mm J point elevation in at least 1 inferior (leads II, III, aVF) or lateral (I, aVL) limb lead. Five hundred sixty-three patients in the database were screened for inclusion in the analysis. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Class I AAD Test

Class I AAD test was performed to unmask the diagnostic ECG pattern. Most frequently, intravenous ajmaline (0.7 to 1 mg/kg, administered in 5 minutes), and less often, flecainide (2 mg/kg) or procainamide (10 mg/kg given over a 10-minute period), were used for this purpose. The test was considered positive for BS if coved type I ECG was documented in ≥1 right precordial lead V1 to V3.

Statistical Analysis

Continuous variables are expressed as mean±SD. The χ² and Fisher exact tests were used to compare categorical values. Two-sided unpaired Student t test was used to compare continuous variables. The baseline values of the PR and QRS intervals were analyzed using 2-way ANOVA considering the presence of spontaneous early repolarization pattern, inferior-lateral coved Brugada pattern, and their interaction as factors. The changes in the PR and QRS intervals after class I AAD administration was investigated using repeated measures ANOVA. The comparison of patients with BS with family members without BS for spontaneous early repolarization pattern controlling for family was performed using the Cochran-Mantel-Haenszel test.

Table 1. Clinical Characteristics of Patients Diagnosed With BS

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td>157 (56%)</td>
</tr>
<tr>
<td>Positive family history of sudden death &lt;65 y</td>
<td>149 (53%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>169 (60%)</td>
</tr>
<tr>
<td>Presyncope, palpitation</td>
<td>44 (16%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>68 (24%)</td>
</tr>
<tr>
<td>Aborted sudden death</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Baseline ECG</td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>65 (23%)</td>
</tr>
<tr>
<td>Type II</td>
<td>49 (18%)</td>
</tr>
<tr>
<td>Type III</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>Normal</td>
<td>151 (54%)</td>
</tr>
<tr>
<td>EPS-inducible VT/VF (performed in 238 patients)</td>
<td>61 (26%)</td>
</tr>
</tbody>
</table>

EPS indicates electrophysiological study; VT/VF, ventricular tachycardia/ventricular fibrillation.
Haenszel test. A probability value \( \leq 0.05 \) was considered statistically significant.

**Results**

**Patient Population**

Two hundred eighty patients with the diagnosis of BS (mean age, 41±18 years; 168 male) were included in the study. The baseline clinical characteristics are shown in Table 1. Two hundred fifty-five patients underwent genetic testing. SCN5A mutation was identified in 39 patients belonging to 8 families. Four patients were lost to follow-up. The mean follow-up of the remaining 276 patients was 61.7±47 months.

**Incidence of Spontaneous or Class I AAD Provoked Inferior-Lateral Repolarization Abnormalities in Patients With BS**

Of the 280 patients diagnosed with BS, 43 patients (15%) had inferior-lateral ECG repolarization abnormality spontaneously or during class I AAD test. The mean age of the 43 patients with inferior-lateral ECG abnormalities was 43±21 years, and 27 patients (63%) were males. Of the 43 patients, 32 patients (11% of the whole population of patients with BS) had the inferior-lateral ECG abnormality present spontaneously and 23 patients (8% of the whole population of patients with BS) after class I AAD test. In 12 patients (4%), the inferior-lateral ECG abnormality was present both spontaneously and after class I AAD (Figure 2).

**Spontaneous Inferior-Lateral Early Repolarization Pattern in BS**

Thirty-two patients (11% of the patients diagnosed with BS) had the inferior-lateral ECG abnormality present spontaneously. All 32 patients had early repolarization pattern (≥1-mm J wave) and none of the patients had coved Brugada pattern (≥2-mm coved ST elevation) spontaneously. In 20 patients (62%), the ECG abnormality was intermittent. Twelve patients (38%) had the repolarization abnormality present only in the lateral leads. Two patients (6%) had the ECG abnormality in both the lateral and inferior leads (Figure 3). The remaining 18 patients (56%) had the ECG abnormal-
ity only in the inferior leads. Patients with spontaneous inferior-lateral early repolarization pattern were less likely to be asymptomatic as compared to patients without these abnormalities (13 of 32 versus 156 of 248 patients, \( P < 0.02 \)). Additionally, right precordial spontaneous type I ECG was recorded more frequently among patients with spontaneous inferior-lateral early repolarization pattern (53 of 248 versus 12 of 32 patients, \( P < 0.05 \)). Among patients with spontaneous inferior-lateral early repolarization pattern, class I AAD provoked more frequently coved Brugada pattern in the inferior-lateral leads (7 of 248 versus 6 of 32 patients, \( P < 0.001 \)). There was no significant difference between the baseline or class I AAD–induced PR and QRS intervals comparing patients with or without spontaneous early repolarization pattern (Table 2).

### Table 2. Comparison of Spontaneous and Class I AAD Test–Induced ECG Conduction Parameters Between Patients With and Without Spontaneous Early Repolarization Pattern and Class I AAD–Induced Inferior Lateral Coved Brugada Pattern

<table>
<thead>
<tr>
<th>Only SERP</th>
<th>Only ICBP†</th>
<th>SERP and ICBP</th>
<th>No SERP/ICBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=26)</td>
<td>(n=7)</td>
<td>(n=6)</td>
<td>(n=241)</td>
</tr>
<tr>
<td>PR, ms</td>
<td>174±22</td>
<td>197±33</td>
<td>217±63</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>105±15</td>
<td>104±13</td>
<td>113±18</td>
</tr>
<tr>
<td>After class I AAD administration, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR, ms</td>
<td>209±33</td>
<td>247±45</td>
<td>260±47</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>135±29</td>
<td>186±57</td>
<td>170±50</td>
</tr>
</tbody>
</table>

SERP indicates spontaneous early repolarization pattern; †ICBP, class I AAD–provoked inferior lateral coved Brugada pattern.

### Class I AAD Test–Provoked Inferior-Lateral Coved Brugada Pattern in BS

Twenty-three patients (8% of the patients with BS) had inferior-lateral repolarization abnormality at the end of the class I AAD test. Thirteen of the 23 patients (4.6% of patients with BS) had \( \geq 2 \)-mm coved Brugada pattern in the inferior-lateral leads provoked by class I AAD administration. The coved ST-elevation response was present in the lateral leads in 1 patient (0.4% of patients with BS) and in the inferior leads in 12 patients (4.3% of patients with BS). Patients with class I AAD test–provoked inferior-lateral coved Brugada pattern were more likely to have early repolarization pattern on the baseline ECG (6 of 13 versus 26 of 267 patients, \( P < 0.001 \)). The baseline PR interval was significantly longer among the 13 patients with class I AAD–provoked inferior-lateral coved Brugada pattern as compared with patients without this abnormality (206±48 versus 172±31 ms, \( P < 0.001 \); Table 2). In contrast, the PR interval prolongation after class I AAD administration was not significantly different between these 2 groups. The baseline QRS interval was not significantly different between patients with or without class I AAD–provoked inferior-lateral coved Brugada pattern. However, after class I AAD administration, the QRS interval prolonged significantly more in patients with class I AAD–induced inferior-lateral coved Brugada pattern (from 108±15 to 178±53 versus from 102±19 to 131±24 ms, \( P < 0.001 \)). SCN5A mutation was identified with similar frequency among patients with or without inferior-lateral coved Brugada pattern (4 of 12 versus 35 of 243, \( P = \text{NS} \)).

Three of the 13 patients (1% of the patient population with the diagnosis of BS) had class I AAD–provoked \( \geq 2 \)-mm coved ST elevation only in the inferior leads and not in the right precordial leads. Therefore, these patients did not meet...
the current consensus criteria for BS. One of these 3 patients had early repolarization pattern on the spontaneous ECG; the other 2 had normal spontaneous ECG. Two of these patients were from the same family with an identified SCN5A mutation. The other family members had the typical type I ECG pattern in the right precordial leads. Both patients presenting with only inferior coved ST elevation from this family were carriers of an SCN5A mutation. The third patient with only inferior class I AAD–provoked coved ST elevation was an asymptomatic family member (Figure 4). The proband (her mother) had typical type I ECG pattern in the right precordial leads.

Class I AAD Test–Provoked Inferior-Lateral Early Repolarization Pattern in BS

The remaining 10 of the 23 patients (4% of the BS patient population) had early repolarization pattern present in the inferior-lateral leads at the end of the class I AAD test. Six (60%) of these patients had early repolarization pattern present also spontaneously before class I AAD administration. In these 6 patients, the early repolarization pattern did not increase significantly with the class I AAD administration. The PR and QRS intervals did not differ significantly between the patients with and without class I AAD test provoked early repolarization pattern.

Inferior-Lateral Early Repolarization Pattern in Family Members Without BS

Two hundred eighty-three family members (age, 35±20 years; 140 male) were diagnosed as not having BS. These healthy young individuals were also screened for the presence of inferior-lateral ECG abnormalities. Twenty-four patients (8.5%) had early repolarization pattern in the inferior-lateral limb leads either spontaneously or after class I AAD challenge. Seventeen patients (6%) had the inferior-lateral early repolarization pattern spontaneously. In 3 patients, the abnormality was in the lateral limb leads and in 14 patients in the inferior leads. Seventeen patients (6%) had the inferior-lateral early repolarization pattern after class I AAD administration. Ten (59%) of these patients had inferior-lateral early repolarization pattern also spontaneously. In these 10 patients, the early repolarization pattern did not increase significantly after class I AAD administration. There was no significant difference in any clinical parameter between the group of patients with or without inferior-lateral early repolarization pattern. However, the baseline QRS interval was significantly longer...
among patients with inferior-lateral early repolarization pattern (98±16 versus 90±13 ms, \(P=0.03\)). No events occurred during the follow-up in any of the patients with inferior-lateral early repolarization pattern.

A global comparison of all patients with BS with the family members who did not have BS showed that spontaneous inferior-lateral early repolarization pattern occurred significantly more frequently (11% [32 of 280 patients] versus 6% [17 of 283 patients], \(P=0.03\)). When considering only patients with BS for whom at least 1 family member was also tested (193 of the 280 patients), we observed an incidence of 9.8% (19 of 193) of the spontaneous inferior-lateral early repolarization pattern. The difference using the Cochran-Mantel-Haenszel test controlling for family was no longer significant (9.8% versus 6%, \(P=0.158\)). This later finding might be attributable to the fact that one third of the patients had no family member tested and thus was excluded from the analysis. Alternatively, spontaneous early repolarization pattern might have a familial occurrence irrespective of the presence of BS. Class I AAD–induced early repolarization pattern occurred with the same frequency among patients with or without BS (4% versus 6%, \(P=\text{NS}\)).

**Discussion**

**Coved Brugada Pattern in the Inferior-Lateral ECG Leads in BS**

BS was originally reported 15 years ago as a peculiar ECG abnormality accompanied with an increased risk of sudden death. The ECG abnormality was described as right bundle branch block and ST elevation in the right precordial leads.\(^1\) Subsequently, large-scale population studies revealed that J point and saddle back–type ST elevation in the right precordial leads was relatively frequent in the healthy general population.\(^14–19\) In contrast, J point elevation with coved type ST elevation was a very infrequent finding among apparently healthy individuals.\(^14–19\) In the meantime, data from international registries revealed that the majority of symptomatic patients had coved type ST elevation.\(^13,20\) These data suggested that the coved type ST elevation carries a higher risk of arrhythmic events. However, the characteristic coved type I ECG has a dynamic nature; during long-term follow-up, in almost all patients, the ECG normalizes transiently. In patients with baseline saddle back–type or normal ECGs, class I sodium channel blockers can unmask the diagnostic coved type I pattern.\(^2,21\) Based on these data, in 2002, a consensus panel defined the diagnostic ECG abnormality as spontaneous or class I AAD–induced coved type ST elevation in the presence of at least 2-mm J wave (type I ECG pattern) in the right precordial leads (V1 to V3).\(^2\) Thus, currently, BS is only diagnosed in the presence of coved type I Brugada pattern in the right precordial leads.\(^2,5\)

However, several cases were reported, in whom the coved Brugada pattern was present in the inferior or in one case in the lateral ECG leads.\(^4–7\) In all of these reports, including a total of 4 patients, either spontaneously or after class I AAD challenge, a diagnostic coved-type I ECG was also recorded in the right precordial leads. Many of these patients presented with ventricular fibrillation or syncope in the setting of a structurally normal heart. In one of these reports, the patient was a proband with inferior coved ST elevation of a family with identified SCN5A mutation. The SCN5A mutation expression in vitro showed a loss-of-function–type effect on the sodium channel, the same effect as observed in the typical form of BS. The 4 other family members carrying the same mutation showed the typical form of BS with diagnostic coved type I ECG pattern in the right precordial leads.\(^4\) All these findings suggest that BS has a phenotype variant in which the diagnostic coved ECG manifests not only in the right precordial but also in the inferior leads.

In the current study, we systematically investigated the occurrence of ≥2-mm coved-type ST elevation in the inferior-lateral leads in a large population of patients with BS. In our study population, the coved Brugada pattern did not occur spontaneously in the inferior or lateral leads. These data suggest that the presence of spontaneous coved ST elevation in the inferior-lateral leads is an exceptional finding in BS.

In contrast, class I AAD administration provoked coved Brugada pattern in the inferior or lateral leads in 4.6% of our study population. The localization of the coved Brugada pattern was the lateral leads in only 1 patient, corresponding to 0.4% of our Brugada patient population. This finding suggests that coved Brugada pattern in the lateral leads is a rather exceptional finding. In contrast, coved Brugada pattern was provoked in the inferior leads in 4.3% of our study population. More importantly, for the first time, we report 3 patients (1% of the patient population with BS) in whom the ≥2-mm coved ST elevation was only present in the inferior leads. These patients do not meet the current consensus criteria for the diagnosis of BS. Two of these patients had an identified SCN5A mutation, and a relative of the third patient had typical BS. These data, together with evidence from previous case reports, support the need to revise the consensus diagnostic criteria. We recommend that patients with class I AAD–provoked ≥2-mm coved-type ST elevation in the inferior leads, even without the diagnostic type I ECG in the right precordial leads, should be diagnosed as BS.

The pathophysiological mechanism of the inferior or lateral location of the coved-type ST elevation is unknown. Currently there are 2 proposed explanations for the presence of the Brugada-type ECG patterns in the right precordial leads: the repolarization disorder and the depolarization disorder theories.\(^22,23\) In our study, we report the important finding that BS patients with coved Brugada pattern in the inferior-lateral leads had spontaneously significantly longer PR intervals than patients without inferior-lateral ECG abnormalities. Furthermore, after the administration of a sodium channel blocker, the QRS interval prolonged significantly more in patients with the inferior-lateral coved Brugada pattern. These findings favor the importance of conduction slowing in the genesis of the coved inferior-lateral Brugada pattern.

**Inferior-Lateral Early Repolarization Pattern in BS**

Aizawa et al\(^11\) reported several cases of idiopathic ventricular fibrillation in Japanese men that were associated with a notch in the late part of the QRS complex in the inferior leads.
Subsequently, other similar cases of idiopathic ventricular fibrillation with accentuated J wave with or without ST elevation in the inferior leads were observed. In 4 patients, the administration of a class I AAD augmented the J wave and ST segment elevation (8.9), but it failed to do so in 4 other patients. Very recently, Haissaguerre et al reported a multicenter study of 206 patients with idiopathic ventricular fibrillation. They found that early repolarization pattern in the inferior or lateral leads was more frequent among patients with idiopathic ventricular fibrillation as in a healthy control group (31% versus 5%, \( P < 0.001 \)). Early repolarization was defined as \( \pm 1 \)-mm elevation of the QRS-ST junction in at least 2 inferior or lateral leads (including V4 to V6). The ECG abnormality was dynamic, but in some cases, increase in the J point and ST elevation preceded spontaneous episodes of ventricular fibrillation. The presence of spontaneous or class I AAD test–provoked right precordial coved ST segment elevation was an exclusion criteria. However, only 65% of the patient population (84% of the patients with early repolarization pattern) underwent a class I AAD test. The type of AAD used for the test was not specified. In the tested patients, sodium channel blockers did not augment the early repolarization abnormalities.

In this study, we investigated the presence of inferior-lateral early repolarization pattern in a large population of BS, using a very similar definition as Haissaguerre et al. Our study has several new important findings connected to the study of idiopathic ventricular fibrillation and early repolarization. First, we report that the inferior-lateral early repolarization pattern also occurs relatively frequently in patients with BS, more frequently than in a control group of family members without BS (11% versus 6%, \( P = 0.03 \)). Secondly, we report that BS has a phenotype variant in which class I AAD–provoked coved Brugada pattern appears in the inferior or lateral leads. These patients with BS have frequently early repolarization pattern on the baseline ECG. Our findings suggest that BS should be carefully excluded in patients with inferior-lateral early repolarization pattern and idiopathic ventricular fibrillation. The main difference between the newly described early repolarization disorder and BS seems to be the appearance of coved ST elevation in response to sodium channel blockers in BS either in the inferior-lateral or in the right precordial leads. In our opinion, without the performance of a class I AAD test, as was the case in 16% of patients reported by Haissaguerre et al., the diagnosis of BS cannot be excluded in patients with early repolarization disorder and ventricular fibrillation. Furthermore, the likelihood of diagnosing BS in patients with early repolarization disorder is also dependent on the type of class I AAD used for the test. It has been reported the flecainide and procainamide are less sensitive than ajmaline. The type of sodium channel blocker used for the class I AAD test has not been reported by Haissaguerre et al. Additionally, in some patients with early repolarization disorder, the class I AAD test will provoke \( \pm 2 \)-mm coved ST elevation in the inferior-lateral or right precordial leads. These patients should be diagnosed with BS or as overlapping phenotype of BS with the new early repolarization disorder. In our opinion, the diagnosis of BS in these patients has important implications for the clinical management and the family screening. For example, if BS is diagnosed, the patient should not receive sodium channel blockers, and the patient’s family should be screened with class I AAD test.

We used the family members who tested negative for BS as a control group to examine the incidence of the inferior-lateral early repolarization pattern in a healthy young population. The incidence of spontaneous inferior-lateral early repolarization pattern was 6%. This finding is similar to the 5% incidence reported by Haissaguerre et al. This data suggests that similar to the saddle back ST elevation in the right precordial leads, early repolarization pattern in the inferior-lateral leads also occurs frequently in young healthy individuals. We believe that before attributing increased arrhythmia risk to the presence of asymptomatic inferior or lateral early repolarization disorder in the general population, further population studies are necessary.

**Limitations**

This study was retrospective and included a limited but significant number of patients. We used family members tested for BS as control instead of an independent age- and sex-matched control group. However, some of these individuals might be silent mutation carriers. Furthermore, we compared the incidence of spontaneous early repolarization pattern between patients with or without BS coming from the same families. It is likely that the presence of spontaneous early repolarization pattern is genetically defined, and thus an increased familial occurrence is expected. This might explain the slightly higher incidence of the early repolarization pattern in our control group as compared with the independent control group of Haissaguerre et al. (6% versus 5%, respectively). Additionally, this might be a reason why when considering only patients with BS for whom at least 1 family member was also tested the difference in the incidence of the early repolarization pattern when controlling for family was no longer significant (9.8% versus 6%, \( P = 0.158 \)). In the future, further studies are necessary to prove these hypotheses.

Our definition of early repolarization was slightly different from the one used by Haissaguerre et al. We included patients with J wave abnormalities present in 1 lead instead of 2 leads. However, we did not include patients with early repolarization in the left precordial leads.

**Conclusions**

In this study, we report that 11% of the patients with BS have spontaneous early repolarization pattern in the inferior-lateral leads. This group of patients seemed to have a more severe phenotype. The inferior-lateral early repolarization pattern occurred more frequently in patients with BS than in their family members not having BS. Class I AAD administration provoked coved Brugada pattern in the inferior-lateral leads in 4.6% of patients with BS. These patients have significantly longer conduction intervals. For the first time, we report 3 patients (1% of the study population) in whom the coved Brugada pattern was only present in the inferior leads. We provide evidence that these patients should be diagnosed with BS.
References


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