Continuous assessment of electrical epileptic activity in acute stroke

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Abstract—Objective: To determine the incidence and risk factors of electrical seizures and other electrical epileptic activity using continuous EEG (cEEG) in patients with acute stroke. **Methods:** One hundred consecutive patients with acute stroke admitted to our stroke unit underwent cEEG using 10 electrodes. In addition to electrical seizures, repetitive focal sharp waves (RSHWs), repetitive focal spikes (RSPs), and periodic lateralized epileptic discharges (PLEDs) were recorded. **Results:** In the 100 patients, cEEG was recorded for a mean duration of 17 hours 34 minutes (range 1 hour 12 minutes to 37 hours 10 minutes). Epileptic activity occurred in 17 patients and consisted of RSHWs in seven, RSPs in seven, and PLEDs in three. Electrical seizures occurred in two patients. On univariate Cox regression analysis, predictors for electrical epileptic activity were stroke severity (high score on the National Institutes of Health Stroke Scale) (hazard ratio [HR] 1.12; $p = 0.002$), cortical involvement (HR 5.71; $p = 0.021$), and thrombolysis (HR 3.27; $p = 0.040$). Age, sex, stroke type, use of EEG-modifying medication, and cardiovascular risk factors were not predictors of electrical epileptic activity. On multivariate analysis, stroke severity was the only independent predictor (HR 1.09; $p = 0.016$). **Conclusion:** In patients with acute stroke, electrical epileptic activity occurs more frequently than previously suspected.

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Patients with acute stroke treated in a stroke unit show a relative reduction in mortality.¹ Recent guidelines^{2–4} have put forward recommendations for the organization of stroke units and defined the usefulness of several acute diagnostic tests, including brain CT and MRI, laboratory examinations, duplex and transcranial ultrasonography, and monitoring of blood pressure, EKG, oxygen saturation, and body temperature. These guidelines also provide strategies for the treatment of acute stroke, including general care and specific therapies, such as recanalization or prevention of complications.

However, the role of continuous EEG (cEEG) monitoring in the stroke unit has not been adequately assessed, despite the high incidence of clinical seizures, which ranges from 2 to 33% in the acute phase of stroke,⁵ and the potentially harmful effect of seizures on acute ischemic tissue.⁶ The information regarding the usefulness of cEEG in acute stroke was obtained in studies on severe stroke patients admitted to intensive care units. Electrical seizures were detected in 9 to 15% of patients, depending on patient selection and the cEEG technique.^{7–9}

In this study, we sought to determine the incidence and risk factors of electrical seizure and epileptic electrical activity in acute stroke patients admitted to our stroke unit.

Methods. *Subject selection.* We prospectively recruited 100 consecutive patients admitted to our stroke unit. Inclusion cri-

teria were acute symptoms and signs consistent with ischemic or hemorrhagic stroke. Exclusion criteria were subarachnoid or posttraumatic hemorrhage; venous thrombosis; structural lesions, such as arteriovenous malformation rupture; and electrolytic or metabolic disorders affecting the EEG, such as hepatic or renal failure. Patients with preexisting epileptic disorders were excluded.

Procedure. On admission, brain CT with perfusion sequences and precerebral angio-CT were performed in the emergency department on all patients. In our stroke unit, where acute stroke patients usually stay for 24 hours or longer, depending on stroke severity, general condition, and complications, the patients underwent cEEG. Typically, cEEG monitoring was started in the morning and was stopped the following day. When premature cEEG interruption occurred, the cause was reported by the nurse team. Intracranial and extracranial Doppler ultrasonography and blood pressure and EKG monitoring were performed on all patients, and MRI with diffusion-weight imaging, perfusion, T1 and T2 sequences, and transthoracic and transesophageal echocardiography were performed on selected patients. Neurologic examination using the National Institutes of Health Stroke Scale (NIHSS) score was performed on admission to the emergency department and at least twice daily in our stroke unit, including at the beginning and end of the cEEG recording and at discharge. Clinical epileptic seizures before admission or during hospitalization were recorded. The causes of ischemic strokes were determined using the TOAST¹⁰ classification. *EEG protocol.* The cEEG was recorded using 10 electrodes according to the International 10-20 system with an eight-channel subset (Fp2-C4, C4-O2, Fp2-T4, T4-O2, Fp1-C3, C3-O1, Fp1-T3, and T3-O1). The impedances of the silver-silver/chloride electrodes, which were glued to the scalp with collodion, were kept below 5 k Ω . The cEEG was acquired using SystemPLUS software (Micromed, Mogliano, Italy) and a sampling frequency of 256 Hz. Filter settings were 1 and 70 Hz. The cEEG trace was continuously displayed at the bedside.

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Figure. Examples of the different epileptic electrical activities. (A) Repetitive focal sharp waves focalized in the temporal area (T4) in a patient with right superficial middle cerebral artery (MCA) stroke (Patient 11, table 2). (B) Periodic lateralized epileptic discharges focalized in the central area (C4) in a patient with right complete MCA stroke (Patient 4). (C) Repetitive focal spikes focalized in the central area (C3) in a patient with left complete MCA stroke (Patient 7). (D) Beginning of a focal electrical seizure (C3) in the same patient (Patient 7).

Epileptic activity was classified according to the following criteria (figure.)

1. RSHWs: Repetition of sharp waves of uniform morphology, duration, and localization, but without a definable and quantifiable interval between consecutive waveforms.
2. RSPs: Repetition of spikes of uniform morphology, duration, and localization, but without a definable and quantifiable interval between consecutive waveforms.
3. PLEDs: Lateralized repetitive sharp waves, spikes, or sharply contoured waves at regular or nearly regular intervals and without a clear evolution in frequency or location.⁷
4. Electrical seizures: Rhythmic discharges or spikes lasting at least 10 seconds with a definite evolution in frequency location or morphology.⁷

Epileptic activity was recorded at the bedside during moment-to-moment online observation and during systematic review at the end of the recording by a board-certified electroencephalographer (E.C.). Each epileptic activity was confirmed by two independent board-certified electroencephalographers (M.M., P.A.D.) blinded to the clinical condition.

The prespecified primary endpoint was the occurrence of electrical epileptic activity according to the defined criteria.

Data were analyzed using commercially available statistical software (STATA 8.2). Cox proportional hazards regression analysis was used to investigate relationships between baseline characteristics (age, sex, cardiovascular risk factors, NIHSS score on admission, duration of cEEG recording, and interval from stroke onset to cEEG monitoring), and the occurrence of electrical epileptic activity. The significance level was set as 0.05. Variables that yielded a univariate $p < 0.1$ were then included in a Cox proportional multivariate hazards analysis.

Results. Patient population. The 100 consecutive patients consisted of 58 men and 42 women. The mean age was 68.7 years (range 31 to 94) and the mean (SD) NIHSS score on admission was 10.8 (7.1). There were 91 patients with ischemic strokes and nine with hemorrhagic strokes. Of the ischemic stroke patients, two presented with generalized tonic-clonic seizures at stroke onset and one with recurrent partial-complex seizures. Six of the 100 patients (three with and three without electrical epileptic activity) died during hospitalization; these six patients had a high NIHSS score (scores of 12, 20, 28, 21, 12, and 20) on admission. Of the 100 patients, 17 were treated with EEG-modifying medication before or during cEEG. During EEG monitoring, one patient (Patient 16) was treated with phe-

nytoin 100 mg/day three times daily and clonazepam 2 mg/day for recurrent partial-complex seizure at stroke onset. The other 16 patients received psychotropic agents because of preexisting psychiatric pathologies, agitation, or sleep disorders. No patients received antiepileptic treatment for electrical epileptic activity without clinical signs. No patients had undergone neurosurgical intervention before EEG monitoring.

cEEG monitoring. The mean duration of cEEG monitoring was 17 hours 34 minutes (range 1 hour 12 minutes to 37 hours 10 minutes). The cEEG was prematurely interrupted in 18 of the 100 patients due to agitation ($n = 10$), spontaneous electrode failure ($n = 2$), computer failure ($n = 2$), or the performance of acute tests, such as brain CT or MRI ($n = 4$).

Electrical epileptic activity. Of the 100 patients, 17 had electrical epileptic activity. The baseline characteristics of the patients with and without electrical epileptic activity are presented in table 1. Electrical epileptic activity consisted of RSHWs in seven patients, RSPs in seven, and PLEDs in three. The details of the individual patients with electrical epileptic activity are presented in table 2. Two patients, one with PLEDs (Patient 3) and one with RSPs (Patient 7), had focal electrical seizures during cEEG monitoring. No patient had generalized electrical epileptic activity or electrical status epilepticus. Among the patients with electrical epileptic activity, one had a hemorrhagic stroke limited to the right lenticular nucleus (Patient 4). Of the three patients with clinical seizures at stroke onset, one (Patient 16) had RSPs and the other two no electrical epileptic activity on the cEEG. No patient had a clinical seizure during EEG recording or after during hospitalization.

Hazard ratios (HRs), estimated using univariate Cox regression, are shown in table 3. Three factors were found to significantly increase the hazard of electrical epileptic activity: these were the NIHSS score on admission (HR 1.12; 95% CI 1.04 to 1.20; $p = 0.002$), cortical involvement (HR 5.71; 95% CI 1.31 to 25.01; $p = 0.021$), and thrombolysis (HR 3.27; 95% CI 1.06 to 10.10; $p = 0.040$). Age, sex, cardiovascular risk factors, stroke type

Table 1 Characteristics of patients with and without electrical epileptic activity

	With electrical epileptic activity, n = 17	Without electrical epileptic activity, n = 83
Patient characteristics		
Age, y (range)	66.7 (31–84)	69.1 (43–94)
Male (%)	7 (41.1)	51 (61.4)
Hypertension (%)	10 (58.9)	59 (71.1)
Diabetes (%)	3 (17.6)	16 (19.3)
Cigarette smoking (%)	3 (17.6)	24 (28.9)
Hypercholesterolemia (%)	7 (41.1)	47 (56.6)
Previous stroke (%)	2 (11.8)	16 (19.2)
On EEG-modifying medication (%)	3 (17.6)	16 (19.2)
NIHSS on admission, mean	15.82	9.81
With cortical involvement (%)	15 (88.2)	44 (53.0)
Without cortical involvement (%)	2 (11.8)	39 (47.0)
Ischemic stroke (%)	16 (94.1)	75 (90.4)
Thrombolysis (%)	4 (23.5)	7 (8.4)
Cause		
Large artery disease (%)	8 (50.0)	33 (44.0)
Cardiac (%)	6 (37.5)	25 (33.3)
Lacunar (%)	0	7 (9.3)
Other (%)	0	1 (1.3)
Undetermined (%)	2 (12.5)	9 (12.0)
Hemorrhagic stroke (%)	1 (5.9)	8 (9.6)
Cause		
Hypertension (%)	1 (100)	7 (87.5)
Anticoagulation (%)	0	1 (12.5)
Technical characteristics		
Interval stroke onset/cEEG start		
<24 h (%)	7 (41.2)	24 (28.9)
24–48 h (%)	6 (35.3)	41 (49.4)
>48 h (%)	4 (23.5)	18 (21.7)
cEEG duration, h:min (range)	18:14 (4:06–23:15)	17:26 (1:12–37:10)

NIHSS = National Institutes of Health Stroke Scale.

(ischemic vs hemorrhagic), side of lesion, stroke etiology, EEG-modifying medication, and the interval from stroke onset to cEEG monitoring were not predictors of electrical epileptic activity. On multivariate Cox regression analysis, including the NIHSS score on admission, cortical involvement, and thrombolysis, the NIHSS score on admission (HR 1.09; 95% CI 1.02 to 1.18; $p = 0.016$) was the only independent predictor of electrical epileptic activity.

Discussion. In this prospective study, based on cEEG in acute stroke patients admitted to a stroke unit, we found that electrical epileptic activity, including ictal and interictal abnormalities, was present in 17% of acute stroke patients. In addition, stroke severity (assessed by the NIHSS score) on admission was the only independent predictor of electrical epileptic activity during cEEG.

The incidence of electrical epileptic activity in our study was higher than suspected on clinical

grounds using “standard” EEG¹¹ in acute stroke patients or continuous EEG in critically ill patients admitted to the intensive care unit.^{7,8} This may be due to the criteria used to classify the electrical epileptic activity in our study. cEEG in acute stroke patients is an emerging technique, and there is no definite consensus regarding the epileptic elements associated with clinical or electrical seizures. In our study, we grouped PLEDs, RSPs, and RSHWs together with electrical seizures. We included patients with PLEDs because PLEDs have been shown to be associated with seizures.^{11–13} The exact significance of PLEDs in the development of seizures is, however, controversial because some patients may present PLEDs in the absence of clinical or electrical seizures.^{14,15} In addition, and in contrast to other studies of EEG monitoring in acute stroke patients,^{7,8} we also reported RSHWs and RSPs because they were also shown, together with PLEDs, to be associated with the development of epilepsy in a study of epileptic EEG findings in acute stroke patients¹¹ and in another study of unselected nonepileptic patients receiving EEG examination.¹⁶ We suggest that RSHWs and RSPs may be indicators of interictal epileptic activity and therefore follow or precede seizures.^{11,17} However, further studies are needed to confirm the prognostic value of these different elements in terms of seizure development and clinical outcome. A continuum between these different “epileptiform” elements may be suggested. In our study, both patients with epileptic seizures had interictal epileptic activity (RSPs in one patient and PLEDs in the other). Another possible reason for the high prevalence of these types of electrical activity in our study is the duration of the cEEG monitoring. Compared with standard EEG in acute stroke patients with or without clinical seizures,¹¹ cEEG recording was performed for a mean duration of 17 hours 34 minutes in our study, increasing the probability of detecting electrical epileptic activity and electrical seizures. Our findings emphasize the potential usefulness of cEEG in detecting electrical epileptic activity in the stroke unit compared with standard EEG, which is usually performed on patients with suspected clinical seizures.^{18–20} Standard EEG may fail to detect epileptic activity and potentially give misleadingly favorable information. The optimal duration of cEEG monitoring in acute stroke patients, however, remains to be defined with a larger sample size and probably depends on the characteristics of the patient. In a previous study of critically ill patients,⁷ 20% of electrical seizures were detected after more than 24 hours of cEEG monitoring.

In the present study, initial stroke severity, assessed by the NIHSS score on admission, was the only independent predictor of electrical epileptic activity. In the literature, stroke severity was found to be a predictor of clinical poststroke seizures in some studies,^{21–24} but not all.²⁵ Recent elec-

Table 2 Patients with electrical epileptic activity

No./sex/ age	CVRF	Medication	Stroke type	Diagnostic	Side	Etiology	Thrombolysis	Clinical seizure at stroke onset	NIHSS score at admission	NIHSS score at discharge	Type of baseline epileptic activity	Time to first epileptic event	Electrical seizure	Time to seizure	Frequency*	Focal slowing†
1/F/80	HTA,DM	—	I	Complete MCA	L	Cardioembolic	—	—	20	D	RSPs	2:18:34	—		+	+
2/F/79	—	—	I	Complete MCA	R	Cardioembolic	—	—	28	D	PLEDs	4:24:48	+	4:24:48	++	++
3/F/84	HTA	—	H	Deep lenticular	R	HTA	—	—	15	9	PLEDs	0:00:05	—		++	+
4/F/70	HTA	—	I	Complete MCA	R	Cardioembolic	—	—	22	28	PLEDs	4:28:00	—		++	+
5/F/50	—	—	I	ACA and complete MCA	R	LAD	+	—	17	13	RSHWs	1:44:12	—		+	++
6/M/57	HTA,HC	—	I	ACA	R	LAD	—	—	10	9	RSHWs	0:46:05	—		+	+
7/M/68	HTA	—	I	Complete MCA	L	LAD	+	—	24	6	RSPs	4:28:45	+	8:04:37	+	+
8/F/66	CS	—	I	Superficial MCA	L	LAD	—	—	5	4	RSPs	0:05:58	—		+	+
9/M/54	HTA,HC	—	I	Complete MCA	R	LAD	+	—	18	17	RSPs	1:02:47	—		+	++
10/M/60	DM	—	I	PCA and complete MCA	L	Cardioembolic	—	—	20	D	RSPs	0:04:37	—		++	++
11/F/73	HTA,HC	—	I	Superficial MCA	R	LAD	—	—	14	3	RSHWs	18:52:23	—		+	+
12/F/75	HTA,HC	—	I	Bilateral PCA	B	Cardioembolic	—	—	17	12	RSPs	5:38:45	—		+	+
13/M/79	HTA	+	I	Watershed ACA-MCA and PCA-MCA	R	Undet	—	—	14	16	RSHWs	4:59:12	—		+	+
14/M/64	HC, CS, DM	—	I	Deep MCA	R	LAD	—	—	18	20	RSHWs	7:58:12	—		++	++
15/F/31	CS,HC	+	I	Superficial MCA	L	Undet.	—	—	6	0	RSHWs	1:31:15	—		+	+
16/F/60	—	+	I	ACA and complete MCA	R	LAD	+	+	16	11	RSPs	1:04:45	—		+	++
17/M/84	HTA,HC	—	I	Superficial MCA	R	Cardioembolic	—	—	5	5	RSHWs	11:53:34	—		+	+

* Frequency: + = rare; ++, frequent; +++ = constant.

† Focal slowing: + = minor; ++ = major.

CVRF = cardiovascular risk factor; NIHSS = National Institutes of Health Stroke Scale; HTA = hypertension; DM = diabetes mellitus; I = ischemic stroke; MCA = middle cerebral artery; H = hemorrhagic stroke; D = death; PLEDs = periodic lateralized epileptic discharges; HC = hypercholesterolemia; ACA = anterior cerebral artery; LAD = large artery disease; RSHWs = repetitive sharp waves; B = bilateral; RSPs = repetitive spike waves; CS = cigarette smoking; PCA = posterior cerebral artery; undet. = undetermined.

trophysiologic studies using cEEG in patients admitted to an intensive care unit^{7,8} did not find stroke severity to be a predictor of electrical epileptic seizures. In our study, the independent effect of stroke severity may be due to patient selection. Rather than including severely disabled patients admitted to an intensive care unit with a high NIHSS score, all patients with acute stroke were recruited, irrespective of stroke severity. These findings suggest that, in a stroke unit, cEEG should be mainly performed on those patients with a high NIHSS score at onset. In these patients, cEEG may help to detect subtle seizures or differentiate coma, stupor, and decreased level of consciousness secondary to electrical seizures from those of other origins, such as brain edema or stroke recurrence.²⁶ Cortical involvement is commonly seen in patients with poststroke clinical seizures^{22,23,27,28}. In our study, cortical involvement of stroke was found to be of predictive value for electrical epileptic activity by univariate analysis, but not in the multivariate model. The fact that cortical involvement lost its prognostic value in the multivariate analysis does not mean that cortical location of stroke is without clinical relevance. The

Table 3 Cox proportional hazards analysis of risk factors for electrical epileptic activity after acute stroke

	Unadjusted Cox hazard (95% CI)	<i>p</i>	Adjusted Cox hazard (95% CI)	<i>p</i>
Age, y	0.98 (0.94–1.02)	0.31	0.98 (0.95–1.02)	0.35
Male	0.50 (0.19–1.31)	0.16	0.43 (0.15–1.23)	0.12
Hypertension	0.64 (0.24–1.67)	0.36	1.00 (0.36–2.73)	0.99
Diabetes	0.95 (0.30–3.02)	0.93	1.03 (0.31–3.41)	0.97
Cigarette smoking	0.54 (0.19–1.53)	0.24	0.65 (0.24–1.72)	0.38
Hypercholesterolemia	0.49 (0.19–1.29)	0.15	0.77 (0.28–2.11)	0.61
Previous stroke	0.26 (0.04–1.97)	0.19	0.17 (0.31–1.84)	0.17
NIHSS on admission	1.12 (1.04–1.20)	0.002	1.09 (1.02–1.18)	0.016
Cortical involvement	5.71 (1.31–25.01)	0.021	3.70 (0.82–16.82)	0.09
Left side involvement	0.51 (0.18–1.45)	0.21	0.51 (0.17–1.50)	0.22
Ischemic stroke	0.69 (0.92–5.23)	0.72	1.39 (0.17–11.58)	0.76
Thrombolysis	3.27 (1.06–10.10)	0.040	1.91 (0.61–5.97)	0.26
Interval stroke-cEEG				
<24 h		0.55		0.85
24–48 h	0.55 (0.18–1.63)	0.28	0.81 (0.21–3.05)	0.76
>48 h	0.82 (0.24–2.82)	0.76	0.69 (0.19–2.49)	0.60
On EEG-modifying medication	1.02 (0.29–3.55)	0.98	0.93 (0.25–3.52)	0.91

NIHSS = National Institutes of Health Stroke Scale.

lack of independent significance was probably due to the fact that patients with the highest NIHSS score, especially those with complete middle cerebral artery stroke, had a cortical lesion. Further studies with a larger sample size are needed to compare patients with isolated subcortical lesions or isolated cortical lesions with the same NIHSS score. IV recombinant tissue plasminogen activator (rt-PA) thrombolysis was found to be of predictive value for electrical epileptic activity in the univariate analysis, but not in the multivariate analysis. Because only 11 patients received thrombolysis (four of whom presented electrical epileptic activity), no definitive conclusion can be drawn about the epileptogenic effect of rt-PA. However, our results suggest it may have a potential epileptogenic effect and warrant a careful follow-up of rt-PA-treated patients, especially those with secondary worsening possibly due to electrical seizures. In animal models, an increased excitotoxicity after IV administration of t-PA has been suggested to occur by amplification of intracellular calcium conductance²⁹ or activation of matrix metalloproteinases (MMPs), for example, MMP-9.^{30,31} In our study, in contrast to observations in other clinical^{22,25,32,33} or electrophysiologic⁸ studies, hemorrhagic stroke was not predictive of epileptic activity. The small sample size (N = 9) of patients with hemorrhagic stroke may be responsible for our results. Age, sex, cardiovascular risk factors, stroke cause, or interval from stroke onset to cEEG had no predictive value for epileptic activity.

Our study has several limitations. The small patient sample size, especially in the hemorrhagic stroke subgroup, is the main limitation because only 17 patients with electrical epileptic activity were recorded. In addition, the rare patients with stroke requiring invasive treatment or ventilation initially were admitted to the intensive care unit rather than the stroke unit. They were therefore not included in our study or were only included once their condition had improved sufficiently to be managed in our stroke unit. Regarding the technique, only 10 electrodes were used, which may have limited the detection of electrical seizures compared with a full set of electrodes. We chose this technique because it is more convenient to use on nonsedated patients admitted to a stroke unit who receive frequent nursing care. However, despite the use of only 10 electrodes, cEEG recording was interrupted in 18 patients, mainly due to patient movement secondary to agitation. Finally, the use of EEG-modifying medications may have influenced the detection of epileptic activity; however, there was no statistical impact of medication on the cEEG findings.

Our results show that, in addition to clinical examination and other acute diagnostic tests such as brain CT and MRI and transcranial Doppler ultrasonography, cEEG monitoring may be useful in the stroke unit. The impact of the electrical epileptic ac-

tivity on the clinical outcome and development of poststroke epilepsy must be assessed in further studies to optimize the management and treatment of acute stroke patients.

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Figure. Ergotism with cyanosis of the fingers bilaterally is evident in our patient while on pergolide (A and B). One week after stopping pergolide and starting ropinirole, the ergotism was remarkably improved (C and D).

Pergolide-induced ergotism

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Ergotism results from generalized vasoconstriction of small and large blood vessels and can lead to cyanosis and gangrene of affected limbs if not recognized. Ergotism occurs most commonly in the treatment of migraine with ergotamines today; however, ergot-derived drugs are also used in the treatment of restless legs

syndrome and Parkinson disease (PD). A 72-year-old African-American woman with advanced PD presented complaining of tingling and blue discoloration of her fingers and toes for 2 months (figure, A and B). She was taking a total of 8 mg per day of pergolide (an ergot-derived dopamine agonist) in order to avoid severe levodopa-induced dyskinesias. A noninvasive vascular evaluation was normal. One week after switching to ropinirole (a non-ergot dopamine agonist) the discoloration of her digits had markedly improved (figure, C and D), and it completely resolved within 3 months. While cardiopulmonary fibrosis is well-recognized with pergolide,^{1,2} clinicians should be aware that pergolide can also cause ergotism.

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