

Relevant obstetric factors associated with fetal heart rate monitoring for cerebral palsy in pregnant women with hypertensive disorder of pregnancy

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Abstract

Aim: The study identifies the relevant obstetric factors associated with fetal heart rate (FHR) monitoring for cerebral palsy (CP) in pregnant women with hypertensive disorders of pregnancy (HDP).

Methods: The subjects were neonates with CP (birth weight ≥ 2000 g, gestational age ≥ 33 weeks) who were approved for compensation for CP by the Operating Organization of the Japan Obstetric Compensation System between 2009 and 2012. After selection of women with antepartum HDP, obstetric characteristics associated with FHR monitoring were analyzed.

Results: The subjects included 33 neonates with CP whose mothers suffered from HDP during pregnancy and 450 neonates whose mothers did not develop HDP. The rates of placental abruption (48.5% vs. 20%; $P < 0.001$) and light-for-gestational age (12.1% vs. 2.2%; $P = 0.011$) were significantly higher in women with HDP than in those without HDP. Regarding FHR pattern analysis, fetal bradycardia was observed on admission to hospital in 94% of women with placental abruption. In women without placental abruption, FHR was likely to indicate a favorable pattern on admission, but became worse with the progression of labor.

Conclusion: This is first study to clinically demonstrate FHR patterns in CP cases in association with HDP. Although antepartum CP is undetectable, pregnant women with HDP should be placed under strict observation and management to minimize fetal hypoxic conditions during labor.

Key words: cerebral palsy, fetal heart rate, hypertension, hypertensive disorder of pregnancy, hypoxia, placental abruption.

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Introduction

Cerebral palsy (CP) is a physical disability that occurs in children. CP is associated with neonatal hypoxia and acidemia involved with non-reassuring fetal status during labor as a result of placental and umbilical cord abnormalities (placental abruption and umbilical cord prolapse).¹

The pathophysiology of hypertensive disorders of pregnancy (HDP) is complex and involves multiple organ systems. In this disorder, increasing resistance of maternal systemic blood vessels adversely affect blood flow, not only in maternal organ systems, but also the placenta, resulting in both maternal and neonatal pathologic conditions.^{2–4} Therefore, identifying the clinical course and obstetric factors of CP associated with HDP could be important for making recommendations for the management of HDP and reducing the rate of CP.

The present study aimed to identify the relevant obstetric factors associated with fetal heart rate (FHR) pattern for CP in pregnant women with HDP.

Methods

The details of the Japan Obstetric Compensation System for Cerebral Palsy (JOCSC) have been described in our previous report.¹ The JOCSC was launched in January 2009 to provide prompt no-fault compensation for children diagnosed with severe CP associated with obstetric factors and for their respective families. The JOCSC also provides information that could help in prevention, early resolution of disputes and improvement in the quality of obstetric health care. A case review for compensation is performed by a review committee. After a child is declared eligible to receive compensation by this review committee, the causes for CP are analyzed individually by the Causal Analysis Committee, which consists of obstetricians, pediatricians, midwives and lawyers. Once collected, the Recurrence Prevention Committee analyzes these individual cases from an epidemiological standpoint. The subjects of the current study were neonates with CP who were approved for compensation by a review of the Operating Organization of JOCSC.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical

standards. The Institutional Review Boards of the JOCSC approved the study. Written informed consent was not obtained from the patients; however, they were provided with a supplemental file announcing the implementation of a 'case-control study of cerebral palsy and prevention of its recurrence'. Although the analysis was retrospective, data from the anonymized JOCSC database were collected in a normal clinical setting and the confidentiality of the patients involved was protected. All patient records/information was de-identified prior to analysis.

Criteria for inclusion in the present study were as follows: neonates born between January 2009 and December 2012; with a birth weight of ≥ 2000 g, and gestational age ≥ 33 weeks; and with severe disability resulting from CP independent of congenital causes or factors during the neonatal period or later, with disability certified to be of first or second-degree severity according to the grade of disability definitions in the Welfare of Physically Disabled Persons Act.

After selection of the neonates of mothers with antepartum HDP, obstetric clinical characteristics associated with FHR pattern and disease course were analyzed. Cases were subcategorized into groups with and without placental abruption and the FHR record was retrospectively analyzed for each group.

We categorized cases into five different groups based on the FHR pattern at admission for labor and just before delivery according to Phelan *et al.*⁵ The bradycardia group comprised fetuses with bradycardia or persistent severe decelerations with loss of variability at admission for labor and no recovery until delivery. The persistent non-reassuring (NR) group comprised fetuses with non-reactive FHR and usually decreased baseline variability at admission for labor that persisted until delivery. The reactive-prolonged deceleration (PD) group comprised fetuses with a normal FHR pattern at admission for labor and acute severe prolonged deceleration or bradycardia before delivery. The Hon pattern group comprised fetuses with a normal FHR pattern at admission for labor. Consequently, recurrent severe decelerations with baseline heart rate increased and baseline variability decreased. Finally, terminal prolonged deceleration or bradycardia occurred before delivery. The persistent reactive group comprised fetuses with a normal FHR range during the entire course.

Cerebral palsy was defined as a disturbance in motor function or posture in neonates that was permanent or variable. This disorder is based on a non-progressive cerebral lesion that develops between

Table 1 Characteristics of the subjects

Characteristic	With HDP (<i>n</i> = 33)	Without HDP (<i>n</i> = 450)	<i>P</i>
Maternal characteristics			
Age	33.2 ± 5.4	31.1 ± 5.2	0.025
Height (cm)	156.4 ± 5.5	157.9 ± 5.6	0.119
Weight at beginning of pregnancy (kg)	56.2 ± 7.4	53.9 ± 10.5	0.214
BMI (kg/m ²)	23.1 ± 3.1	21.6 ± 4.2	0.055
Weight at delivery (kg)	66.0 ± 8.1	64.0 ± 10.1	0.267
Weight gain (kg)	9.6 ± 4.6	10.1 ± 4.1	0.463
Parity (median, range)	0 (0–4)	0 (0–5)	0.895
<i>In vitro</i> fertilization	6.1% (2)	3.6% (16)	0.352
Mode of delivery			
Normal spontaneous	15.2% (5)	28.2% (127)	0.204
Instrumental	12.1% (4)	16.2% (73)	
Elective CS	3.0% (1)	2.0% (9)	
Emergency CS	69.7% (23)	53.6% (241)	
Delivery at			
Hospital	90.9% (30)	64.4% (290)	0.008
Small hospital with < 20 beds	9.1% (3)	34.7% (156)	
Midwifery home	0.0% (0)	0.9% (4)	
Maternal transport after onset of labor	18.2% (6)	8.7% (39)	0.110
Neonate			
Multiple pregnancy	6.1% (2)	4.2% (19)	0.647
Gestational weeks	37.4 ± 2.1	38.3 ± 1.9	0.011
Birth weight (g)	2582 ± 372	2889 ± 453	< 0.001
Birth weight (SD)	−0.7 ± 0.7	−0.1 ± 1.1	0.005
Male	36.4% (12)	53.6% (241)	0.070
Apgar score 1 min (median, range)	1 (0–8)	2 (0–10)	0.017
Apgar score 5 min (median, range)	3 (0–8)	4 (0–10)	0.016
Umbilical artery PH	6.844 ± 0.235	6.990 ± 0.269	0.015

BMI, body mass index; CS, cesarean section; HDP, hypertensive disorder of pregnancy; SD, standard deviation.

conception and the neonatal period (within 4 weeks after birth). However, this definition excludes motor retardation that is either transient or normalizes in the future.

The definition and classification of HDP used in this study followed the guidelines published by the Japan Society for the Study of Hypertension in Pregnancy for Japanese obstetric care providers.⁶ HDP was defined as hypertension (blood pressure ≥ 140/90 mmHg) with or without proteinuria (0.3 g in a 24 h urine specimen or a protein-to-creatinine ratio of > 0.30) emerging after 20 weeks of gestation and resolving up to 12 weeks post-partum. Mild HDP was diagnosed when blood pressure was ≥ 140/90 mmHg, but < 160/110 mmHg after 20 weeks' gestation, and proteinuria was ≥ 300 mg/24 h without exceeding 2.0 g/24 h or 3+ dipstick test results were observed. Severe HDP was diagnosed when blood pressure was ≥ 160/110 mmHg and proteinuria exceeded 2.0 g/24 h or a 3+ dipstick test results were

observed. HDP that emerged earlier than 32 weeks' gestation was referred to as early-onset and HDP that emerged after 32 weeks' gestation was referred to as late-onset.

Light-for-gestational age infants were diagnosed as weighing lower than the 10th percentile based on the standard of Japanese birth for the gestational period.

Statistical analysis

A two-sided *P* value of 0.05 was used to define statistical significance. All analyses were conducted using STATA version 13.0. Continuous variables are reported as mean ± standard deviation and were compared using Student's *t* or Mann–Whitney *U* tests. Integer variables are reported as median and range, and were compared using the Mann–Whitney *U* test. Categorical variables are reported as frequencies and were compared using Fisher's exact test.

Table 2 Major relevant obstetric factors for cerebral palsy reviewed by the Operating Organization of the JOCSC in neonates and mothers with and without HDP

Major relevant obstetric factors for cerebral palsy	With HDP (<i>n</i> = 33)		Without HDP (<i>n</i> = 450)		<i>P</i>
Light for gestational age	4	12.1%	10	2.2%	0.011
Placental abnormalities	17	51.5%	115	25.6%	0.002
Placental abruption	16	48.5%	90	20.0%	< 0.001
Placental abruption	(15)		(86)		
Placental abruption and cord abnormality	(0)		(3)		
Placental abruption with uterine rupture	(0)		(1)		
Maternal shock after placental abruption	(1)		(0)		
Bleeding of placenta previa	0	0.0%	2	0.4%	1.000
Feto-maternal blood transfusion	0	0.0%	14	3.1%	0.613
Monochorionic-diamniotic twins	1	3.0%	9	2.0%	0.511
Umbilical cord abnormalities	2	6.1%	111	24.7%	0.011
Umbilical cord prolapse	1	3.0%	20	4.4%	
Umbilical cord prolapse with cord abnormality	0	0.0%	1	0.2%	
Cord abnormalities	1	3.0%	77	17.1%	
Cord abnormalities and infectious disease	0	0.0%	12	2.7%	
Cord abnormalities and IVH in neonate	0	0.0%	1	0.2%	
Maternal complications	2	6.1%	47	10.4%	0.561
Uterine rupture	0	0.0%	17	3.8%	
Infectious disease	0	0.0%	22	4.9%	
Maternal cardiopulmonary arrest	0	0.0%	2	0.4%	
Amniotic fluid embolism	0	0.0%	3	0.7%	
Eclampsia	2	6.1%	0	0.0%	
Gestational diabetes mellitus	0	0.0%	2	0.4%	
Diabetes mellitus	0	0.0%	1	0.2%	
Neonatal complications	0	0.0%	10	2.2%	1.000
Blood type incompatibility	0	0.0%	1	0.2%	
IVH	0	0.0%	3	0.7%	
Cerebral infarct	0	0.0%	2	0.4%	
Hypoglycemia	0	0.0%	1	0.2%	
Tension pneumothorax	0	0.0%	1	0.2%	
Ventricular tachycardia	0	0.0%	1	0.2%	
Persistent pulmonary hypertension of the newborn	0	0.0%	1	0.2%	
Other causes or unexplained	8	24.2%	157	34.9%	0.256

Umbilical cord abnormalities included velamentous or marginal cord insertion, hypercoiled cord, cord entanglement, a true knot, a single umbilical artery and umbilical cord constriction. Events associated with intervention during labor included vacuum extraction, forceps delivery, induction of labor and uterine fundal pressure. HDP, hypertensive disorder in pregnancy; IVH, intraventricular hemorrhage; JOCSC, Japan Obstetric Compensation System for Cerebral Palsy.

Results

Four hundred and eighty-three cases of CP from the JOCSC database were included in the study. Thirty-three neonates with CP born from pregnant women complicated by HDP during pregnancy and 450 neonates born from pregnant women without HDP were compared. The characteristics of these subjects are shown in Table 1. Neonates born to mothers with HDP were smaller and of an earlier gestational age.

The major relevant obstetric factors for CP reviewed by the JOCSC in pregnant women with and without HDP are shown in Table 2. The rate of light-for-gestational age was significantly higher in children

born to mothers with HDP than in those born to mothers without HDP ($P = 0.011$). Placental abruption was significantly in higher in children born to mothers with HDP than in those born to mothers without HDP ($P < 0.001$).

A summary of 16 neonates with CP after placental abruption in mothers with HDP is shown in Table 3. There were no light-for-gestational age infants. Severe HDP at the onset of placental abruption was observed in three (19%) women. Transfer of the mother and newborn to intensive care was required after the occurrence of placental abruption in four women because treatment was difficult in the clinic. In FHR pattern analysis, bradycardia was observed on

Table 3 Summary of cases of cerebral palsy associated with placental abruption in HDP cases

Case	GA onset of HDP	Initial symptom at onset of PA	Severity of HDP at onset of PA	GA at delivery	BW (g)	(SD)	Apgar score	UApH	Mode	Initial abnormal FHR	Interval between initial abnormal FHR and delivery	Interval between decision and delivery	Category of FHR monitoring	Delivery institution
1	31	Abdominal pain	Mild	33 + 1	2026	0.1	0/0	6.61	emCS	On admission	01:10	01:10	Persistent bradycardia	Hospital
2	30	Bleeding	Severe	34 + 4	2114	-0.5	0/0	6.71	emCS	With abdominal pain	02:07	00:28	Persistent bradycardia	Hospital
3	35	Abdominal pain during hospitalization for HDP	Mild	35 + 4	2332	-0.4	1/1	6.58	emCS	On admission	00:35	00:31	Persistent bradycardia	Hospital
4	35	Abdominal pain, PROM	Severe	35 + 6	2290	-0.7	0/0	n/r	emCS	On admission	04:13	01:03	Persistent bradycardia	Hospital
5	33	Bleeding	Mild	36 + 1	2148	-1.3	6/7	7.01	emCS	On admission	03:37	00:45	Hon pattern	Hospital
6	36	Abdominal pain	Mild	36 + 2	2450	-0.4	0/0	n/r	emCS	On admission	00:15	00:15	Persistent bradycardia	Hospital
7	36	Bleeding	Severe	36 + 5	2522	-0.3	1/2	6.57	emCS	On admission	01:18	01:21	Persistent bradycardia	Hospital
8	36	Headache	Mild	36 + 5	2568	-0.2	0/4	n/r	emCS	On admission	00:57	00:57	Persistent bradycardia	Clinic-Hospital (transport)
9	36	Abdominal pain loss fetal movement	n/r	36 + 6	2334	-1.0	0/2	6.67	emCS	On admission	00:32	00:27	Persistent bradycardia	Hospital
10	37	Abdominal pain	Mild	37 + 3	2444	-1.0	0/0	n/r	emCS	On admission	01:38	01:38	Persistent bradycardia	Clinic-Hospital (transport)
11	35	Abdominal pain, PROM	Mild	37 + 4	2448	-1.0	0/3	6.62	emCS	On admission	06:03	00:11	Persistent bradycardia	Hospital
12	38	Abdominal pain	Mild	38 + 1	2478	-1.2	2/4	6.75	emCS	On admission	00:48	00:33	Persistent bradycardia	Clinic
13	38	Bleeding	Mild	38 + 2	2680	-0.6	1/1	6.70	NSD	On admission	00:36	00:36	Persistent bradycardia	Clinic-Hospital (transport)
14	38	Abdominal pain	Mild	38 + 2	2736	-0.4	1/5	6.71	emCS	On admission	02:24	00:35	Persistent bradycardia	Hospital
15	36	Hypotension	Mild	38 + 2	2824	-0.2	1/2	n/r	emCS	On admission	00:52	00:52	Persistent bradycardia	Clinic-Hospital (transport)
16	37	Onset of labor	Mild	38 + 6	2806	-0.5	0/0	6.76	VEG, UFP	On admission	01:55	00:11	Persistent bradycardia	Hospital

BW, birth weight; emCS, emergency cesarean section; FHR, fetal heart rate; GA, gestational age; HDP, hypertensive disorder of pregnancy; LD, late deceleration; NSD, normal spontaneous delivery; n/r, not reported; PA, placental abruption; PD, prolonged deceleration; SD, standard deviation; UA pH, umbilical artery pH; UFP, uterine fundal pressure; VEG, vacuum extraction.

admission to hospital in 94% (15/16) of fetuses. Most women with placental abruption underwent immediate emergency cesarean section. Only one woman had an umbilical artery pH of > 7.0 .

A summary of 11 cases of CP without placental abruption in mothers with HDP is shown in Table 4. Five of these 11 (45%) neonates were light-for-gestational age. FHR pattern analysis showed that the reassuring pattern was noted on admission, including reactive-PD, Hon pattern and persisting reassuring in 64% (7/11) of fetuses. However, they were considered to have suffered asphyxia during labor, resulting in CP, because prolonged deceleration or the Hon pattern of FHR was observed before delivery, except in cases of monochorionic diamniotic twins. The reactive-PD group was associated with umbilical cord prolapse, vasa previa, light-for-gestational age and eclampsia.

Discussion

In our study, neonates with CP who weighed ≥ 2000 g at birth after at least 33 weeks' gestation were more frequently terminated because of light-for-gestational age and placental abruption in women who suffered from HDP than in women without HDP. Furthermore, FHR pattern analysis showed bradycardia suspected long before admission may lead to CP from placental abruption in mothers of HDP. On the other hand, in women without placental abruption, the FHR pattern was likely to indicate a favorable fetal condition on admission, but FHR became worse, such as loss of baseline variability, late decelerations and prolonged decelerations, with the progression of labor.

Impaired placentation, placental insufficiency, intra-uterine hypoxia and uteroplacental underperfusion are considered important mechanisms causing placental abruption.^{7–10} In our study, infants of CP had been induced hypoxic condition because of persistent bradycardia in association with placental abruption in women with HDP. In fact, some pregnant women with HDP required maternal transport to a higher-grade hospital to receive intensive care because of the occurrence of placental abruption.

Even if placental abruption does not occur, because it is thought that conditions including HDP and fetal growth restriction associated with ischemic placental disease can originate during the first trimester, these may be linked through a unified pathophysiological mechanism.^{11,12} Contrary to CP with placental

abruption in HDP, newborns with CP delivered by mothers with HDP without placental abruption were likely to be light-for-gestational age and were associated with a persistent non-reassuring pattern on admission. In women without placental abruption, bradycardia and non-reassuring fetal status at delivery were observed with the progression of labor in association with CP, while FHR pattern indicated a reassuring condition on admission. Such unfavorable conditions of hypoxia might have been induced by uteroplacental underperfusion with reduced placental function as a result of HDP and uterine contractions.

Our results suggest that if a pregnant woman with HDP is at a hospital in which emergency cesarean section is not available, the patient should be immediately transferred to a tertiary hospital, even those with mild HDP. This will enable preparation of an acute delivery when progression to crucial conditions occurs, such as placental abruption or eclampsia. Additionally, caregivers in delivery services should perform FHR monitoring strictly in mothers with HDP because FHR is likely to worsen with the progression of labor, especially in growth-restricted fetuses in women with HDP. Daily improvement of obstetric systems in hospitals, including suitable staffing and education and training for obstetric emergency personnel in HDP, is also required.

Whether acute delivery can prevent CP after the occurrence of fetal growth restriction and placental abruption occurring in pregnant women with HDP is unclear. HDP is considered to be related to chronic uteroplacental underperfusion with its origin in the first trimester.^{11,12} Therefore, in some cases of HDP, antepartum CP might already be present when placental abruption occurs. In fact, a persistent NR pattern on admission was observed in our case series with HDP.

Although fetal and neonatal death was not evaluated in the present study, intensive care, even in cases of mild HDP, and preparation of immediate delivery will reduce the mortality rate associated with HDP. However, it is unclear whether the incidence of CP can be reduced. Furthermore, no fetal growth restriction was observed in women complicated with HDP and placental abruption in our study. This is because newborns with CP who were enrolled in the JOCSC weighed ≥ 2000 g after at least 33 weeks' gestation. It is thought that newborns with CP were more frequently observed when delivered by mothers suffering severe HDP during earlier gestation. Further research on the management of severe fetal growth restriction and earlier HDP onset are needed.

Table 4 Summary of cases of cerebral palsy without placental abruption in HDP cases

Case	GA at onset of HDP	GA at admission	Cause of admission	Severity of HDP on admission	GA at delivery (g)	BW (g)	SD	Apgar	UApH	Mode (indication)	Onset of abnormal FHR	Interval between initial FHR abnormality and delivery	Interval between decision and delivery	Category of FHR monitoring	Final Causation of cerebral palsy	Delivery institution
1	33	33	HDP	Severe	34 + 2	2310	0.4	3/6	7.09	Elective CS (MD twin, GH)	No	n/a	Elective CS	Persistent reassuring	Monochorionic diamniotic twin	Hospital
2	33	35	HDP	Severe	35 + 4	2009	-1.5	4/5	7.00	emCS (NRFS)	On admission	32:32	02:50	Persistent NR	Light for gestational age	Hospital
3	34	36	Headache, stomachache and HDP	Severe	37 + 0	2095	-1.9	4/4	6.64	NSD	On admission	14:43	No acute delivery	Persistent NR	Light for gestational age	Clinic-Hospital (transport)
4	32	32	HDP	Severe	37 + 4	2116	-2.0	1/5	7.20	emCS (DD twin, PROM)	NST during hospitalization	25:43	01:57	Persistent NR	Light for gestational age	Hospital
5	39	39	PROM	Severe	39 + 2	3194	0.5	3/4	6.63	VEG, FD (GH, NRFS)	During labor	02:13	00:48	Hon pattern	Others	Clinic
6	40	40	Onset of labor	Mild	40 + 0	2430	-1.9	3/4	7.02	emCS (NRFS)	During labor	00:42	00:12	Reactive-PD	Light for gestational age	Hospital
7	40	40	PROM	Severe	40 + 4	3160	-0.1	1/2	n/r	emCS (GH, NRFS)	On admission	49:59	00:34	Persistent NR	Eclampsia	Hospital
8	39	39	Onset of labor	Mild	40 + 0	3326	0.6	0/1	n/r	VEG (NRFS)	During labor	02:11	01:07	Hon pattern	Others	Hospital
9	38	40	Oligohydramnios at pregnancy check up	Mild	40 + 3	2594	-1.5	1/3	n/r	VEG, emCS (umbilical cord prolapse)	During labor	00:53	00:33	Reactive-PD	Umbilical cord prolapse	Hospital
10	37	38	HDP	Severe	38 + 5	2503	-1.3	1/1	n/r	emCS (Vasa previa, NRFS)	During labor after ROM	00:48	00:39	Reactive-PD	Vasa previa	Hospital
11	41	41	PROM	Severe	41 + 5	3250	-0.2	2/6	6.89	emCS (eclampsia)	During labor	01:24	00:27	Reactive-PD	Eclampsia	Clinic-Hospital (transport)

BW, birth weight; CS, cesarean section; DD, dichorionic diamniotic; emCS, emergency CS; FD, forceps delivery; FHR, fetal heart rate; GA, gestational age; LD, late deceleration; MD, monochorionic diamniotic; NRFS, non-reassuring fetal status; n/r, not reported; NSD, normal spontaneous delivery; PD, prolonged deceleration; PROM, premature rupture of membrane; SD, standard deviation; UApH, umbilical artery pH; VD, variable deceleration; VEG, vacuum extraction.

In conclusion, this large nationwide study shows that relevant obstetric factors for CP after 33 weeks' gestation in association with HDP are light-for-gestational age and placental abruption. This is the first study to clinically demonstrate FHR patterns in CP cases in association with HDP. Most newborns with CP whose mothers suffer placental abruption already have fetal bradycardia when the mother is admitted to hospital. In cases without placental abruption, newborns were likely to be light-for-gestational age and FHR pattern was associated with a persistent non-reassuring pattern on admission. Even in cases of a favorable FHR pattern on admission, FHR is likely to become worse with the progression of labor. Therefore, although detection of antepartum CP is impossible, pregnant women with HDP should be placed under strict observation, including maternal and fetal monitoring, to minimize fetal hypoxic conditions during labor.

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Disclosure

No authors have any conflict of interest to report.

Author contributions

All authors have read and approved the final version of the manuscript.

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