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Original Article

Impact of blood glucose fluctuation on endothelial dysfunction and severity of stenosis in aged acute coronary syndrome patients

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Abstract: Background: We evaluated the impact of blood glucose fluctuation to endothelial cell damage and the severity of coronary artery lesion in elderly acute coronary syndrome (ACS) patients with or without type 2 diabetes mellitus (T2DM). Methods: A total of 128 patients with ACS were enrolled, 80 of them with T2DM were recruited in group A; the other 48 without T2DM were recruited to group B, 40 healthy volunteers were selected as control (group C). The level of vWF in each group were measured, CGM (72 hours) were conducted to evaluate LAGE, MAGE, SDBG, MODD, MPPGE and MPMG. Results: Compared with control group, the level of FPG, CRP, HOMA-IR, vWF, LAGE, MAGE, SDBG in group A and group B were significantly higher (P<0.01). The level of MODD, MPPGE, MPMG, PPGE1, PPGE2, PPGE3 in group A were significantly higher (P<0.01); Compared with group B, the level of HbA1c, Fins, HOMA-IR, vWF, LAGE, MAGE, SDBG, MODD, MPPGE, MPMG, PPGE1, PPGE2, PPGE3 were significantly higher in group A (P<0.01). MAGE were positively related with age, HbA1c, HOMA-IR, CRP, vWF (P<0.01); LAGE, MAGE, SDBG and MPPGE were positively related with HOMA-IR (P<0.05); Multiple stepwise regression analysis showed MAGE, MODD, and CRP were independently associated with Gensini score (P<0.001). MAGE and CRP were the impact factors of endothelial dysfunction. Conclusion: Compared with persistent hyperglycemia, acute glucose fluctuations further aggravate the degree of coronary lesions.

Keywords: Type 2 diabetes mellitus, coronary disease, continuous glucose monitoring, von Willebrand factor

Introduction

Acute coronary syndrome (ACS) has become one major factor causes high morbidity and mortality for diabetic patients with s acute onset [1-3]. Numerous research results have revealed that the hyperirritability of blood glucose in ACS patients is very common [4, 5]. In fact, blood glucose persistent increase only reflected certain aspects of the glucose metabolism disorders, the tempestuously fluctuation of blood glucose value between maximum and minimum also cannot be ignored. The dysfunction and damage of endothelial cells is the initial step of chronic diabetic vascular complications [6], which have been proved in patients with diabetes or insulin resistance, and type 2 diabetes patients with high risk factors [7]. In recent years, many studies have shown that compared with persistent high blood glucose, intermittent high blood glucose more exacerbated vascular endothelial cell damage and dysfunction, thereby accelerated the development of the complications [8, 9] while the precise mechanism are few elucidated.

Research focused on the relationship between glucose fluctuation and endothelial cell damage in acute coronary syndrome patients with the application of continuous glucose monitoring system (CGMS) is rare, in this study, the 72 hours continuous glucose monitoring for acute coronary syndrome patients were performed, they all in acute phase after hospitalization, we tested the Von Willebrand factor (vWF) level and compared the blood glucose fluctuation, endothelial cell damage extent of acute coronary syndrome patients with or without type 2 diabetes. The relationship between blood glucose fluctuation, the impact to the vascular

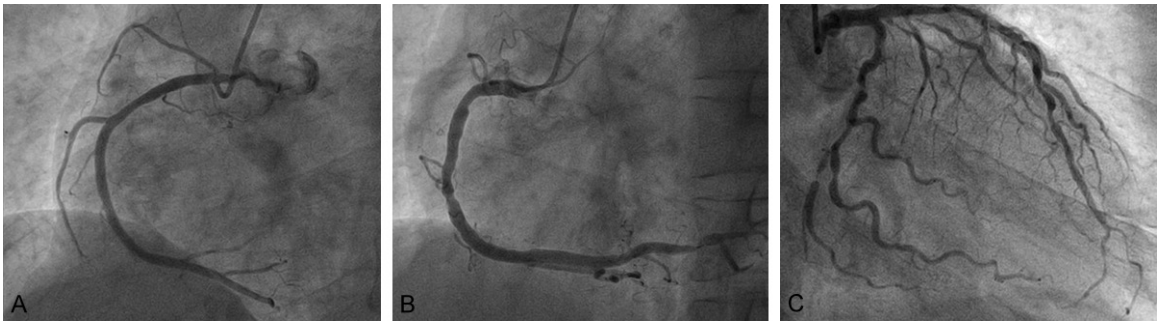

Figure 1. Coronary angiography evaluated by Gensini score. A. Mild stenosis of right coronary artery and its branch with Gensini of 2; B. Moderate stenosis of right coronary artery and its branch with Gensini of 23; C. Severe stenosis of left coronary artery and its branches with Gensini of 112.5.

endothelial cell damage and the severity of coronary lesion in acute coronary syndrome patients were analyzed to provide the basic information for clinical prevention and treatment in ACS patients with type 2 diabetes.

Methods

The study has been approved and registered in Ethics Committee of the First Hospital Affiliated to General Hospital of PLA in January 2011, the Ethics committee approved relating screening, treatment, and data collection of these patients, all subjects signed written informed consent form. Eligibility for the study was based on a diagnosis over a minimum 6 months' period. All works were undertaken following the provisions of the Declaration of Helsinki.

Subjects

A total of 128 patients diagnosed of ACS were enrolled in this study according to the ESC diagnostic criteria 2007 [10] and ACC/AHA diagnostic criteria in 2007 [11]. Forty of them were diagnosed of T2DM according to the WHO diagnostic criteria in 1999 [12].

The inclusion criteria of these ACS patients were: Resting or minor labor typical chest pain lasting more than 20 min; Attack with an electrocardiogram reversible ST-elevation >0.1 mm at least two adjacent leads ischemic; Myocardial enzyme creatine kinase (CK) and creatine kinase isoenzyme (CK-MB) activity rise more than 2 times of high normal range can be diagnosed with ST elevation myocardial infarction; ECG is not typical of ST segment elevation, normal, lower ST segment is the non ST-elevation myocardial infarction; lower ST segment with no myocardial enzyme increased was diagnosed of unstable angina.

The excluded criteria were: patient had acute complications of diabetes nearly a month; had spinal cord injury, nerve muscle joint or muscle disease; Traumatic and other neurological diseases caused by genetic, autoimmune, toxic or peripheral neuropathy; had chronic glomerulonephritis and other serious kidney disease such as systemic lupus erythematosus, allergic purpura; severe acute infection or tumor patients; patients with hyperthyroidism, acromegaly and endocrine diseases; patients had rheumatic valvular disease, cardiomyopathy disease. Such strict criteria aimed to guarantee that the ACS patients in the current study mainly have diabetes except for other major diseases, so avoiding other disease intervention to blood glucose fluctuation as much as possible.

Healthy individuals without history of diabetes mellitus and coronary artery disease were recruited from hospital employee, as well as community inhabitants in Beijing. Exclusion criteria included patients treated with steroid or nonsteroidal anti-inflammatory drugs, patients who had experienced an acute concurrent illness during the 6-month period preceding the investigation. They were set as normal control group (Group A, n=40).

Coronary angiography

For ACS patients, coronary angiography was performed to assess the coronary artery lesion severity in Beijing Military General Hospital. According to coronary angiography results, 128 patients were divided into 2 groups: with T2DM (group B, n=80) and without T2DM (Group C,

Table 1. Clinical data and laboratory test results in ACS patients and control

	Control	ACS group	*P* value
Systolic pressure (mmHg)	113.5±13.1	124.1±16.8	0.077
Diastolic pressure (mmHg)	72.0±11.8	75.3±10.2	0.391
M/F (N)	16/24	80/48	0.425
Age (yr)	56.3±6.1	59.3±10.9	0.277
Smoking (%)	60%	62.5%	0.000
Drinking (%)	80%	68.7%	0.112
HbA1c (%)	5.3±0.3	7.2±1.8	0.000
FPG (mmol/L)	5.1±0.4	10.1±4.8	0.000
TC (mmol/L)	4.2±0.3	4.2±0.9	0.705
LDL (mmol/L)	2.1±0.2	2.8±0.8	0.000
HDL (mmol/L)	0.9±0.1	1.0±0.2	0.680
Fins (mIU/L)	7.0±0.4	18.9±20.9	0.003
CRP (mg/L)	1.0±0.2	12.0±13.0	0.000
TG (mmol/L)	1.6±0.7	1.3±0.6	0.006
HOMA-IR	1.6±0.2	8.2±9.0	0.000
LVEF (%)	60±2	55±8	0.093
vWF (U/L)	141.9±46.4	454.2±230.9	0.000

P value was calculated by student's t-test.

Table 2. Comparison of blood glucose index between ACS group and control

	Control	ACS group	*P* value
LAGE	3.3±0.9	8.8±4.1	0.000
MAGE	2.5±0.4	5.5±3.4	0.000
SDBG	0.8±0.3	2.2±1.2	0.000
MODD	0.7±0.2	2.4±1.5	0.000
MPPGE	2.0±0.2	2.7±1.7	0.019
MPMG	2.9±0.7	12.4±3.5	0.000

P value was calculated by student's t-test.

n=48). All subjects signed an informed consent form.

Medical records and laboratory test

According to the original medical records, we collected patient's age; gender, diabetes duration, and smoking, drinking history data, blood pressure of these patients were measured after they were admitted.

Venous blood samples were drawn at morning at 1th day of admitted. The following laboratory measurements were obtained: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) and insulin. Homeostasis model assessment of insulin resistance (HOMA-IR) measure were be used as index of insulin resistance. We obtained left ventricular ejection fraction (LVEF) according to the results from echocardiography. In this study, von Willebrand factor (vWF) was detected by enzyme linked immunosorbent assay (ELISA) according to the vWF kit (Roche Diagnostics, Tokyo, Japan) guidance.

CGMS measurements

All ACS patients were wearing continuous glucose monitoring system (CGMS, Medtronic MiniMed, USA) in 2th day admitted to hospital; Control group were monitored after oral glucose tolerance test (OGTT) finished; ACS patients without T2DM were performed OGTT in a stable condition to exclude abnormal glucose tolerance and diabetes. The monitored data obtained from an abdominal subcutaneous sensor probes, a total of 576 measurements data were obtained every day, these data were corrected 4 times by blood glucose value of fingers every day, the monitoring lasted 72 hours; the range of effective monitoring value is 2.2-22.2 mmol/L. The meals time per day were fixed and unified during CGMS monitor, the mean absolute deviation of CGMS is (9.4±0.4)%. The Largest amplitude of glycemic excursions (LAGR), mean amplitude of glycemic excursions (MAGE), mean level of 24 h standard deviation of blood glucose (SDBG), absolute means of daily differences (MODD), mean of postprandial glucose excursion (MPPGE), mean post meal maximum glucose (MPMG), postprandial glucose excursion (PPGE) after breakfast (PPGE1), lunch (PPGE2) and dinner (PPGE3) were measured according to CGMS monitoring data. The entire indexes in the current study were tested at the same day, and the testing times are close. We made sure that all the indexes are consistent at the same physical condition.

Quantitative coronary arteriography

QCA was carried out by the GE Innova 3100 digital equipment according to standard techniques, and multiple views were stored on a CD-ROM. The angiograms were evaluated by

Table 3. Clinical data and laboratory test result in 3 groups

	Control	Group B	Group A
Systolic pressure (mmHg)	113.5±13.1	123.8±16.4	124.2±17.5
Diastolic pressure (mmHg)	72.0±11.8	77.3±9.0	74.1±10.8
M/F (N)	16/24	32/16	48/32
Duration of diabetes (month)			68.9 (40.5~117.1)
Age (yr)	56.3±6.1	57.9±11.2	60.2±10.9
Smoking (%)	37.5%	45.5%	33.3%
Drinking (%)	44.4%	45.5%	37.5%
HbA1c (%)	5.3±0.3	5.3±0.4	8.3±1.4$^{\#\#}$
FPG (mmol/L)	5.1±0.4	9.1±5.3*	10.7±4.5**
TC (mmol/L)	4.2±0.3	4.7±0.6	3.9±1.0$^{\#\#}$
LDL (mmol/L)	2.1±0.2	3.1±0.7**	2.6±0.9
HDL (mmol/L)	0.9±0.1	1.1±0.1	1.0±0.2
Fins (mIU/L)	7.0, 6.8~7.3	10.4, 9.7~11.1	18.5, 13.6~25.1$^{**,\#\#}$
CRP (mg/L)	1.0±0.2	10.5±8.6*	12.9±15.3*
TG (mmol/L)	1.6±0.1	1.4±0.5	1.3±0.6
HOMA-IR	1.6, 1.5~1.7	3.7, 2.6~5.3**	7.8, 5.6~11.0$^{**,\#\#}$
LVEF (%)	60±2	54±7	56±8
vWF (U/L)	141.9±46.4	266.6±91.9*	521.7±247.7$^{**,\#}$
Gensini		55±20	66±42

*, P<0.05, compared with NC group; **, P<0.01, compared with NC group. #, P<0.05, compared with group B; ##, P<0.01, compared with group B.

Table 4. Comparison of dynamic blood glucose monitoring index and 3 postprandial blood glucose fluctuations between 3 groups

	Control	Group B	Group A
LAGE	1.2, 27.~3.8	1.6, 4.7~5.7**	2.3, 8.7~12.4$^{**,\#\#}$
MAGE	0.4, 1.2~1.8	0.9, 1.8~3.1*	1.8, 4.8~8.1$^{**,\#\#}$
SDBG	0.3, 0.6~1.0	0.1, 1.1~1.2*	0.9, 2.1~3.2$^{**,\#\#}$
MODD	0.7±0.2	1.5±0.8	2.9±1.6$^{**,\#\#}$
MPPGE	2.0±0.2	2.3±0.5	3.6±1.6$^{**,\#\#}$
MPMG	2.9±0.7	8.9±0.5**	14.5±2.8$^{**,\#\#}$
PPGE1	0.7±0.3	1.1±0.3*	2.2±1.0$^{**,\#\#}$
PPGE2	0.3±0.1	0.5±0.1*	0.7±0.4$^{**,\#\#}$
PPGE3	0.4±0.1	0.3±0.1*	0.7±0.4$^{**,\#\#}$

*, P<0.05, compared with NC group; **, P<0.01, compared with NC group. ##, P<0.01, compared with group B.

two experienced imaging doctor who were blinded to the results of the experiment. The 4 main coronary branches-left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) and side branches with a diameter of ≥2.0 mm-were diagnosed of significant narrowing (≥50% diameter reduction) of the lumen. Stenosis of coronary arteries was categorized according to the reporting system proposed by the American Heart Association. The stricture level and affected area and extension were quantified based on the Gensini scoring system [13] (**Figure 1**).

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 software. Measurements were expressed as mean ± SD. T-test was used in comparison of two groups and single factor analysis of variance was used in comparison in three groups. Non-normal distribution data were logarithmic converted to normal distribution data. The general linear model was used to compare the means among multi-groups. The Dunnett T3 test was used to measure heterogeneity of variance during the multiple comparisons of the means of all groups. In addition, Pearson's correlation analysis was performed for multiple stepwise regression analysis. *P*<0.05 was taken as the level of significance.

Results

Comparison between ACS patients and normal control

As we can see from **Table 1**, compared with control, the age, blood pressure and sex ratio of ACS patients have no significant difference (P>0.05). Smoking ratio, FPG, Fins, CRP, HbA1c, LDL, HOMA-IR and vWF were significantly increased significantly in ACS patients (62.5%, 10.1±4.8 mmol/L, 18.9±20.9 mIU/L, 12.0±13.0 mg/L, 7.2±1.8%, 2.8±0.8 mmol/L, 8.2±9.0, 454.2±230.9 U/L) compared with control (60%, 5.1±0.4, 7.0±0.4, 1.0±0.2, 5.3±0.3, 2.1±0.2, 1.6±0.2, 141.9±46.4) (P<0.05). The LAGE, MAGE, SDBG, MODD, MPPGE and MPMG in ACS patients (8.8±4.1, 5.5±3.4, 2.2±1.2, 2.4±1.5, 2.7±1.7, 12.4±3.5) increased significantly compared with control (3.3±0.9, 2.5±0.4,

Table 5. The correlation analysis result of MAGE and related factors in ACS patients

MAGE (mmol/L)	r value	*P* value
Age (yr)	0.107	0.28
HbA1c (%)	0.618	0
HOMA-IR	0.405	0.011
SBP (mmHg)	0.259	0.076
DBP(mmHg)	-0.087	0.319
LVEF (%)	0.124	0.429
PPGE1 (mmol/L)	0.479	0.002
PPGE2 (mmol/L)	0.31	0.042
SDBG (mmol/L)	0.618	0
MPPGE (mmol/L)	0.405	0.011
vWF (U/L)	0.479	0.002
CRP (mg/L)	0.365	0.02

0.8±0.3, 0.7±0.2, 2.0±0.2, 2.9±0.7) with statistical significance (P<0.05) (**Table 2**).

Comparison between the 3 groups

Result showed in **Table 3**, compared with control, FPG, LDL, CRP, HOMA-IR and vWF in group B increased significantly (P<0.05); HbA1c, FPG, Fins, CRP, HOMA-IR, vWF, MODD and MPPGE in group A increased significantly (P<0.05). LAGE, MAGE, SDBG, MPMG and postprandial glucose excursions of 3 dinners in group A and B increased significantly with statistical significance (P<0.05); While SBP, DBP, sex ratio, age, smoking and drinking, TC, TG, LVEF have no significant difference (P>0.05); Compared with group B, HbA1C, Fins, HOMA-IR, vWF LAGE, MAGE, SDBG, MODD, MPPGE, MPMG and postprandial glucose excursions of 3 dinners in group A increased significantly with statistical significance (P<0.01); while SBP, DBP, sex ratio, smoking and drinking, age, HDL, LDL, TG, FPG, CRP, LVEF and Gensini score have no significant difference (P>0.05) (**Table 4**).

The linear correlation analysis of MAGE and related factors in ACS patients

The correlation analysis result (**Table 5**) showed MAGE was correlated with HbA1c, HOMA-IR, CRP, vWF, SDBG, MPPGE, PPGE1 and PPGE2 positively with r value of 0.618, 0.405, 0.365, 0.479, 0.618, 0.405, 0.479 and 0.310 separately with P<0.01.

Stepwise multiple regression analysis result

We analyzed the relevant factors of coronary artery disease severity and endothelial cell damage in ACS patients, Gensini score was considered as the dependent variable, the age, sex ratio, smoking and drinking, SBP, DBP, TG, TC, LDL, HDL, CRP, LVEF, HOMA-IR, HbA1c, LAGE, MAGE, SDBG, MODD, MPPGE and MPMG were considered as the independent variables. Forward method, regressive method and stepwise regression were used for screen meaningful independent variables respectively, and then meaningful independent variables were screened as descripted above together. We finally selected independent variables include MAGE, MODD and CRP, which had better fitted regression equation, and acquire equation of Gensini score=82.386+24.892MAGE+7.244CRP+49.396MODD (F=29.440, 20.471, 16.757, *P*<0.001, independent variables have linear regression correlation linked to dependent variable) (**Table 6**).

When vWF was considered as the dependent variable, screened independent variables include CRP and MAGE, which has better fitted regression equation (**Table 6**). The regression equation was vWF=204.733+28.314MAGE+7.505CRP (F=14.902, 13.656, *P*<0.001, independent variables have linear regression correlation linked to dependent variable).

Discussion

Recent studies show that most of the ACS patients were found to have abnormal glucose metabolism, such as impaired fasting glucose, impaired glucose tolerance and diabetes [14]. Compared with simple persistent high glucose concentration, the intermittent high glucose concentration more easily induce vascular endothelial cells apoptosis by increasing inflammatory factors and adhesion factors [15, 16], which can cause more serious damage on vascular endothelial cells. Von Willebrand factor (vWF) as a glycoprotein presence in plasma, endothelial cells and platelet surface, is an ideal specific marker for vascular endothelial damage [17, 18]. In this study, we explored the relationship between glucose fluctuations and the affection of glucose variability to endothelial cells damage and coronary artery lesions.

The LAGE, SDBG and MAGE in control group, group B an A increased, which illustrated that the stress-induced hyperglycemia is one of the reasons for blood glucose variety in ACS patients. Abnormal glucose metabolism patients with cardiovascular disease are more

Table 6. Stepwise multiple regression analysis, Gensini score and vWF were considered as the dependent variable respectively

	Variable	β	SE	Sβ	*P* value
Gensini score	The constant term	82.386	56.256		0.154
	MAGE	24.892	11.13	0.361	0.033
	CRP	7.244	2.316	0.395	0.004
	MODD	49.396	23.405	0.317	0.044
vWF	The constant term	204.733	59.063		0.002
	MAGE	28.314	9.595	0.442	0.006
	CRP	7.505	2.556	0.42	0.006

prone to have blood glucose excessive increase and volatility. Compared with healthy subjects, the level of MAGE, MODD, MPPGE, CRP and vWF in serum of ACS patients were significantly increased. vWF was positively correlated with CRP and MAGE, which demonstrate that both MAGE and CRP are independent risk factors for vascular endothelial damage, high volatility of blood glucose increased formation of free radicals and reactive oxygen, induced oxidative stress effect, at the same time excessive reactive oxygen activate nuclear factor kappa B (NFκB) predominate, which could induce pro-inflammatory cytokines gene expression, resulting in inflammation [19, 20]. In our study, glutathione (GSH)-as an important oxidative stress-has been measured, result showed for patient with T2DM, their GSH level was much lower ($P<0.05$) compared with normal control; and comparison in patients with T2DM showed the greater the glucose excursion, the lower their GSH level was, this result prompts the clinical practice that reduce blood glucose fluctuation could slow down endothelial damage, thus could prevents acute cardiovascular issues and improves the prognosis.

According to Judkins' coronary angiography, Gensini scoring system was used to measure the extent of coronary artery disease and quantitatively assess each vascular lesion. Studies have shown that the incidence of multi-vessel coronary lesion in patients with abnormal metabolism was significantly higher than normal glucose metabolism patients [21, 22]. In this study, we analyzed the relationship between glucose fluctuation indexes of ACS patients in acute stage and the parameters of coronary artery stenosis (Gensini score). The results display both MGAE and MODD are independent risk factors for Gensini score, compared with persistent hyperglycemia, acute glucose fluctuations may further aggravated the extent of coronary artery disease. If the application of drugs can make the postprandial blood glucose and daytime blood glucose excessive fluctuation decrease, we can reduce the incidence rate of cardiovascular events and also reduce the occurrence of acute myocardial infarction.

Insulin resistance increased the risk of cardiovascular disease and death such as diabetes, hypertension and metabolic syndrome, and it also considered to be a precursor to diabetes and early onset of cardiovascular disease pathological mechanism [23-25]. We can speculate that due to the serious insulin resistance exists in ACS patients, the poor blood glucose control causes endothelial cells damage while the release of cytokines and chemokines also further aggravates insulin resistance and endothelial dysfunctions, which can be proved in our study: ACS patients have serious insulin resistance whether or not associated with T2DM.

Conclusion

Compared with healthy people, the amplitude of glycemic excursions, insulin resistance, inflammatory situation and endothelial cell damage severity in ACS patients increased significantly, especially in patients with T2DM. Compared with persistent hyperglycemia, acute glucose fluctuations may further aggravate the severity of coronary lesions.

Abbreviations

ACS, acute coronary syndrome; CGM, continuous glucose monitoring; CK, Creatine Kinase; CRP, C-reactive protein; ELISA, Enzyme linked immunosorbent assay; FPG, Fasting plasma glucose; Fins, Fasting Insulin; HDL-C, High-density Lipoprotein cholesterol; HbA1c, Glycosylated hemoglobin; HOMA-IR, Homeostatic model assessment insulin resistance; LAGE, largest amplitude of blood glucose excursion; LDL-C, Low-density Lipoprotein cholesterol; MAGE, mean amplitude of glycemic excursions; MODD, absolute means of daily differences; MPPGE, postprandial glucose excursion; OGTT, oral glucose tolerance test; TG, Triglyceride; TC,

Total cholesterol; T2DM, type 2 diabetes mellitus; SDBG, standard deviation of blood glucose; vWF, Von Willebrand Factor.

Disclosure of conflict of interest

None.

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