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Original Article

When heart goes "BOOM" to fast. Heart rate greater than 80 as mortality predictor in acute myocardial infarction

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Abstract: Many prospective studies established association between high heart rate and increased cardiovascular morbidity and mortality, independently of other risk factors. Heart rate over 80 beats per minute more often leads to atherosclerotic plaque disruption, the main step in developing acute coronary syndrome. Purpose was to investigate the incidence of higher heart rate levels in patients with anterior wall acute myocardial infarction with ST-segment elevation and the influence of heart rate on mortality. Research included 140 patients with anterior wall acute myocardial infarction with ST-segment elevation treated in Coronary Unit, Clinical Center Kragujevac in the period from January 2001-June 2006. Heart rate was calculated as the mean value of baseline and heart rate in the first 30 minutes after admission. Other risk factors were also followed to determine their connection with elevated heart rate. Results showed that the majority of patients survived (over 70%). In a total number of patients, more than 75% had a heart rate levels greater than 80 beats per minute. There was a significant difference in heart rate on addmision between survivors and patients who died, with a greater levels in patients with fatal outcome. Both, univariate and multivariate regression analysis singled out heart rate greater than 80 beats per minute as independent mortality predictor in these patients. Heart rate greater than 80 beats per minute is a major, independent risk factor for morbidity and important predictor of mortality in patients with acute myocardial infarction.

Keywords: Heart rate greater than 80 beats per minute, mortality, acute myocardial infarction

Introduction

As the most important determinant of myocardial oxygen demand and cardiac workload heart rate is playing a fundamental role in cardiac metabolic requirements [1, 2]. High heart rate is a major determinant of myocardial ischemia because it increases myocardial oxygen consumption, and decreases myocardial perfusion due to shortened diastole. The higher the baseline heart rate is, the greater is the probability of an ischemic episode. At a baseline heart rate less than 60 beats per minute, the likelihood of heart rate acceleration triggering an ischemic episode is 8.7%, compared with 18.5% at heart rate over 90 beats per minute [3].

Many epidemiological studies showed that individuals with elevated heart rate are more likely to develop accelerated atherosclerosis and acute coronary syndromes, with a higher mortality risk. Large body of evidence is showing that increased heart rate is very important factor influencing bad outcomes in these patients, and some studies have shown that heart rate is related to cardiovascular diseases after adjustment for other, risk factors. It remains unclear whether the effects of heart rate may have the same predictive value in both genders, and in both younger and older subjects. One of the hypothesis is that increased sympathetic activity may have the most important role in a relationship between high heart rate and cardiovascular mortality, and also, as a component of

cardiovascular pulsatile stress, heart rate may have a direct effect on the cardiovascular system [4].

Although heart rate is now considered to be a major cardiovascular risk factor and association between heart rate and increased cardiovascular morbidity and mortality was shown in many studies, independently of other risk factors, there is still discrepancy between scientific evidence and clinical guidelines [5].

Observational studies suggest that lower heart rate has a protective effect on cardiovascular system. It is also confirmed that morbidity and mortality is increased and longevity decreased at heart rate exceeding 60 beats per minute. High resting heart rate predicts mortality in a wide variety of populations, including general population, patients with coronary artery disease, hypertension, heart failure and after myocardial infarction. Evidence also showed that high heart rate triggers plaque disruption, causing acute coronary syndromes, and worseness prognosis in diffuse atherosclerosis [6].

The resting heart rate of a healthy human is approximately 50 to 75 beats per minute, depending upon age, sex and lifestyle. Heart rate is determined by the activity of the cardiac pacemaker cells of the sinus node, influenced by the autonomic nervous system, but it also reacts to a wide variety of physiological and pathological stimuli and conditions, and adapts in order to maintain cardiac output and preserve perfusion to vital body tissues and organs. Resting heart rate is also determined by numerous non-modifiable, as well as certain potentially modifiable factors specific to individuals and certain populations [7].

Increased heart rate tends to intensify the pulsatile nature of the arterial blood flow, thereby favoring the occurrence of injury to the arterial wall. Changes in shear stress direction expose susceptible regions to a greater number of oscillations in flow direction over time. The hemodynamic wall stress may perturb intercellular junctions, increase permeability of the endothelial cells, and favor the ingress of atherogenic particles. Moreover, high heart rate implies an increase in total time spent on systole because of the shortening of diastolic time. Individuals with high heart rate also have reduced arterial compliance [1, 8].

Sustained heart rate elevation may play a direct role in the pathogenesis of coronary atherosclerosis and its complications, as it was shown in experimental and clinical studies. Both mechanical and metabolic factors may account for the accelerated atherogenesis associated with increased heart rate [3].

One Italian study showed that heart rate was an independent predictive factor for total and cardiovascular mortality [9], and in a French patients population study, with 603 cardiovascular deaths, including 118 sudden deaths and 192 myocardial infarction, the risk of sudden death increased linearly with the level of resting heart rate in men. Taking into account age, BMI, systolic blood pressure, tobacco consumption, parental history of myocardial infarction and sudden death, cholesterol level and physical activity of these patients, an elevated heart rate remained an independent risk factor for sudden death [10, 11].

Studies conducted before the beginning of the thrombolytic era showed that heart rate at admission for acute myocardial infarction is predictive of both, in-hospital and long-term mortality [12]. One of the first large studies that investigated the associations between cardiovascular mortality and heart rate was the Chicago People Gas Company Study, in 1980. that confirmed association between the levels of heart rate and cardiovascular mortality [13].

In 1985, one of the first Framingham substudies concerning heart rate was published. The report on the relationship between heart rate and cardiovascular mortality showed that for both sexes, all-cause, cardiovascular and coronary disease mortality increased progressively relative to the antecedent resting heart rates determined biennially. The effect on mortality or sudden death was independent of associated cardiovascular risk factors, with higher mortality rate in male patients [14].

The relationship between heart rate, coronary artery disease and death was also investigated systematically in National Health And Nutrition Examination Survey I Epidemiologic Follow-up in more than 5,000 participants. The relative risk for the incidence of coronary heart disease was significantly elevated in men with heart rate greater than 84 beats per minute as com-

pared to those with rates less than 74 beats per minute, after correcting for multiple risk factors [15, 16].

More recent studies, such as the Paris Prospective Study, the Italian CArdiovascular STudy in the ELderly, and the Cardiovascular Occupational Risk factor Determination in ISrael study, confirmed the relationship between resting heart rate and cardiovascular mortality even after adjustment for several other risk factors and other confounding factors [17-19].

Numerous studies have shown that elevated heart rate is associated with many other, modifiable and non-modifiable, risk factors for cardiovascular diseases, including: age and gender, hypertension (high systolic and/or diastolic blood pressure levels), pulse pressure, obesity, smoking, high levels of total cholesterol, triglycerides, LDL-cholesterol, low HDL-cholesterol, hematocrit and fibrinogen.

Materials and methods

This partly retrospective, and mostly prospective, population-type, longitudinal study included 140 patients with anterior wall acute ST-segment elevation myocardial infarction treated in Coronary Unit, Clinic of Cardiology, Clinical Center Kragujevac for 5,5 years (January 2001–June 2006). The aims were to determine the predictors of a bad outcome (intrahospital mortality) in the observed group, investigating the incidence and importance of high heart rate levels (> 80 beats per minute), and the connection between high heart rate and other risk factors so we could determine whether high heart rate can be independent predictor of mortality [1].

As an independent variables we examined the following parameters: Gender, age, smoking habbit, BMI, Killip class, dyslipidemias, history of hypertension, angina pectoris, prior cardiovascular therapy. Hemodinamic status of patients on the admission in Coronary Unit included: Heart rate as primary parameter that was calculated as the mean value of baseline and heart rate in the first 30 minutes after admission, recorded on monitor and electrocardiogram. Patients were constantly monitored in the intensive care unit, with electrocardiogram done two times daily. Beside heart rate, hemodinamic monitorig included: blood pressure measured in a lying position, after 5 minutes resting, and systemic pulse pressure determined as a difference between systolic and diastolic blood pressure on admission. Body mass index (ratio of body weight in kilograms and body height in squared meters) was calculated. Lipoprotein profile components (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, atherogenic indices calculated from these parameters) were measured and classified according to the National Cholesterol Educational Program guidelines. Hematocrit and fibrinogen were also measured and levels were included in analysis [1].

Detailed materials and methods used in research were already described in reference 1.

Results

In total sample of respondents mortality rate was about 30% (100 patients survived and 40 patients died during research). Mean age of patients in total sample showed a difference between survivors and respondents who died (survivors – 63,02 ± 11,34 (65,5; 27-83) and 69,60 ± 8,68 (70; 46-83) for those who died). Patients who survived were significantlly younger (Mann Whitney U test; p = 0,002*). There was no significant gender-related difference between groups (χ^2 test; p = 0,252), although both had a slightly higher distribution of male patients.

Heart rate on admission was significantlly different between survivors and patients with fatal outcome, with higher levels in patients who died (Mann Whitney U test; p = 0,000*). Mean heart rate among these patients was approximately 102, while 87 beats per minute was approximate baseline heart rate in survivors. According to the outcome, significant difference in the incidence of heart rate lower/greater or equal to 80 beats per minute was present between survivors and patients who died (χ^2 test; p = 0,008*). Among survivors 72% had heart rate > 80 beats per minute and 28% had lower heart rate, and in a group of patients who died 92,5% had heart rate greater than 80 beats per minute and 7,5% had lower heart rate.

After analyzing the data for the total sample we divided patients according to the heart rate lev-

Table 1. Hemodynamic characteristics and cardiovascular risk factors associated with high heart rate in subgroup of patients with anterior wall ST-segment elevation myocardial infarction and heart rate > 80 bpm who survived and those who died

Subgroup of patients with heart rate greater than 80 bpm		Fatal outcome		Significance
		Yes	No	
History of hypertension	Yes	51 (70,8%)	32 (86,5%)	[a]p=0,069*
	No	21 (29,2%)	5 (13,5%)	
Systolic blood pressure (X ± SD (Med, min-max))		139,64 ± 22,32 (140,0; 90-190)	130,54 ± 22,99 (130,0; 80-180)	[c]p=0,049*
Diastolic blood pressure (X ± SD (Med, min-max))		87,15 ± 14,81 (90,0; 60-120)	84,19 ± 14,51 (90; 50-110)	[c]p=0,322
Pulse pressure (X ± SD (Med, min-max))		52,49 ± 13,85 (51,0; 25-82)	46,35 ± 13,79 (40,0; 20-80)	[b]p=0,031*
Pulse pressure > 40 mmHg	Yes	68 (94,4%)	36 (97,3%)	[a]p=0,500*
	No	4 (5,6%)	1 (2,7%)	
Obesity	Yes	56 (77,8%)	30 (81,1%)	[a]p=0,689
	No	16 (22,2%)	7 (18,9%)	
Triglycerides > 1,7 n (%)	Yes	39 (54,2%)	23 (62,2%)	[a]p=0,425
	No	33 (45,8%)	14 (37,8%)	
Total cholesterol > 5,2 n (%)	Yes	44 (61,1%)	26 (70,3%)	[a]p=0,345
	No	28 (38,9%)	11 (29,3%)	
HDL < 1,03-man; < 1,29-woman n (%)	Yes	37 (51,4%)	25 (67,6%)	[a]p=0,106
	No	35 (48,6%)	12 (32,4%)	
HDL (X ± SD (Med, min-max))		1,17 ± 0,33 (1,20; 0,33-2,10)	1,00 ± 0,31 (0,99; 0,34-1,58)	[b]p=0,011*
LDL > 4,1 n (%)	Yes	25 (34,7%)	16 (43,2%)	[a]p=0,106
	No	47 (65,3%)	21 (56,8%)	
Hematocrit (X ± SD (Med, min-max))		0,437 ± 0,084 (0,430; 0,226-0,682)	0,399 ± 0,078 (0,422; 0,228-0,532)	[c]p=0,026*
Fibrinogen (X ± SD (Med, min-max))		5,34 ± 1,65 (4,98; 2,45-11,50)	5,23 ± 1,74 (5,11; 2,36-12,02)	[b]p=0,972
Smoking n (%)	Yes	48 (66,7%)	28 (75,7%)	[a]p=0,332
	No	24 (33,3%)	9 (24,3%)	

*statistically significant difference; [a]χ^2-test; [b]Mann Whitney U test; [c]t-test; med – median, min – minimal, max – maximal value; SD – standard deviation; bpm – beats per minute; STEMI – ST-segment elevation myocardial infarction, bpm – beats per minute, HDL – high density lipoprotein, LDL – low density lipoprotein. Some results are adapted from reference 1.

Table 2. Univariate and multivariate analysis of risk factors influencing the mortality of patients with anterior wall STEMI and heart rate greater than 80 bpm

Risk factors	Univariate		Multivariate	
	#expB (95% CI)	Significance	expB (95% CI)	Significance
Heart rate on admission ≥ 80	1,040 (1,017-1,063)	p = 0,000*	1,076 (1,006-1,151)	p = 0,033*
Hypertension	0,379 (0,130-1,107)	p = 0,076	/	/
Systolic blood pressure	0,982 (0,965-1,000)	p = 0,052	/	/
Diastolic blood pressure	0,986 (0,960-1,014)	p = 0,319	/	/
Pulse pressure	0,472 (0,051-4,384)	p = 0,509	/	/
Obesity	0,817 (0,303-2,204)	p = 0,689	/	/
Triglycerides	1,144 (0,760-1,772)	p = 0,519	/	/
Total cholesterol	1,069 (0,811-1,410)	p = 0,636	/	/
HDL-cholesterol	0,194 (0,052-0,717)	p = 0,014*	8,078 (0,115-10,192)	p = 0,327
LDL-cholesterol	1,073 (0,730-1,579)	p = 0,719	/	/
Hematocrit	0,003 (0,000-0,560)	p = 0,029*	0,000 (0,000-2,333)	p = 0,067
Fibrinogen	0,959 (0,752-1,222)	p = 0,735	/	/
Smoking	0,643 (0,262-1,576)	p = 0,334	/	/

Analysis of heart rate refers to a total sample, and other risk factors were analyzed in the subgroup with heart rate > 80 beats per minute, *statistically significant difference, #exponentiation of the B coefficient, which is an odds ratio; CI – confidence interval; bpm – beats per minute, HDL – high density lipoprotein, LDL – low density lipoprotein. Some results are adapted from reference 1.

els to those with heart rate lower and greater than 80 beats per minute with aim to investigate if there was association between high heart rate and other risk factors.

In the subgroup of patients with heart rate > 80 beats per minute, hypertension was more often in those who died comparing to survivors, but without significant difference. It was present on admission, according to anamnestic data, in 70,8% of survivors, and in 86,5% of those who died (**Table 1**).

Systolic blood pressure significantlly differed in the subgroup, with the higher values in survivors. For diastolic blood pressure, the results were similar in the subgroup as in the total sample: mean values were between 84 and 88 mmHg in both, survivors and those who died, but with no significance. Mean pulse pressure was significantly different between survivors and those who died, with higher levels recorded in patients who survived. Among the groups, no significant difference was found in pulse pressure lower and greater than 40 mmHg (**Table 1**).

For obesity (higher body mass index) analysis showed no significant difference in the prevalence, in subgroup with heart rate > 80 beats per minute. More than 3/4 (75%) of patients were obese in the group with fatal outcome and in survivors in the subgroup but with no influence on mortality (**Table 1**).

Lipoprotein profile disorders didn't show significant incidence, except low HDL-cholesterol. Triglycerides, total cholesterol and LDL-cholesterol were mostly normal or desirable. Compared according to the mortality in the subgroup, there was no statistically significant difference in mean triglycerides, total cholesterol and LDL-cholesterol levels. These parameters were mostly normal or desirable. HDL-cholesterol significantly differed between survivors and patients who died, with lower values in patients who died. No difference in distribution of HDL-cholesterol lower than 1,03 mmol/l for male and < 1,29 mmol/L for female patients according to mortality was present. More than 50% of patients had lower levels in both groups (**Table 1**).

Fibrinogen did not differ significantly according to the mortality in the subgroup (Mann Whitney U test, p = 0.972). Hematocrit was significantly different between patients who died and survivors in the subgroup, with higher levels recorded in survivors (**Table 1**). Prevalence of smoking didn't differ significantly, there were more than

66.7% of smokers among survivors and patients who died (**Table 1**).

Logistic regresion was used to discover the predictors or independent risk factors for mortality. Univariate logistic regresion analyzed the influence of each observed factor in the presence of all others risk factors, and those that showed significance were included in multivariate regresion model. Univariate model singled out heart rate > 80 beats per minute as statistically significant risk factor for mortality, among other risk factors. When we included heart rate in multivariate model, it remained significant, and was singled out as independent risk factor with a high influence on mortality in the observed sample (**Table 2**).

We used this method also to define the independent predictors for mortality of patients in subgroup. Several risk factors were singled out as independent predictors of high risk for mortality in a total sample, and some of them showed significance in univariate model. When they were analyzed in the subgroup, with the method of multivariate analysis, they lost that value, leaving the high heart rate as independent predictor (**Table 2**).

Discussion

Coronary heart disease is common in general population and represents a significant public health problem. Numerous epidemiological and clinical studies have identified dyslipidemia, hypertension, diabetes, smoking and obesity as risk factors that can enhance atherosclerosis of coronary arteries, the basic mechanism in the pathogenesis of ischemic heart disease with a wide spectrum of clinical manifestations. It was recently recognized that the resting heart rate is independently associated with coronary heart disease, total and cardiovascular mortality. Experimental data, epidemiological studies and clinical observations have shown that heart rate is an integral part of the continuum of cardiovascular disease. By analyzing the data of these studies it was demonstrated that heart rate plays an important role in the development of atherosclerotic plaque, its instability and rupture [20].

In the last 20 years, different groups of researchers examined epidemiological aspects of the impact that heart rate have on the development of cardiovascular complications. Data review of recent epidemiological studies, revealed 38 studies that have examined the connection of heart rate with morbidity and mortality. After exclusion of other risk factors, 36 of 38 studies confirmed the association between heart rate and cardiovascular mortality [21].

There is a significant association between elevated heart rate and sudden death. When heart rate is greater than 88 and 99 beats per minute, risk of sudden death in men increases by 5-6 times, and twice in women, compared to those who have a heart rate lower than 65 or 60 beats per minute [13]. Twofold increase in overall mortality is clinically, significantly associated with any increase in heart rate of 40 beats per minute.

The major risk factors for coronary heart disease are age, gender, total cholesterol, systolic and diastolic blood pressure, smoking and diabetes. Less predictive factors include obesity, physical inactivity, and a positive family history of coronary artery disease (especially in younger patients). All patients included in this research had above mentioned risk factors except diabetes which was excluding criteria. Recently, heart rate and metabolic syndrome were recognized as new risk factors [22].

Maximum heart rate decreases with age, independently of other factors such as gender and level of physical activity. Reduction of the maximum heart rate during the years is a key factor in the ability of progressive reduction of exercise tolerance, mainly through the reduction of the maximum cardiac output. The mechanisms involved in the reduction of the maximum heart rate in healthy aging are still not completely understood [23].

Coronary heart disease is significantly more often in the general population after age of 60 years [24]. The results of this research are consistent with these data because the average age of patients with anterior wall acute myocardial infarction with ST-segment elevation in survivors was approximately 63 years, and 69 years of approximate in those who died. According to the Framingham study, the risk for coronary heart disease in men aged 40 years was 48%, while for the women of the same age the risk was 31% [25]. This research showed no

gender-related difference between survivors and patients with fatal outcome.

Studies in the general population that examined other risk factors showed that women always have higher heart rate at rest than men of the same age and with the same risk factors. This gender-related difference, in the range of 3 to 7 beats per minute, is present in both developed and developing countries, in all ages, and according to some, but not all studies, tends to increase with aging [23]. When we are looking according to age as a risk factor, this difference in risk, in both groups of patients with anterior wall acute myocardial infarction with ST-segment elevation, was lost due to the average age of patients included in the research.

Coronary arteries are considered to be highly susceptible to atherosclerosis because of their complex three-dimensional geometry which is associated with the phase of the cardiac cycle duration, so epicardial coronary blood vessels, which are directly connected with the heart, periodically retain the curvature-shape, despite the movements that lead to their torsion. Result of these effects is a periodic change of the geometry of coronary blood vessels with large hemodynamic stress, and exposure of specific places, such as coronary artery bifurcation to atherogenic changes [26].

Ischemia occurs as a result of imbalance between myocardial oxygen demand and supply. Oxygen comes to the heart mainly during diastole, so every increase in heart rate which decreases the part of cardiac cycle responsible for diastole, also decreases the amount of oxygen. Heart rate lowering increases the period of diastole, the time of perfusion and improves myocardial contraction. These mechanisms have important role in ischemia. In the presence of coronary artery stenosis, changes of heart rate provide a redistribution of blood flow to the coronary arteries that are intact, or with less pronounced stenosis. Any increase in heart rate is harmful because it reduces perfusion during diastole, increasing the area of ischemia in the myocardium through the stealing phenomenon in blood flow, and disrupts the flow in the coronary blood vessel with obstruction (the Inverse Robin Hood phenomenon) [20].

It was proved that the incidence of ischemia in patients with stable coronary heart disease is related to their mean values of heart rate, and those patients with heart rate at rest > 80 beats per minute showed signs and symptoms of ischemia, nearly two times more than those with the heart rate < 70 beats per minute [27]. Considering the final outcome of patients, results of this research showed the significant difference in the prevalence of patients with a heart rate ≥ 80 beats per minute. We can confirm that heart rate is greater than 80 beats per minute in those with acute events and not just in patients with stable coronary heart disease. Heart rate of about 100 beats per minute speeds up the atherosclerosis, atherosclerotic plaque formation and rupture of its fibrous cap. Results of this research are consistent with this data because heart rate greater than 80 beats per minute was present in 72% in a group of survivors, and in 92.5% of patients with a fatal outcome.

One study showed that the risk of cardiovascular death was more than doubled in patients with a heart rate > 90 beats per minute, compared with patients with heart rate < 90 beats per minute [19]. Guillaume CP, Joly L, Benetos A, investigated if there is a clinically significant increase in cardiovascular risk in patients with a heart rate > 80 beats per minute. Data from this study, on patients with coronary heart disease, have shown the benefit of pharmacological heart rate reduction even in patients with a moderate acceleration of heart rate-70 beats [28].

Generally speaking, the literature on this issue shows that heart rate greater than 80 beats per minute significantly increases the risk of cardiovascular complications, morbidity and mortality, and that heart rate greater than 80-85 beats per minute can be considered as a threshold for tachycardia [29].

Three studies conducted in Chicago have demonstrated predictive value of resting heart rate in the general mortality in a large population [13]. A multivariate analysis that included age, blood pressure, total cholesterol, smoking and body weight showed that heart rate is an independent predictor of sudden cardiac death and non-cardiovascular mortality in 2 of 3 studies conducted in Chicago. A limitation of the study conclusions, that they are not based on a sufficiently large number of patients, was disproved by the Framingham study which showed corre-

lation between heart rate variability and sudden death in both sexes [14].

In the Angina and Silent Ischemia Study increase in heart rate recorded during the 48-hour ambulatory electrocardiographic monitoring preceded the majority of ischemic events. Likelihood of developing ischemia was proportional to heart rate levels at rest, magnitude and duration of elevated heart rate. Patients with resting heart rate greater than 80 beats per minute were twice as likely to develop ischemia than those with a heart rate less than 60 beats per minute (16.6% vs. 8.7%), which was confirmed also in this research where 109 patients with a heart rate greater than 80 beats per minute had an acute myocardial infarction [30].

Multivariate regression analysis in this research singled out heart rate as an independent predictor of mortality which is consistent with previous studies that have assessed the cardiovascular mortality. Analysis showed that elevated heart rate plays a major role in precipitating coronary events, and confirmed the significant association between high heart rate and myocardial infarction with fatal outcome.

Conclusions

This research conducted on 140 patients confirmed numerous results from previous studies that high heart rate is one of the major risk factors. Analysis of total sample showed that high heart rate is important risk factor, but also that it has a huge influence on mortality. When we analyze the results of the research we can see that heart rate is often associated with some other risk factors for cardiovascular diseases, and that they can also have major/minor influence on the final outcome of these patients, but neither one of them was singled out as independent predictor like it was with high heart rate. These findings show us that heart rate must be used in the risk estimation in patients with myocardial infarction like the best predictor for mortality. Connection with other risk factors does exist but the heart rate is the one which we should rely on when we estimate the risk for our patients.

Disclosure of conflict of interest

None.

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