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SYMPATHOVAGAL IMBALANCE IN THYROID DYSFUNCTIONS IN FEMALES : CORRELATION WITH THYROID PROFILE, HEART RATE AND BLOOD PRESSURE

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Abstract : The aim of the study was to investigate the role of spectral analysis of heart rate variability (HRV) for assessing the type and degree of sympathovagal imbalance (SVI) and their link to cardiovascular morbidities in thyroid dysfunctions. Forty-five female subjects (15 control subjects and freshly diagnosed untreated 15 hypothyroid and 15 hyperthyroid patients) were recruited for the study. Thyroid profile, body mass index (BMI), basal heart rate (BHR), blood pressure (BP) and spectral indices of HRV (TP, LFnu, HFnu and LF-HF ratio, mean RR, SDNN and RMSSD) were assessed in all the three groups. LF-HF ratio was correlated with thyroid profile, BMI, BHR and BP. SVI was more prominent in hyperthyroid ($P<0.001$) compared to hypothyroid ($P<0.05$) subjects. LF-HF ratio was correlated with thyroid profile in both hypo and hyperthyroid subjects; but correlation with BHR and BP was significant only in hyperthyroidism. Though the SVI was found to be due to both vagal withdrawal and sympathetic activation, especially in hyperthyroidism, contribution by vagal inhibition was prominent. Vagal inhibition contributes significantly to SVI in thyroid dysfunctions, especially in hyperthyroidism. As the present study indicates poor cardiovascular health due to vagal inhibition in patients suffering from thyroid dysfunctions, attempt should be made to improve vagal tone especially in hyperthyroid subjects to attain a stable sympathovagal and cardiovascular homeostasis.

Key words : hypothyroidism hyperthyroidism LF-HF ratio sympathovagal imbalance vagal tone

INTRODUCTION

Thyroid dysfunctions are common global health problems, hypothyroidism accounting for 5–15% and hyperthyroidism 0.3 to 0.6% in general population (1). Recently, the incidence of thyroid dysfunctions has increased considerably and presently, the

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burden of thyroid disorders in India is about 42 millions (2). It is not clearly known; whether the increased occurrence of thyroid dysfunctions is directly linked to the change in life style in the society. However, it is well documented that diabetes, hypertension and coronary artery diseases are directly associated with the degree of stress and physical inactivity (3), and the common pathophysiological basis of these disorders has recently been attributed mainly to the autonomic imbalance (4). Thyroid hormones are the major regulators of metabolism, and the degree of metabolism has a direct impact on sympathovagal balance (5). Affection of cardiovascular system is one of the most frequent and most serious clinical manifestations of thyroid dysfunctions (6, 7). Nevertheless, the type and the degree of autonomic imbalance and its contribution to cardiovascular abnormalities in thyroid dysfunctions have not yet been fully investigated.

Hyperthyroidism is a hypermetabolic state associated with features of increased sympathetic activity, as thyroid hormones are known to facilitate functions of catecholamines (8). Though, hyperthyroidism is characterized by both increased sympathetic and decreased parasympathetic modulation of cardiac activities (9, 10), the degree of parasympathetic inhibition in hyperthyroidism has not been properly assessed. Recently, from our laboratory, we have reported considerable vagal inhibition proportionate to sympathetic activation in a case of hyperthyroidism (11). Autonomic nervous system has profound influence on cardiovascular regulations in health and diseases (12, 13). Therefore, we postulated that cardiovascular dysfunctions in hyperthyroidism are contributed by both sympathetic activation and vagal withdrawal. Hence, in the present study we have assessed the association of sympathovagal imbalance (SVI) with heart rate and blood pressure in hyperthyroid patients.

Hypothyroidism in general is a prominent hypometabolic state and sympathetic activities are anticipated to be less in this condition (14). However, cardiovascular morbidities are not uncommon in hypothyroidism (14), though the pathophysiology of cardiovascular dysfunctions in hypothyroidism has not yet been fully understood. Recently, it has been reported that hypothyroidism is associated with decreased sympathovagal modulation of cardiac activities (15). It has also been reported that patients with hypothyroidism often have autonomic neuropathies with a higher level of vagal tone that partly improves with thyroxine therapy (16). However, the details of sympathovagal imbalance and their link to cardiovascular complications have not yet been fully studied in hypothyroidism. Therefore, in the present study we have assessed nature of sympathovagal imbalance in hypothyroidism and its plausible link to the cardiovascular dysfunctions in this condition.

Thyroid dysfunctions are more common in females compared to males; especially in hypothyroidism the male-female ratio is 1: 6 to 8 (1). Therefore, in the present study we have exclusively assessed SVB in thyroid dysfunctions in females. Though there is a battery of autonomic function tests to assess sympathovagal balance (17), recently, power spectral analysis of heart rate variability (HRV) has been documented to be the most

specific and sensitive indicator of SVI (18). Therefore, in the present study we have used spectral analysis of HRV to assess the nature and degree of SVI in thyroid dysfunctions.

MATERIALS AND METHODS

The present study was conducted in the department of physiology, Jawaharlal institute of postgraduate medical education and research (JIPMER), Pondicherry, India. After obtaining approval of the project plan from research and ethics committees of JIPMER, 45 female subjects (15 in control group, 15 in hypothyroid and 15 in hyperthyroid groups) were recruited from the endocrinology clinic and outpatient unit of the ENT department of JIPMER. Written informed consent was obtained from all the participants prior to initiation of the study.

Patients

Subjects of study groups were freshly diagnosed untreated female hyperthyroid and hypothyroid patients.

Inclusion criteria

In hypothyroid group, female patients freshly diagnosed as primary hypothyroidism, before initiation of the treatment were included. Likewise, freshly diagnosed female patients with primary hyperthyroidism, before initiation of the treatment were taken in hyperthyroid group. Control group had age and gender matched normal healthy individuals.

Exclusion criteria

Patients, who were already on treatment for thyroid disorders, known cases of diabetes mellitus, hypertension, heart diseases, autonomic failure or endocrine disorders and those were on any chronic medications were excluded from the study.

Brief procedure

The subjects reported to polygraph laboratory about two hours after a light breakfast devoid of coffee or tea. Height and weight were measured to calculate body mass index (BMI). Following 10 minutes of supine rest in polygraph laboratory (room temperature maintained at 25°C), the following recordings were done.

Recording of baseline HR, BP and HRV

Lead II – ECG recordings were done for at least 330 seconds to determine resting heart rate variability. Baseline blood pressure was recorded in the left arm after 10 minutes of rest in the supine position. Systolic and diastolic blood pressures were recorded using Colin PressMate 8800 (Colin Corporation, Tokyo, Japan) non-invasive blood pressure monitor. For recording of short-term HRV, recommendation of the Task Force on HRV was followed (19). For the purpose, ECG electrodes were connected and Lead II ECG was acquired at a rate of 1000 samples/second during supine rest using BIOPAC MP 100 data acquisition system (BIOPAC Inc., CA, USA). The data was transferred from BIOPAC to a windows-based PC with Acqkowledge software version 3.8.2. Ectopics and artifacts were removed from the recorded ECG. RR tachogram was extracted from the edited 256 sec ECG using the R wave detector in the Acqkowledge software and saved in ASC-II format which was later

used offline for short term HRV analysis. HRV analysis was done using the HRV analysis software version 1.1 (Bio-signal Analysis Group, Finland).

Mean RR was measured in second(s). Variance, defined as power in a portion of the total spectrum of frequencies was measured in milliseconds squared (ms^2). Different frequency domain indices such as total power (TP), low frequency component expressed as normalized unit (LFnu), high frequency component expressed as normalized unit (HFnu) and LF/HF ratio, and time domain indices such as mean RR, standard deviation of normal to normal interval (SDNN) and square root of the mean squared differences of successive normal to normal intervals (RMSSD) of HRV were recorded.

Thyroid profile measurements

Five ml of blood samples were collected from all the subjects for estimation of serum T3, T4 and TSH. T3 and T4 were assayed by radioimmunoassay and TSH by immunoradiometric assay by fully-automated multi-well gamma counter (Wallac, Finland) using kits procured from the Bhaba Atomic Research Center (BARC, Mumbai, India).

Statistical analysis

SPSS version 13 was used for statistical analysis. All the data were expressed as mean±SD. One-way ANOVA with Tukey-Krammer post-hoc was used in analyzing the data among the three groups. The association of LF-HF ratio with thyroid profile and other parameters was assessed by Pearson correlation analysis. The P values less than 0.05 were considered significant.

RESULTS

General parameters

In the present study, there was no significant difference in age of subjects in all the three groups (Table I). However, body weight was significantly high in hypothyroid subjects compared to controls ($P<0.05$) and hyperthyroid subjects ($P<0.01$). The BMI of the hypothyroid subjects was significantly more ($P<0.05$) than hyperthyroid subjects. Though there was no significant difference between control and hypothyroid subjects,

TABLE I: General parameters, basal heart rate (BHR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) of euthyroid (control), hypothyroid and hyperthyroid subjects (n=15 in each group).

	Euthyroid	*Hypothyroid*	*Hyperthyroid*	*P*	*F/dF*
Age (years)	27.80±6.6	29.20±5.7	33.1±9.6	0.1456	2.018/2,42
BW (Kg)	53.05±8.1	60.80±8.2*	50.14±7.88$^{\#\#}$	0.0024	7.008/2,42
BMI (Kg/m^2)	24.30±4.5	26.83±5.47	22.14±3.66$^{\#}$	0.0279	3.901/2,42
BHR (beats/min)	76.99±6.69	74.06±10.55	100.49±17.97***,$^{\#\#\#}$	<0.0001	19.720/2,42
SBP (mmHg)	104.44±11.66	116.92±12.2	129.92±16.7***	<0.0001	12.959/2,42
DBP (mmHg)	74.41±8.81	70.84±10.1	65.10±8.2*	0.0252	4.021/2,42

Values are mean±SD; BW: body weight; BMI: body mass index; The star mark (*) mark depicts comparison with control and hash ($^{\#}$) mark depicts comparison between hypothyroid and hyperthyroid patients. The analysis of data was done by one-way ANOVA and post-hoc by Tukey-Krammer test. *P<0.05; ***P<0.001; $^{\#}$P<0.05; $^{\#\#}$P<0.01; $^{\#\#\#}$P<0.001.

basal heart rate (BHR) of hyperthyroid subjects was significantly high compared to both control and hypothyroid subjects (P<0.001). Similarly, the systolic blood pressure (SBP) was significantly high (P<0.001) and diastolic blood pressure (DBP) was significantly less (P<0.05) in hyperthyroid subjects compared to subjects of control group.

Thyroid profile

There was a significant decrease and increase in T3 and T4 in hypothyroid and hyperthyroid patients respectively compared to control subjects (Table II). TSH was significantly high and low (P<0.001) in hypothyroid and hyperthyroid subjects respectively compared to controls. However, there was a significant difference in T3, T4 and TSH between hypothyroid and hyperthyroid groups (P<0.001).

Frequency domain indices of HRV analysis

Total power (TP) of HRV spectrum was reduced significantly in hypothyroid subjects (P<0.05) and hyperthyroid subjects (P<0.001) compared to the control subjects (Table III). TP in hyperthyroid subjects was significantly less (P<0.001) compared to hypothyroid subjects. LFnu was increased both in

TABLE II: Thyroid profile of euthyroid (control), hypothyroid and hyperthyroid subjects (n=15 in each group).

	Euthyroid	*Hypothyroid*	*Hyperthyroid*	*P*	*F/dF*
T_3 (ng/dl)	145.40±22.70	50.20±18.85***	374.6±52.65***,###	<0.0001	343.50/2,42
T_4 (µg/dl)	8.80±1.72	2.62±1.10**	20.35±7.30***,###	<0.0001	63.430/2,42
TSH (µU/ml)	1.94±0.70	88.52±20.26***	0.056±0.02###	<0.0001	279.69/2,42

Values are mean±SD; T_3: tri-iodothyronine; T_4: thyroxine; TSH: thyroid stimulating hormone; The star mark (*) depicts comparison with control and hash (#) mark depicts comparison between hypothyroid and hyperthyroid patients. The analysis of data was done by one-way ANOVA and post-hoc by Tukey-Krammer test. **P<0.01; ***P<0.001; ###P<0.001.

TABLE III: Frequency domain and time domain indices of spectral HRV analysis of control (euthyroid), hypothyroid and hyperthyroid subjects (n=15 in each group).

	Euthyroid	*Hypothyroid*	*Hyperthyroid*	*P*	*F/dF*
TP (ms^2)	890.46±470.71	555.77±284.75*	87.77±50.24***,###	<0.0001	23.970/2,42
LFnu	33.08±14.34	49.24±13.31*	68.03±24.27***,#	<0.0001	14.167/2,42
HFnu	66.92±14.20	51.80±13.43*	32.1±14.34***,##	<0.0001	23.345/2,42
LF-HFratio	0.573±0.41	1.94±0.42*	3.97±2.4***,##	<0.0001	19.511/2,42
Mean RR(s)	0.789±0.075	0.829±0.12	0.617±0.12***,###	<0.0001	16.586/2,42
SDNN (ms)	52.96±32.72	46.94±19.86	49.86±11.69	0.7414	1.234/2,42
RMSSD (ms)	57.92±22.10	43.10±15.34	50.63±17.20	0.1009	2.424/2,42

Values are mean±SD; TP: total power; LFnu: normalized low frequency component; HF: normalized high frequency component; Mean RR: mean-RR intervals; SDNN: standard deviation of the averages of NN intervals in all 5 min segments of the entire recording; RMSSD: the square root of the mean of the sum of the squares of differences between adjacent NN intervals; The star mark (*) depicts comparison with control subjects and hash (#) mark depicts comparison between hypothyroid and hyperthyroid patients. The analysis of data was done by one-way ANOVA and post-hoc by Tukey-Krammer test. *P<0.05; ***P<0.001; #P<0.05; ##P<0.01; ###P<0.001.

hypothyroid (P<0.05) and hyperthyroid subjects (P<0.001) compared to control subjects. LFnu increase in hyperthyroid subjects was statistically significant (P<0.05) compared to hypothyroid subjects. HFnu was reduced in both hypothyroid (P<0.05) and hyperthyroid subjects (P<0.001) compared to controls. Also, reduction in HFnu in hyperthyroid subjects was statistically significant (P<0.01) compared to hypothyroid subjects.

LF-HF ratio was increased in hypothyroid (P<0.05) and hyperthyroid subjects (P<0.001) compared to controls. The increase in LF-HF ratio in hyperthyroid subjects was statistically high (P<0.01) compared to hypothyroid subjects.

Time domain indices of HRV analysis

Though the mean-RR in hypothyroid group did change significantly compared to control group, it was significantly reduced in hyperthyroid group (P<0.001) compared to both control and hypothyroid groups (Table III). Changes in SDNN and RMSSD were not statistically significant between the groups.

Correlation values

LF-HF ratio was not correlated with T3, T4, and TSH of control group. However, there was a significant correlation between LF-HF ratio and all the thyroid profile parameters in hypothyroid and hyperthyroid groups (Table IV). LF-HF ratio was not correlated with BMI of any of the group. However, LF-HF ratio was significantly correlated with BHR (P, 0.000), SBP (P, 0.001) and DBP (P, 0.002) in hyperthyroid but not in hypothyroid groups (Table V).

TABLE IV: Correlation of LF-HF ratio with thyroid profile of control (euthyroid), hypothyroid and hyperthyroid subjects.

	Euthyroid		*Hypothyroid*		*Hyperthyroid*	
	r	*p*	*r*	*p*	*r*	*p*
T3	0.012	0.198	–0.516	0.001	0.590	0.000
T4	0.056	0.148	–0.482	0.002	0.509	0.002
TSH	0.347	0.076	0.394	0.018	–0.416	0.013

The P values less than 0.05 was considered significant.

TABLE V: Correlation of LF-HF ratio with body mass index (BMI), basal heart rate (BHR), systolic blood pressure (SBP), diastolic blood pressure (DBP) of control (euthyroid), hypothyroid and hyperthyroid subjects.

	Euthyroid		*Hypothyroid*		*Hyperthyroid*	
	r	*p*	*r*	*p*	*r*	*p*
BMI	0.013	0.194	0.031	0.155	–0.310	0.102
BHR	0.378	0.08	–0.330	0.09	0.765	0.000
SBP	0.362	0.070	0.390	0.062	0.610	0.001
DBP	0.044	0.120	–0.048	0.118	–0.506	0.002

The P values less than 0.05 was considered significant.

DISCUSSION

In the present study, we found a significant reduction in total power (TP) in both hypothyroid ($P<0.05$) and hyperthyroid ($P<0.001$) patients, in which decrease was profound in hyperthyroid ($P<0.001$) compared to hypothyroid group as revealed by spectral analysis of HRV, indicates diminution in vagal cardiovascular control in both forms of thyroid dysfunctions as TP in general reflects the magnitude of vagal modulation of cardiovascular functions (18, 19). This was further supported by a proportionate reduction in HFnu in both hypothyroidism and hyperthyroidism, as HFnu is an indicator of vagal activity (18, 19). The present study clearly indicates profound reduction in vagal activity in hyperthyroid subjects in comparison to hypothyroid subjects. Though the reduction in vagal activity in hyperthyroidism as observed in this study corroborates with the findings of previous reports (9, 10), findings in hypothyroid subjects contradicts the report of Xing et al who had reported autonomic imbalance in hypothyroid patients is due to a higher level of vagal tone that subsides with thyroxine treatment (16). This difference in vagal activity in hypothyroidism of our study from that of Xing et al could be due to difference in interpretation of the data of HRV. Xing et al reported higher vagal activity as they observed HF component of HRV more than the LF component in hypothyroid subjects. But, in their study, the HF component of hypothyroid subjects was less than that of control subjects, which clearly depicts reduction in vagal activity in hypothyroids compared to normal subjects, which they did not emphasize and analyze. As in a normal supine HRV, the contribution of HF component (parasympathetic activity) to the total spectral power is about two-third compared to one-third contribution by LF and VLF components (18), any degree of reduction in HF power in hypothyroid patients compared to the level of HF in euthyroid subjects indicates decreased vagal activity hypothyroid patients even if HF remains more than LF power in the same subjects.

Vagal tone is an important determinant of cardiovascular health of an individual as it has profound influence on the control of heart rate, cardiac output and blood pressure (19). Persons with poor vagal tone are more susceptible to cardiovascular diseases such as myocardial infarction, heart failure, and hypertension etc (20, 21). Thus, the present study indicates poor cardiovascular status in patients with thyroid dysfunctions, especially in hyperthyroid patients, as they were found to have severely decreased parasympathetic activity compared to both control and hypothyroid subjects.

LFnu was significantly increased in hyperthyroid subjects compared to both control ($P<0.001$) and hypothyroid subjects ($P<0.05$), which indicates significantly increased sympathetic activity in hyperthyroidism as LF power is an index of sympathetic activity (18, 19). Also, significant increase in LFnu in hypothyroid patients compared to control subjects ($P<0.05$) indicates some degree of increased sympathetic activity in these patients. Our findings support the report by Cacciatori et al that sympathetic influence on cardiovascular system is increased and vagal influence is decreased in hypothyroidism, which occurs secondary to adaptations to

altered cardiovascular responses (22), though it does not confirm the report of Xing H et al that the sympathetic activity does not change much in hypothyroidism (16).

As LF-HF ratio is the most sensitive indicator of sympathovagal balance (18, 19) increased LF-HF in both hypothyroid and hyperthyroid patients indicated presence of sympathovagal imbalance (SVI) in both the forms of thyroid dysfunctions. Increase in LF-HF ratio in resting supine condition of an individual indicates increased sympathetic and reduced parasympathetic activity (18, 23). In the present study, as the LF-HF ratio was increased in hyperthyroid and hypothyroid groups, SVI in both the dysfunctions are due to increased sympathetic and decreased parasympathetic activity. The increase in LF-HF ratio was maximum in hyperthyroid subjects, which indicates sympathetic overactivity is associated with severe depression in parasympathetic activity in hyperthyroidism. But, as total power was grossly reduced in hyperthyroid subjects to about 10% of control values, it appears, vagal inhibition was more intense compared to the level of sympathetic activation. The increased LF-HF ratio in the presence of reduced total power of HRV indicates poor cardiovascular status of the subject (18). Therefore, the present study reveals a poor cardiovascular prognosis in thyroid dysfunctions, especially, in hyperthyroidism.

Time domain indices of HRV indicate mainly the parasympathetic functions (18, 19). As mean-RR inversely reflects heart rate, it was reduced in hyperthyroidism and increased in hypothyroidism. Heart rate at supine rest of an individual is a good index of parasympathetic activity (17). As BHR of hyperthyroid subjects was significantly more than the euthyroid and hypothyroid subjects (Table I), it further reflects decreased vagal activity in these subjects. As RMSSD and SDNN represent long-term vagal modulation of cardiac functions, these parameters did not change significantly in hyperthyroid and hypothyroid groups compared to euthyroid group, the recording of present study being that of short-term HRV.

LF-HF ratio was highly correlated with all thyroid profile parameters in both hypothyroid and hyperthyroid subjects (Table IV), indicating that the alteration in sympathovagal balance has a direct association with the magnitude of the thyroid dysfunctions, which is linked to the levels of thyroid hormones and TSH in serum.

One may suggest that significantly high body weight and BMI in hypothyroid subjects (Table I) could be a major contributor to the SVI in this dysfunction as obesity has been reported to cause sympathetic overactivity (24, 25). However, obesity in hypothyroidism is not a pure increase in adiposity as increase in bodyweight in thyroid deficiency is mostly due to accumulation of water and mucopolysaccharides in subcutaneous tissues (14). Therefore, increase in BMI contributing to increased sympathetic activity in hypothyroid dysfunction is a remote possibility. Moreover, there was no significant correlation of LF-HF ratio with BMI in both hypothyroidism and hyperthyroidism (Table V).

There was no significant correlation of LF-HF ratio with BHR and blood pressure in hypothyroid subjects, indicating that

alteration in heart rate and blood pressure in hypothyroidism may not be directly linked to SVI. Moreover, heart rate and blood pressure in hypothyroid subjects were within the normal range and were not significantly different from euthyroid subjects. Also, significant alteration in heart rate and blood pressure are not common in hypothyroidism, except that diastolic hypertension occurs sometimes in this endocrine disorder (14). However, in hyperthyroid subjects, as LF-HF ratio was significantly correlated with heart rate, SBP and DBP, cardiovascular dysfunctions could be directly linked to SVI in hyperthyroidism. Profound tachycardia, atrial fibrillation, systolic hypertension and diastolic hypotension are common features of hyperthyroidism (14). It appears that these cardiovascular problems in hyperthyroidism are considerably linked to vagal withdrawal, in addition to the already known contribution by sympathetic activation.

Though there are few reports indicating alteration in sympathovagal balance in thyroid dysfunctions (10, 11, 15, 16) the present study is the first of its kind to compare SVI in both hypothyroid and hyperthyroid disorders. We found that SVI is prevalent in both forms of thyroid dysfunctions in females, which was due to both increased sympathetic and reduced parasympathetic activities. However, SVI was found to be more intense in hyperthyroid subjects, which could be contributed more by vagal withdrawal than the sympathetic activation. As profound reduction in TP along with significant SVI indicate poor cardiovascular health that were observed in hyperthyroid patients in this study, we suggest that physicians should regularly monitor cardiovascular functions while treating the patients suffering from hyperthyroidism. In addition to use of sympatholytic drugs in the treatment of hyperthyroidism, attempt should be made to improve vagal tone in patients with thyroid disorders. Recently we have reported improvement of vagal tone by practicing slow breathing exercises (20). Therefore, future works should address to attain sympathovagal homeostasis in thyroid dysfunctions, especially in hyperthyroidism by practicing non-pharmacological methods such as slow breathing exercises that improve parasympathetic functions.

Thyroid dysfunctions are more common in females compared to males (1). However, till date, no report is available on comparison of SVI exclusively in female hypo- and hyperthyroid patients. Therefore, in the present study we had solely assessed sympathovagal balance in thyroid dysfunctions in females, which is a study of its first kind. In the present study, as there was no significant difference in age of the subjects of all the three groups (Table I), it can be suggested that the results obtained in thyroid dysfunctions are not due to the effect of age. All subjects of the present study were in their reproductive age. However, as females after menopause are more prone to cardiovascular complications (26), further study should assess the degree and nature of SVI linked to cardiovascular dysfunctions in post-menopausal hypo- and hyperthyroid patients.

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