Failure of Plasma Norepinephrine to Consistently Reflect Sympathetic Activity in Humans

JOHN FLORAS, JOHN VANN JONES, M. OSMAN HASSAN, BARBARA A. OSIKOWSKA, PETER S. SEVER, AND PETER SLEIGHT

SUMMARY To determine whether venous plasma norepinephrine concentrations consistently reflect changes in sympathetic nervous activity, the influence of mental arithmetic, static handgrip, and submaximal bicycle exercise on intra-arterial blood pressure, heart rate, and plasma norepinephrine was studied in 51 subjects with untreated essential hypertension (mean age, 46 years; range, 16–69 years). At rest, plasma norepinephrine was unrelated to age or blood pressure. Mental arithmetic increased mean arterial pressure from 108 ± 18 to 127 ± 18 mm Hg (mean ± S.D.; p<0.001) and heart rate from 69 ± 7 to 93 ± 13 beats/min (p<0.001) but not plasma norepinephrine (547 ± 297 to 518 ± 250 pg/ml). Isometric exercise raised mean arterial pressure from 115 ± 18 to 148 ± 21 mm Hg (p<0.001) and heart rate from 76 ± 9 to 95  ± 13 beats/min (p<0.001) but not plasma norepinephrine (683 ± 253 to 741 ± 253 pg/ml). Bicycle exercise increased mean arterial pressure from 114 ± 20 to 146 ± 26 mm Hg (p<0.001), heart rate from 77 ± 9 to 128 ± 19 beats/min (p<0.001), and plasma norepinephrine from 645 ± 228 to 1151 ± 462 pg/ml (p<0.001). Both the maximum mean arterial pressure and the peak heart rate attained during bicycle exercise were related to the exercise plasma norepinephrine level (r = 0.33, p<0.02 and r = 0.28, p<0.03, respectively). Increases in plasma norepinephrine with exercise were not greater in older or more hypertensive subjects. In fact, the relative rise in mean arterial pressure and the absolute increase in plasma norepinephrine during cycling were greater in those with lower resting blood pressures. As only bicycle exercise increased plasma norepinephrine, and as there was no direct relationship between plasma norepinephrine and arterial blood pressure in subjects studied supine, seated, and during these three activities, we conclude that plasma norepinephrine concentrations do not consistently reflect variations in sympathetic neuronal activity and therefore are relatively insensitive measures of sympathetic tone in humans. (Hypertension 8: 641–649, 1986)

KEY WORDS • essential hypertension • sympathetic nervous system • exercise • isometric exercise • mental arithmetic • aging

PLASMA norepinephrine (PNE) concentrations are considered sensitive to changes in sympathetic tone. Stimulation of sympathetic nerves in pithed rats leads to a gradual rise in PNE and an immediate proportional increase in blood pressure.

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the initiation or maintenance of this disorder is not well defined. Early reports of a relationship between resting PNE concentrations and blood pressure have not been confirmed consistently. Several factors may account for this. Differences between subjects in norepinephrine reuptake, clearance, or conjugation may make the interpretation of individual or group comparisons of PNE concentrations difficult. Age, for example, alters norepinephrine clearance. Because of individual variability in the vascular reactivity to the neurotransmitter norepinephrine, comparing pressor responses to various stimuli with changes in PNE may be misleading. Finally, as Folkow et al caution, activities that increase blood pressure in humans usually do so by effecting differentiated rather than generalized increases in sympathetic discharge. Selective increases in cardiac, renal, or splanchic sympathetic nerve activity could initiate marked hemodynamic changes in hypertensive persons without altering basal venous PNE concentrations, because of hepatic clearance of catecholamines, regional differences in the vascular response to released norepinephrine, or quantitative differences in the adrenergic innervation to these vascular beds. Indeed, PNE correlates well with efferent sympathetic nervous system reflexly do not always reflect changes in sympathetic tone or reveal a neurogenic contribution to essential hypertension. Recent work suggests that activation of the sympathetic nervous system by mental stress or isometric exercise produces smaller changes in PNE than described initially. Further, maneuvers that stimulate the sympathetic nervous system reflexly do not always elevate PNE.

We examined resting, exercise, and postexercise blood pressure, HR, and PNE in hypertensive subjects who performed isometric and bicycle exercise while seated. Ten subjects also completed a mental arithmetic test while supine. We wished to determine the disposition of resting PNE concentrations with respect to age and the level of blood pressure, to study PNE during three activities known to evoke differential patterns of sympathetic nervous discharge, and to determine whether increases in blood pressure and PNE during these activities were related to the level of arterial pressure or to the ages of these subjects.

Subjects and Methods

Subjects (40 men, 11 women) were referred by general practitioners for the investigation of newly diagnosed, untreated hypertension. Their mean age was 46.2 ± 10.8 (SD) years (range, 19–69 years). Hypertension was diagnosed if supine cuff readings of 140/90 mm Hg (Korotkoff phase V) or more were obtained on three or more separate visits. In some subjects, readings less than 140/90 mm Hg were observed on other occasions. Secondary hypertension was excluded by routine investigations. Some subjects (n = 22) had evidence of Grade 1 or 2 eye ground changes; the remainder were free of target organ damage. The purpose and nature of the protocol were explained on recruitment and again on the morning of the study, at which time informed written consent was obtained. Permission for these investigations was granted by our hospital ethics committee.

Protocol

Subjects arrived at 0930 after a light breakfast at home, free of tea, coffee, or cigarettes. There were no other dietary restrictions. With the subjects under local anesthesia, a Teflon cannula (external diameter, 1.0 mm; internal diameter, 0.6 mm; length, 11 cm; Seldangh, Grandjean Plastimed, Saint-Leu-La-Forêt, France) was placed in the left brachial artery according to the Seldinger technique and connected by a manometer line to a strain-gauge transducer (Statham P23 Gb or Gould Statham P23 1D, Hato Rey, Puerto Rico) positioned at the midst level and calibrated against a mercury column each time the subject changed position. A second cannula was inserted into an adjacent antecubital vein connected to a three-way stopcock (used to withdraw venous blood) and taped to the subject’s forearm to permit free arm movement.

Lead II of the electrocardiogram was displayed along with blood pressure on an oscilloscope and recorded simultaneously onto ultraviolet light-sensitive paper, magnetic tape (Racal Store 4, Racal Recorders, Hythe, Southampton, UK), and into a minicomputer (Data General Eclipse S-200, Hounslow, Middlesex, UK). A continuous record of blood pressure and pulse interval was obtained throughout the study.

Blood Pressure and Heart Rate During Mental Stress

and Exercise

After 15 minutes of quiet rest, 90 seconds of baseline blood pressure and HR were recorded. The nature of the test to follow then was explained, and after a 30-second pause, the activity began. Subjects performed mental arithmetic (n = 10), isometric exercise (n = 51), and bicycling (n = 51) in the same order. Before going on to the next test, subjects rested until blood pressure and HR returned to baseline.

Mental arithmetic, performed supine, consisted of serial subtraction of 7’s from 300. As the subject called out each answer, he or she was chastised for tardiness or for errors. These 10 patients (9 men and 1 woman) were aged 35 to 52 (mean, 43.6 ± 6.6 [SD]) years.

Subjects sat for 15 minutes before isometric exercise. A sphygmomanometer bulb, attached to a gauge that displayed grip strength in pounds per square inch, was squeezed with the noncannulated hand with maximal effort for 30 seconds, then released slowly until 30% of maximum voluntary contraction was reached. This level, usually 3 to 5 lb/in², was sustained for another 4.5 minutes. Subjects were instructed to breathe naturally during handgrip to avoid performing a Valsalva maneuver.

The subject then pedaled a bicycle ergometer for 10 minutes: 5 minutes at a load of 50 W (300 kpm/min), then a further 5 minutes at 75 W (450 kpm/min). To
avoid adding any isometric component to this activity, subjects rested their hands, palms up, on the handlebars.

The blood pressure signal was sampled by an analog-to-digital converter at a frequency of 100 Hz. A second channel of the converter was used for an event switch, which marked the periods of rest and exercise. Systolic, mean, and diastolic blood pressure, as well as the pulse interval, were calculated on a beat-by-beat basis using a suite of multitasking real-time Fortran IV blood pressure analysis programs. At the end of each exercise, the average systolic, mean, and diastolic pressures, their standard deviations, and the average pulse interval, with its standard deviation, were calculated for each 15-second segment of the recording. The minimum, maximum, and mean of each of these four values for each period of the exercise (i.e., baseline, exercise, recovery) also were obtained.

**Definitions**

Baseline blood pressure, pulse interval, or HR values were defined as the mean of all cardiac cycles recorded during the resting period (usually 1.5 minutes) before the explanation or initiation of an exercise. Exercise blood pressure, pulse interval, or HR values represented the highest (or lowest, in the case of pulse interval) mean values recorded over each 15-second segment during the exercise. Recovery values were obtained from the 15-second segment occurring 3 minutes after the end of each activity.

**Plasma Norepinephrine Determinations**

Blood was withdrawn from the venous cannula 1) after the 15 minutes of quiet rest, before the test was explained, 2) in the last minute of each exercise, and 3) 3 minutes after its completion. A 10-ml sample then was obtained and immediately centrifuged for 10 minutes at room temperature (1000 g). The plasma was aspirated immediately, frozen, and stored at −40°C. Of the 330 samples acquired, 10 were discarded because of storage problems. The PNE concentrations were measured by a radioenzymatic assay based on the technique of Henry et al. The mean coefficients of inter-assay and intra-assay variation for these determinations were 9.6% and 8.7%, respectively.

**Statistics**

The Statistical Package for the Social Sciences program was used for paired comparisons (Student’s t test), multiple regression analysis, and calculation of partial correlation coefficients. The Bonferroni method was used to calculate a modified t statistic when multiple comparisons were performed. Means and their standard deviations are used throughout.

**Results**

Resting PNE concentrations in the 10 subjects who completed all three activities were similar before each exercise: mental arithmetic, 547 ± 297 pg/ml (supine); isometric exercise, 686 ± 243 pg/ml (sitting); and cycling 683 ± 239 pg/ml (sitting). The PNE concentration at rest, before bicycle exercise (642 ± 227 pg/ml; n = 49), represented baseline PNE concentrations in subsequent calculations. These resting values were normally distributed and unrelated to subjects’ ages (r = 0.03; Figure 1), to systolic, mean (r = 0.01; Figure 2), or diastolic blood pressures, or to resting heart rates (r = 0.15).

Mental arithmetic (n = 10) raised mean arterial pressure (MAP) 18% (p < 0.001) and HR 35% (p < 0.001; Table 1). The increases in systolic, mean, and diastolic blood pressures were similar. The PNE concentrations rose by 8% (0.10 > p > 0.08; see Table 1). We observed an increase in 23 subjects, no change in 9, and a decrease in 1 figure 1. Relationship between resting plasma norepinephrine concentrations and age (n = 49; n.s. = not significant).
FIGURE 2. Relationship between resting plasma norepinephrine concentrations and mean arterial pressure (n = 49; n.s. = not significant).


TABLE 1. Plasma Norepinephrine Concentrations, Mean Arterial Pressure, and Heart Rate Before, During, and 3 Minutes After the End of Mental Arithmetic, Isometric Exercise, or Bicycle Exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Stimulus</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental arithmetic (n=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>547 ± 297</td>
<td>518 ± 250</td>
<td>481 ± 205</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>108 ± 18</td>
<td>127 ± 18*</td>
<td>109 ± 18†</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>69 ± 7</td>
<td>93 ± 13*</td>
<td>71 ± 8†</td>
</tr>
<tr>
<td>Isometric exercise (n=50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>684 ± 253</td>
<td>741 ± 253</td>
<td>780 ± 352</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>115 ± 18</td>
<td>148 ± 21*</td>
<td>116 ± 21†</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>76 ± 9</td>
<td>95 ± 13*</td>
<td>77 ± 10†</td>
</tr>
<tr>
<td>Bicycle exercise (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>645 ± 228</td>
<td>1151 ± 462*</td>
<td>940 ± 266†</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>114 ± 20</td>
<td>146 ± 26*</td>
<td>119 ± 19†</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>77 ± 9</td>
<td>128 ± 19*</td>
<td>95 ± 15†</td>
</tr>
</tbody>
</table>

Values are means ± SD. PNE = plasma norepinephrine; MAP = mean arterial pressure; HR = heart rate.

*p < 0.001, compared with resting values.
†p < 0.001, compared with exercise values.
Plasma Norepinephrine in Hypertension

Related with exercise PNE. Subjects with higher PNE concentrations during bicycling also had higher heart rates \( (r = 0.28, p < 0.03) \). When the influence of confounding variables was removed by calculation of partial correlation coefficients, subjects with lower blood pressures had greater absolute increases in PNE \( (r = -0.27, p < 0.05) \). Three minutes after the end of bicycle exercise, MAP, HR, and PNE were lower than exercise levels but higher than baseline values, by 4\% \((p < 0.001)\), 22\% \((p < 0.001)\), and 45\% \((p < 0.001)\), respectively (see Table 1).

Increases in MAP \((r = 0.12)\) or HR \((r = -0.08)\) during mental arithmetic or handgrip \((r = 0.01, \text{ and } r = -0.24, \text{ respectively, } 0.10 > p > 0.05)\) were unrelated to age.

During bicycle exercise, older subjects showed greater increases in MAP \((r = 0.47, p < 0.001)\) but smaller increases in HR \((r = -0.32, p < 0.02)\). Neither exercise PNE concentrations nor increases in PNE with exercise were age-related.

All three activities evoked sympathetically induced changes in blood pressure and HR, yet two of them, mental arithmetic and handgrip, did not raise PNE (see Table 1). Thus, unlike Watson et al., we were unable to demonstrate a positive relationship between the systolic blood pressure and PNE of the 10 subjects studied supine, sitting, and during these three stimuli (Figure 6).

**Discussion**

The role of the sympathetic nervous system in the initiation and maintenance of hypertension has been investigated by both direct and indirect means. Direct microneurographic records of sympathetic discharge...
have their disadvantages: only efferent activity to skin and muscle can be quantified, and stable records are best obtained in resting subjects.\textsuperscript{33} Hence, few activities that might increase sympathetic nerve discharge can be studied, and efferent traffic to organs that are likely to be of hemodynamic importance in the development of hypertension cannot be measured. Therefore, fluctuations in sympathetic tone usually are estimated indirectly, by recording changes in blood pressure, HR, or the concentration of PNE.

Resting PNE concentrations were independent of age, blood pressure, or HR. Although a positive correlation between arterial pressure and PNE has been described,\textsuperscript{5, 12, 13, 34} most authors have not been able to demonstrate a relationship between PNE concentrations and blood pressure\textsuperscript{13-15} or age\textsuperscript{15, 36, 38} in a hypertensive population. In contrast, it is generally agreed that PNE increases with age in normal subjects.\textsuperscript{12, 19, 25, 38} It has been suggested, and recently demonstrated, that the differing disposition of resting PNE with respect to age in these two groups is due to an increase in PNE in some young hypertensive subjects as opposed to age-matched normal subjects.\textsuperscript{11, 14, 15, 34-36, 39, 40} The lack of relationship between PNE and age (see Figure 1) or MAP (see Figure 2) in this study is consistent with this concept.

A number of studies have used sensitive and specific assays for norepinephrine to determine the role of sympathoneural factors in hypertension, either by establishing a correlation between PNE and arterial pressure\textsuperscript{9, 12, 15, 34} or by documenting differences in PNE between normal and hypertensive subjects at rest\textsuperscript{5, 9, 11, 14, 34-36} or during activity.\textsuperscript{10, 20, 35} The power of such studies to detect differences in sympathetic nerve activity between individuals depends on the responsiveness of antecubital vein PNE to regional variations in sympathetic nerve discharge. Since venous PNE did not increase during mental arithmetic or handgrip, we would conclude that venous PNE determinations do not detect changes in sympathetic activity within individuals consistently and are likely to be insensitive to modest or regional increases in sympathoneural tone in hypertensive subjects, even if present.

Although resting PNE concentrations in this study are higher than commonly described (see Reference 11 for review), it should be noted that PNMT assay values for norepinephrine have always been higher than those obtained by the COMT assay.\textsuperscript{14} This has never been adequately explained. Further, most studies report recumbent norepinephrine concentrations obtained under basal conditions. One would anticipate recording higher levels in this study, since venous samples were drawn with subjects seated and after only 15 minutes of rest. Other factors, unknown to us, may have predisposed these subjects to higher PNE concentrations. For example, a number of these subjects had resting intra-arterial blood pressures within the normal range, as can be seen in Figure 1, despite a diagnosis of hypertension on the basis of three or more readings obtained with conventional sphygmomanometry. This discrepancy raises the possibility that some of these subjects may have had increased blood pressure variability and sympathoneural tone. Finally, curtailment of sodium intake by some subjects, as an initial antihypertensive measure, either on their own initiative or on the advice of a general practitioner, would also tend to increase their PNE.

These higher resting PNE concentrations might obscure any further increase during these three activities, and we cannot be certain that this did not occur. However, if PNE concentrations were indeed sensitive to changes in sympathetic neural discharge, increases in PNE with sympathetic activation should be relatively independent of baseline values, and the marked rise in blood pressure and HR observed during mental arithmetic and isometric exercise should be accompanied by proportionate increases in PNE. That they were not supports the observations of other authors\textsuperscript{25-27, 41, 42} who reported little or no increase in PNE from lower initial levels during mental stress or isometric exercise and leads us to suggest instead that selective activation of sympathetic efferent discharge to different vascular beds during these three activities may be responsible for these findings.

A selective increase in splanchnic nerve discharge, for instance, could raise the blood pressure of hypertensive persons but not antecubital vein PNE concentrations if the majority of the norepinephrine released by these nerves was cleared by the liver.\textsuperscript{22} Furthermore, elevations in renal, splanchnic, or cardiac sympathetic discharge could alter cardiac output or vascular resistance to a much greater extent than PNE concentrations if only a small proportion of circulating norepinephrine comes from these organs.\textsuperscript{21, 22, 43} In humans, renal, splanchnic, and cardiac sympathetic nerves together contribute approximately one third of norepinephrine measured in plasma, the lungs another third, and skeletal muscle one fifth.\textsuperscript{41}

Changes in venous PNE concentration appear to parallel changes in sympathetic nerve discharge to muscle. Both increase with age and are on the whole similar in normal subjects and those with renal or established essential hypertension.\textsuperscript{44, 45} This close correspondence between antecubital venous PNE and muscle sympathetic nerve activity may be due to the fact that up to 45% sampled from this site is derived from forearm tissues and up to 70% of the norepinephrine in the venous effluent from the legs is derived from skeletal muscle.\textsuperscript{22, 46} Norepinephrine release from renal sympathetic nerves is increased in some subjects with essential hypertension.\textsuperscript{45} It is not known whether muscle sympathetic nerve activity is greater in borderline hypertensive subjects than in age-matched normal subjects; however, the substantial contribution of muscle sympathetic discharge to venous PNE concentrations could well obscure any local increase in sympathetic nerve activity in this disorder.

Since PNE increased during bicycle exercise but not mental arithmetic or handgrip, the incremental relationship between PNE and systolic blood pressure described by Watson et al.\textsuperscript{6} clearly applies only in selected circumstances. Indeed, these authors' observations during isometric exercise are not consistent with this relationship.\textsuperscript{27} Whereas generalized increases
in sympathetic activity, as during tilt or standing, increase PNE more than blood pressure or HR,19,28 discrete activation of specific efferent sympathetic pathways could achieve marked increases in blood pressure and HR in some instances, and in PNE in others, depending on the regional circulations involved. Thus, the Valsalva maneuver and the carotid sinus reflex alter splanchnic resistance, blood pressure, and HR but not PNE, whereas deactivate cardiopulmonary reflexes changes muscle sympathetic nerve activity and forearm vascular resistance without influencing blood pressure or HR.26,41 These latter observations support the hypothesis that changes in venous PNE in humans are determined primarily by alterations in efferent muscle sympathetic nerve activity.

The dissociation between sympathoneural activity and PNE we observed is consistent with the mechanisms by which cardiac output, regional vascular resistance, and sympathetic nerve discharge to muscle change during these activities. In particular, an increase in norepinephrine clearance that is proportional to cardiac output could in part explain our inability to detect a significant increase in PNE during mental arithmetic and isometric exercise in this study.

Mental stress increases HR, cardiac output, and renal, epidermal, and splanchnic vascular resistance. Vasodilation occurs in skeletal muscles, and systemic vascular resistance falls.41,46,48 Sympathetic nerve discharge to muscle and norepinephrine release from muscle are reduced. The progressive fall in PNE from baseline to exercise to recovery that we observed in patients who display an exaggerated sympathetic response to arterial pressure or HR.

Handgrip at 30% of maximum voluntary contraction increases cardiac output through parasympathetic withdrawal and modest sympathetic activation. Vascular resistance increases in some hypertensive and in older normotensive subjects.55 Increases in PNE have been reported by some5,52 but not all authors.27,42 Watson et al.28 described a small increase in PNE (+ 17%) after 3 minutes of handgrip that was similar in normal and hypertensive subjects.

As in this study, in which PNE increased in 23 subjects, did not change in 9, and decreased in 18, microneurographic recordings have shown that muscle sympathetic nerve discharge increases in some subjects but does not change, or decreases, in others.33 As discussed earlier, increased release of norepinephrine from cardiac and splanchnic sympathetic nerves could mediate these hemodynamic changes and increase norepinephrine clearance, resulting in minor decreases in antecubital vein PNE.

During bicycle exercise, peripheral resistance falls while sympathetic nerve discharge to the heart, incresive vasculature, and capacitance vessels rises.33-35 Neither PNE nor plasma epinephrine is increased by mild dynamic exercise.54,56 Norepinephrine is elevated with moderate treadmill or bicycle exercise (75% of maximum oxygen consumption), and both catecholamines are increased at intense workloads.34,56 Our results are consistent with these studies.

The significant relationship between exercise MAP and PNE concentration observed during bicycling but not present at rest (see Figure 5) suggests that circulating norepinephrine may be a determinant of MAP during dynamic exercise.

Some investigators,5,20,57 noted a strong positive relationship between PNE and HR during exercise and postulated that cardiac sympathetic nerves become the primary source of circulating PNE during exercise. Exercise PNE concentrations correlated with exercise heart rates in the present study but isometric exercise and mental arithmetic also increased HR without affecting PNE concentrations. In contrast, tilting and standing evoke smaller changes in HR but increase PNE substantially.7,25,28

Whether hypertensive subjects exhibit greater increases in PNE than do normal subjects during exercise remains disputed.5,10,20,58-61 Henquet et al.59 found identical PNE and plasma epinephrine concentrations at rest and after 10 minutes of bicycle exercise in young (age, 18–30 years) normal subjects and patients with borderline hypertension. Bertel et al.56 described larger absolute and relative increases in PNE with exercise in their young normal group than in their hypertensive subjects. In contrast, both the absolute increase in PNE during bicycle exercise and the relative increase in MAP were greater in our subjects with lower resting blood pressures, observations that support the concept that it is the borderline or mild hypertensive subjects who display an exaggerated sympathetic response to exercise.

In summary, hypertensive subjects completed three activities that increase sympathetic nerve discharge, blood pressure, and HR. Bicycle exercise increased PNE concentrations substantially, whereas mental arithmetic and isometric exercise did not. Changes in PNE concentrations followed documented patterns of efferent sympathetic discharge to muscle during these activities and affirmed the preponderant influence of norepinephrine released from skeletal muscle on antecubital vein PNE concentrations. Our findings reinforce current reservations over the ability of PNE measurements to detect changes in sympathetic activity to important hemodynamically vascular beds and hence their usefulness in estimating the role of the sympathetic nervous system in essential hypertension.

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