

Daily variability of resting energy expenditure in acute kidney injury patients on dialysis

Variabilidade diária do gasto energético de repouso em pacientes com lesão renal aguda em tratamento dialítico

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ABSTRACT

Introduction: It is needed for nutrition prescription correct estimate of resting energy expenditure (REE), which is a challenge given the possible daily variation in critically ill patients with acute kidney injury (AKI). **Objective:** To evaluate the daily variability of REE measured by indirect calorimetry (IC) in patients with AKI and dialysis indication and identify clinical variables associated with REE. **Methods:** The REE was measured on the time of dialysis indication and the subsequent four days. We also evaluated parameters that can influence the REE. The daily differences were analyzed by generalized linear model for repeated measures. We also used Spearman correlation and multiple linear regression. **Results:** There were 301 IC measurements in 114 patients, mean age of 60.65 ± 16.9 years and 68.4% were male. The average REE was 2081 ± 645 kcal, rising on day 5 (2270 ± 556 kcal) compared to the days 2 and 3 (2022 ± 754 ; 2022 ± 660 kcal, respectively, $p = 0,04$). When normalized to weight, there was no significant difference in REE (kcal/kg/day) during follow-up. REE was positively correlated with total leukocyte count, C-reactive protein, minute volume (MV), fraction of inspired oxygen (FiO_2) urea nitrogen appearance (UNA), weight and height and inversely with age. After multiple regression, MV, FiO_2 , weight and age are correlated independently with REE. **Conclusion:** Patients with AKI have REE stable. The REE was associated independently with FiO_2 , MV, body weight and age. Thus, ventilatory parameters should be evaluated each day for the necessary dietary changes may be made.

Keywords: acute kidney injury; energy consumption; energy metabolism.

RESUMO

Introdução: É imprescindível a correta estimativa do gasto energético de repouso (GER), que pode apresentar considerável variação diária no paciente crítico com lesão renal aguda (LRA). **Objetivo:** Avaliar a variabilidade diária do GER medido por calorimetria indireta (CI) em pacientes com LRA e indicação dialítica e identificar as variáveis clínicas associadas ao GER. **Métodos:** O GER foi medido no dia da indicação do procedimento dialítico e nos quatro dias subsequentes. Também foram avaliados parâmetros que podem influenciar o GER. As diferenças diárias foram analisadas pelo modelo linear generalizado para medidas repetidas, com distribuição gama, além da correlação de Spearman e regressão linear múltipla. **Resultados:** Foram 301 medidas de CI realizadas em 114 pacientes, com idade de $60,65 \pm 16,9$ anos e 68,4% do sexo masculino. O GER médio foi de 2081 ± 645 Kcal, com aumento no dia 5 (2270 ± 556 Kcal), quando comparado aos dias 2 e 3 (2022 ± 754 ; 2022 ± 660 kcal, respectivamente, $p = 0,04$); quando normalizado para peso, não houve diferença significativa no GER (kcal/kg/dia) durante o acompanhamento. GER correlacionou-se positivamente com temperatura corporal, contagem total de leucócitos, proteína C reativa, volume minuto (VM), fração inspirada de oxigênio (FiO_2), aparecimento de nitrogênio ureico (UNA), peso corporal e estatura e inversamente com idade. Após a regressão linear múltipla, somente VM, FiO_2 e peso corporal e idade se correlacionaram independentemente. **Conclusão:** Pacientes com LRA dialíticos apresentam GER estável. O GER foi associado independentemente com FiO_2 , VM, peso e idade. Assim, requisitos ventilatórios precisam ser avaliados diariamente para que alterações necessárias na prescrição dietética sejam feitas.

Palavras-chave: consumo de energia; lesão renal aguda; metabolismo energético.

INTRODUCTION

Acute renal injury (AKI) is defined as an abrupt drop in glomerular filtration rate (GFR), resulting in increased nitrogen slag, acid-base balance disorders, fluid and electrolyte disturbances.¹ AKI is a common complication in hospitalized patients, and it can affect 10% to 30% of patients admitted to intensive care units (ICUs). Approximately 5% of these patients required renal replacement therapy (RRT).²

AKI usually develops in the context of multiple organ failure in the ICU. Nutritional therapy for these patients has the purpose of reversing or attenuating the negative effects of catabolism and hypermetabolism associated with these acute diseases. The basis of nutritional support is to preserve lean body mass and the immune function, as well as to prevent complications related to under and overfeeding.

Thus, adequate nutritional support is essential in the therapeutic strategy of both AKI and the failure of multiple organs and systems. In addition, when RRT is required, it should be carefully adjusted, given the characteristic metabolic disturbances and the effects of RRT on nutrient balance.³

In order to prescribe the best nutritional intake, a correct estimation of nutritional needs is essential, and indirect calorimetry (IC) is considered the gold standard for measuring energy expenditure (EE) in critically-ill patients.⁴

However, many factors can alter the EE in ICU patients, such as pain, medications, body temperature, diet, heart rate, among others.⁵ In addition to these factors, patients with severe AKI may also have an altered EE due to loss of kidney homeostasis and the adverse effects of the chosen RRT.^{1,3} Thus, only one EE measure alone may not characterize the patient's correct energy needs.

Studies with critical patients reported a change in daily EE between 4% and 56%, and that more clinically stable patients presented lower variability.⁶⁻⁸ In patients with AKI, few studies evaluated the EE by IC and only one longitudinal study evaluated resting EE (REE) in critically-ill, mechanically ventilated patients, with AKI in continuous RRT.

The authors showed that the resting energy expenditure (REE) measured on the first day was 2.153 ± 380 Kcal and there was an increase of 56 ± 24 cal/d during the study period of 6 days, with an end value of REE of 2.431 ± 498 Kcal ($p < 0.0001$).⁹ However, in this study, IC was performed in patients

during RRT and IC guidelines contraindicate this moment for the measurement of EE, due to possible interferences of the dialysis procedure in gas exchange, which would lead to errors in the measurement of EE using IC.^{5,10,11}

The present study aims to evaluate the daily variability of REE measured by IC in patients with AKI and dialytic indication and to identify the clinical variables associated with REE.

METHODS

A prospective cohort study that evaluated patients older than 18 years, from March 2013 to December 2015.

PATIENTS

We included patients admitted to the ICU with a diagnosis of AKI according to the KDIGO criteria,¹² clinical symptoms suggestive of acute tubular necrosis (ATN), need for RRT (stage 3), and mechanically ventilated.

We excluded those patients with AKI of other etiologies, renal transplanted or those with chronic renal disease stages 4 and 5 (Glomerular Filtration Rate - GFR - < 30 ml/min estimated by the Modification of Diet in Renal Disease - MDRD,¹³), considering the patient's baseline creatinine for the calculation, defined as the serum creatinine value most recently obtained prior to admission, not preceding 12 months of hospitalization. If this value is unknown or obtained 12 months before hospitalization, we considered baseline creatinine as the lowest value observed during follow up.¹⁴

Other exclusion criteria were fraction of inspired oxygen (FiO_2) greater than 0.60; Expiratory Positive Airway Pressure (PEEP) > 10 cm H_2O ; Maximum airway pressure > 60 cm H_2O ; stirring presence; use of neuromuscular blockers; air leakage into the ventilator circuit, around the endotracheal tube cuff, or from a bronchopleural fistula: because these factors lead to inaccuracies in the REE measurement by IC.

The patients had IC performed daily. The protocol was started on the day of the dialysis appointment, the first REE measurement being done before the start of therapy. The patient was followed up for four consecutive days, and the daily ICs were done before the beginning of the daily dialysis procedure. Thus, patients were followed for up to five consecutive days, or less if the dialysis were to be withdrawn due to renal function recovery or death.

This study was approved by the Research Ethics Committee of the institution (protocol 4383/2012). The Term of Consent was signed by the legal guardian of the participant before entry into study.

ENERGY EXPENDITURE MEASUREMENT

Resting energy expenditure (REE) is measured because of the impossibility of achieving the conditions to measure baseline EE of critically-ill patients. To ensure REE measurement, the patient needed to be in supine position and rested for at least 30 minutes prior to measurement; In a thermoneutral environment (22-25 °C) for at least 30 minutes before and during measurement; without having used additional analgesics and sedatives within 30 minutes of initiation of IC; without procedures within 60 minutes of IC initiation; without general anesthesia within 8 hours of IC initiation; And continued parenteral and/or enteral nutrition during the data collection period.

IC was performed using the RMR Quark apparatus (Cosmed, Rome, Italy). The RMR Quark is designed to accurately and instantly measure the energy needs of patients breathing spontaneously or mechanically. For our study, the calorimeter was used connected to the patient's mechanical ventilator, with connectors in the exhalation line of the ventilator and in the respiratory circuit: in this way, it is possible to collect both inspired and expired gases. The device has a paramagnetic oxygen sensor to measure oxygen concentrations and analyzes them based on infrared absorption for carbon dioxide measurements.

The calorimeter was calibrated before each use. The examination had an average duration of 30 minutes. Patients were expected to reach steady state during the test. The steady-state was defined as a variability of < 10% in the measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2), and < 5% in the respiratory quotient from minute to minute.

In addition to the measured REE, baseline EE (BEE) was estimated using the Harris and Benedict formula.¹⁵ For the calculation of the patient's height equation (cm), it was measured upon admission to the ICU when possible, or using the value documented in the medical record. Weight (kg) was measured using hospital beds, calibrated upon admission, for most of the patients. If the patient had edema at the time of the measurement, according to the medical assessment,

we asked relatives about the patient's habitual weight, and used it as the real weight in the formula.

We also evaluated parameters that may influence REE, such as ventilatory (minute volume, respiratory rate, PEEP, FIO_2), vasoactive drugs and body temperature.

STATISTICAL ANALYSIS

The results were described by median and interquartile range, or mean and standard deviation. The daily differences in the studied parameters were analyzed by the generalized linear model for repeated measures, with gamma distribution.

To evaluate the parameters correlated with REE, and those that could influence its daily variability, all measures of REE, clinical parameters, laboratory, ventilatory and catabolism markers performed during follow-up were used. Spearman's univariate correlation was used first, and the variables with significant *p* were placed in multiple linear regression to analyze which was independently associated with REE.

Variables with asymmetric distribution were transformed by the log function for inclusion in the multivariate analysis. The collinearity of the predictive variables was tested by the tolerance (Tolerance) and the Variance Inflation Factor (VIF), and if the tolerance was < 0.1 and/or the FIV > 4, then one of them was removed from the multivariate models.

A *p* < 0.05 was used as statistically significant.

RESULTS

A total of 114 patients were evaluated, with mean age of 60.65 ± 16.9 years and 68.4% were males. Diagnoses of sepsis and cardiovascular disease (CVD) accounted for 79.8% of the hospitalizations. AKI was the etiology associated with sepsis in most patients (81.6%). The specific prognostic index for ATN (ATN-ISS) was 0.64 ± 0.18 . The BEE estimated by the Harris-Benedict formula averaged $1,540 \pm 346$ Kcal; whereas the REE measured by the IC on day 1 was significantly higher (2061 ± 700 Kcal, *p* < 0.001). Table 1 shows the clinical characteristics of the general population studied at the time when dialysis was indicated.

A total of 301 IC measures were performed. Seventy-six patients completed two days of evaluation, 53 three days and 35 four days. Only 24 patients had five IC measures on consecutive days. These patients were

TABLE 1 CLINICAL CHARACTERISTICS OF THE POPULATION WITH AKI

Parameters	
Age (years)	60.6 ± 16.9
Male gender (%)	78(68.4)
AKI (%)	
Sepsis-related	93 (81.6)
ischemic	13 (11.4)
Nephrotoxic	6(5.3)
Mixed	2 (1.8)
ATN-ISS	0,64 ± 0.18
REE (Kcal)	1540 ± 346
Race (%)	
White	98(86)
Brown	5 (4.4)
Black	11 (9.6)
Weight (kg)	77,6 ± 22.4
Main diagnosis:	
CVD	35(30.7)
Sepsis, severe sepsis, shock	56 (49.1)
Neoplasia	9(7,9)
Liver diseases	8 (7)
Trauma	6 (5.3)
Death	73 (63)

Values shown in frequency, mean and standard deviation or median and interquartile intervals. CVD: cardiovascular disease; AKI: acute kidney injury; ATN-ISS: Individual Severity Score in Acute Tubular Necrosis; BEE: Baseline Energy Expenditure.

taken off the study because of the suspension of the dialysis procedure, recovery of renal function, or death. Of these, 73 patients left the study due to death (63%).

The mean REE measured by IC was 2,081 ± 645 Kcal (27.7 ± 10 kcal/kg/day). There was an increase in REE on day 5 (2270 ± 556 Kcal) when compared to days 2 and 3 (2,022 ± 754; 2,022 ± 660 kcal, respectively, $p = 0.04$), only when total ERR (kcal/day) was found. When normalized by weight, there was no significant difference during follow-up days.

The vasoactive drug dose (VAD), minute ventilation (MV) and body temperature variables remained constant during follow-up. There was a significant decrease in serum urea and creatinine levels from day 3. The fraction of inspired oxygen (FiO₂) and C-reactive protein (CRP) also decreased on day 5, when compared to days 1 and 2 ($p < 0.05$); while nitrogen balance (NB) and respiratory rate (RR) parameters increased on days 4 and 5, when compared to days 1 and 2.

The percent increase (or decrease) in REE was calculated to investigate the mean variability in EE from one day to the other. This calculation was done by subtracting the REE from the day of interest by the REE from the previous day, and dividing that difference by the REE from the previous day, times 100 (percentage). This variability had a median of 0.44% (-14, 14).

Table 2 shows the evolution of clinical and laboratory parameters during the 5-day follow-up.

REE correlations with clinical parameters (temperature and dose of VAD), laboratory [serum urea and creatinine, total leukocyte count (WBC) and CRP], ventilatory variables (VM and FiO₂) and catabolism (NB and urea nitrogen - UNA). The correlations are presented on Table 3. REE correlated positively and significantly with body temperature, WBC, CRP, MV, FiO₂ and BUN, weight and height, and inversely with NB and age.

After multiple linear regression, only MV, FiO₂, body weight and age were independently correlated with REE. The result of the regression is shown on Table 4.

DISCUSSION

Information about the energy expenditure assessment of patients with AKI is scarce in the literature. Our study found that the baseline EE estimated by the Harris and Benedict formula¹⁵ was significantly lower than that measured by IC. This finding corroborates the indication not to use this formula in critically-ill patients,^{7,16-18} and in patients with AKI.¹⁹

The best way to assess the energy needs of critically-ill patients with AKI is by means of IC.¹⁹ In the present study, REE increased as measured by IC on the fifth day of follow-up, compared to days 2 and 3. However, this Significant increase was seen only in REE without normalization for weight. When normalized (kcal/kg/day), there was no significant difference during follow-up.

Increased REE was observed by Scheinkestel *et al.*⁹ in patients under RRT, and the mean REE value in the patients in this study was also close to that of the present study (2,153 ± 380 Kcal and 2,081 ± 645 Kcal, respectively). Despite this similarity in EE, our study evaluated the patients during non-dialysis time, as recommended by the guidelines for IC use.^{5,20,21}

This recommendation is because during dialysis, the correction of metabolic acidosis and CO₂

TABLE 2 EVOLUTION OF CLINICAL AND LABORATORY PARAMETERS OF PATIENTS IN DIALYSIS WITH ACUTE KIDNEY INJURY DURING 5 DAYS

	Day 1 N = 114	Day 2 N = 76	Day 3 N = 52	Day 4 N = 35	Day 5 N = 24
REE (Kcal)	2061 ± 700	2022 ± 754 ^a	2022 ± 660 ^a	2150 ± 539	2270 ± 556
REE (Kcal/Kg/d)	27.9 ± 10.4	26.6 ± 10.6	26.6 ± 9.6	29.2 ± 8.9	30.4 ± 8.3
REE variability (%)		-5 (-16. 7).	-1.6 (-10. 12).	0 (-11. 17).	8 (-13. 25).
VAD (mcg/Kg/min)	0.18 (0.06-0.58)	0.1 (0-0.28)	0.04 (0-0.19)	0.06 (0-0.33)	0 (0-0.19)
VM	8.5 ± 2.6	8.3 ± 2.4	9.1 ± 2.6	8.8 ± 2.7	9 ± 3.6
Freq. (resp/min)	16 ± 4	16 ± 5	18 ± 5.5 ^{a,b}	18 ± 6 ^b	19 ± 6 ^b
PEEP	6 ± 2	6 ± 2	6 ± 2	6 ± 1	6 ± 1
FIO ₂	40 ± 11.3 ^a	40 ± 12 ^a	37.5 ± 10 ^c	37.6 ± 9.1	34.2 ± 10
Temperature (°C)	37.7 ± 0.95	37.5 ± 0.8	37.6 ± 0.9	37.6 ± 0.83	37.8 ± 1
Urea (mg/dl)	178 ± 79	160 ± 63 ^b	142 ± 51 ^{b,c}	131.4 ± 46.4 ^{b,c}	143 ± 68.7 ^b
WBC (mm ³)	17050 (12300-22400) ^d	17600 (10600-25500) ^d	17800 (13700-26100) ^d	22300 (14800- 29300)	16900 (12500- 22600)
PCR (mg/dl)	273 (11- 35.3)	25.2 (7.8-31)	23 (6.7-31) ^b	26.7 (7.4-36.7)	19.3 (6.6-37.3) ^b
NB (g/day)	-5.51 (-14.12;-0.68)	-7.74 (-18.13; -1.63)	-6.1 (-11.7; 3.1)	-1.27 (-5.8; 1.98) ^b	-0.81 (-7.98; 3.12) ^b
BUN (g/day)	13.65 (7.56; 19.12)	18 (9.87; 24.6) ^b	14.24 (8.6; 22.5)	15.6 (9.5; 23.3)	14.13 (9.93; 20)

Values shown in frequency, mean and standard deviation or median and interquartile intervals. REE: Resting Energy Expenditure, VAD: vasoactive drug; FIO₂: Fraction of Inspired Oxygen; Mv: Minute volume; RR: respiratory rate; PEEP: expiratory positive airway pressure; Creat: serum creatinine; WBC: white blood-cell count; CRP: C-reactive protein; NB: Nitrogen Balance; BUN: blood urea nitrogen. REE variability was calculated as: (REE day 1 want to assess - REE previous day)/REE previous day. ^a $p > 0.05$ when compared to day 5; ^b $p < 0.05$ when compared to day 1; ^c $p < 0.05$ when compared to day 2; ^d $p < 0.05$ when compared to day 4.

removal²²⁻²⁴ can result in an underestimation of the EE. In addition, RRT may also lead to a reduction in body temperature and decrease REE.²⁵ Thus, the comparison between these two studies may be impaired.

Koukiasa *et al.*,²⁶ when evaluating critically-ill patients with non-septic intracranial hemorrhage, also found elevated REE during follow-up on the seventh day of the study. This increase in EE is usually seen in critical ICU patients. The peak metabolic rate is reached during the second week post admission, and some explanation for this are complications or discontinuation of sedation. The increase seen by Koukiasa *et al.*,²⁶ in EE can be partially explained by increases in body temperature.

In the present study, there was no change in body temperature during follow-up. Only ventilatory parameters such as RR and FiO₂ changed on day 5, compared to the initial days.

The daily variability on REE in our study was 0.44% (-14, 14). The variability reported in the

literature is higher. Reid⁷ obtained a daily variability of 31.7 ± 22.6% and Weissman *et al.*⁶ reported a mean variability of 21 ± 16%. Both were studies with critically-ill ICU patients. Evaluating patients with intestinal failure using parenteral nutrition at home, Ławiński *et al.*²⁷ found a variability closer to that of our study (8% ± 7%), when evaluating two REE measures.

This difference in variability seen in ICU studies may be due to the heterogeneity of the studied population, since EE can be altered by several factors, such as disease severity and course, sedation, mechanical ventilation, infectious complications, neurological deficits, among others.²⁶

In the present study, some parameters correlated with the EE, such as body temperature, WBC, CRP, MV, FiO₂, BUN, weight, height and age, and after multiple analysis, MV, FiO₂, weight and age remained independently associated with the REE measured by IC.

MV and FiO₂ Influences are expected, since the calculation of REE by IC is done based on the Weir

TABLE 3 UNIVARIATE ASSOCIATION BETWEEN RESTING ENERGY EXPENDITURE AND CLINICAL, LABORATORY, VENTILATORY AND NUTRITIONAL PARAMETERS OF PATIENTS WITH DIALYSIS ACUTE KIDNEY INJURY (N = 301)

Spearman correlation coefficient with REE		<i>p</i>
VAD	0.009	0.883
mV	0.246	< 0.001
FiO ₂	0.183	0.001
Temperature	0.167	0.004
UR	0.105	0.068
Creat	0.100	0.085
WBC	0.159	0.11
CPR	0.105	0.045
NB	-0.129	0.05
BUN	0.158	0.026
Weight	0.320	< 0.001
Height	0.158	0.006
Age	-0.361	< 0.001

REE: rest energy expenditure; VAA: vasoactive agent; UR: serum urea; Creat: serum creatinine; WBC: White blood cell count; CRP: C-reactive protein; NB: nitrogen balance; BUN: Blood Urea Nitrogen; FiO₂: fraction of inspired oxygen, mV: minute volume.

formula²⁸, which considers the inspired volume of O₂ (VO₂) and expired CO₂ (VCO₂). To calculate VO₂ and VCO₂ by IC, the required measures are inspired and expired concentrations of oxygen (FIO₂, FEO₂), carbon dioxide (IRCO₂, ERCO₂) and the volume of inspired and expired air (VI, VE).²⁹

As for MV, its increase may be due to an increase in carbon dioxide volume (VCO₂) during the increase of metabolism, according to Kiiski & Takala.³⁰ Kinney *et al.*³¹ have shown that the increase in MV is not proportional to the increase in metabolic rate. In addition, it is still possible that fever, by itself,

stimulates the exhaled volume increase, regardless of the increase in oxygen consumption or CO₂ production. Despite these variable effects, there is a linear relationship between MV and the metabolic rate in critically-ill patients.³²

The linear relationship between weight and REE is known. Body weight and fat-free mass are two variables that directly affect energy expenditure. Changes in body weight (gain and/or loss) show a direct relationship with increase or reduction in REE.^{33,34} This association is also seen from REE with age; but in a negative correlation, nonetheless.

Aging is associated with a lower mass of some organs that contribute to energy metabolism and with changes in lean body mass (reduction), and in adipose tissue (increase).³⁵ Studies have reported a progressive decline in REE of about 1-2 % per decade, and that this decline is largely explained by changes in body composition.³⁶⁻³⁹ In addition, it has also been suggested that the appearance of these REE changes may depend on gender, adiposity, and lean body mass.^{35,40}

The study has some limitations. First, it was performed in a single center, and despite the substantial number of IC measurements, only 24 patients completed the five-day follow-up. In addition, our study presents an evaluation of a specific ICU population: patients with AKI on dialysis, that is, their results cannot be extrapolated to all critical patients or all patients with AKI. Despite these limitations, to our knowledge, this is the first study to evaluate REE variability in patients with AKI, outside the dialysis time.

As a conclusion, patients with dialytic AKI showed a small REE variability during 5 days of

TABLE 4 DETERMINANTS OF RESTING ENERGY EXPENDITURE IN PATIENTS WITH ACUTE KIDNEY INJURY (N = 301)

	Beta	Standard error	t	<i>p</i>	Tolerance	VIF
mV (l/min)	51.776	19.119	2.708	0.008	0,925	1.081
FiO ₂ (%)	14.248	5.033	2.831	0.005	0,764	1.309
Temperature (°C)	96.952	64.394	1.506	0.134	0,859	1.164
Weight (Kg)	5.504	2.608	2.111	0.036	0,761	1.314
Height (m)	-6.184	7.046	-0.878	0.382	0,671	1.491
Age (Years)	-15.127	3.142	-4.814	0.000	0,915	1.093
CRPLN	39.621	64.314	0.616	0.539	0,797	1.255
UNALN	-25.165	71.799	-0.350	0.726	0,781	1.280
WBCLN	73.657	78.287	0.941	0.348	0,828	1.207

mV: minute volume; FiO₂: fraction of inspired oxygen; WBCNL: Napierian logarithm of total leucocyte count; CRPNL: C-reactive protein Napierian logarithm; UNANL: urea nitrogen appearance Napierian logarithm.

follow-up. REE in these patients was independently and positively associated with FiO_2 , MV and weight, and inversely related with age. Thus, ventilatory requirements need to be evaluated daily, so that necessary changes in dietary prescription are made in these patients to avoid the known negative influences of under and overnutrition in critically-ill patients.

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