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Research Article

Does Acute Kidney Injury Alter Energy Metabolism of Septic Patients?

Abstract

Background: The determination of resting energy expenditure (REE) in critically ill patients is essential to prevent hypo and hyper alimentation.

Objectives: This study aims to describe the REE in septic patients with and without acute kidney injury (AKI) and compare by examining the REE estimated by Harris-Benedict equation (HB) with the REE measured by indirect calorimetry (IC).

Methods: Prospective study was performed in septic patients older than 18 years, undergoing mechanical ventilation, with or without AKI defined by KDIGO criteria, and admitted to the Intensive Care Unit of University Hospital. The REE was estimated by HB equation and measured by IC within 72 hours after the diagnosis of sepsis and seven days after the initial measure.

Results: Sixty-eight patients were evaluated, age was 62.49±16.6 years, 63.2% had AKI, and SOFA was 9.81±2.35. The measured REE was 1857.53±685.32 kcal, while the estimated REE was 1514.87±356.72 kcal, with adequacy of 123.49±43%. Septic patients without AKI (n=25) and with AKI (n=43) had measured REE statistically higher than the estimated one (1855 kcal (1631.75-2052.75) vs. 1551 kcal (1349 -1719.25), p=0.007 and 1868.0 kcal (1219.5-2364.75) vs. 1388 kcal (1254-1665.5), p=0.026, respectively). There was no significant difference between the two groups in measured and estimated REE and in evolutional REE.

Conclusion: The REE measured by IC was significantly higher than that estimated by HB in both septic patients with and without AKI. There was no significant difference between the septic patients with and without AKI in REE, suggesting that AKI does not influence the REE of septic patients.

Introduction

Sepsis, defined as systemic inflammatory response syndrome associated with infection, is an important cause of morbidity and mortality in patients admitted to intensive care units (ICU) [1,2].

It is the most frequent cause of acute kidney injury (AKI) in critically ill patients, occurring in approximately 51% of patients with septic shock and positive cultures. Septic patients developing severe AKI have increased risk of mortality, despite advanced vital organ support [3,4].

It is well know that sepsis and AKI can affect the energy metabolism and treatments based on a better understanding of these alterations may help to prevent weight loss and muscle wasting [5]. Accurate determination of energy needs is obviously important in critically ill patients because both over and underfeeding may be associated with complications and undesirable consequences such as over and underfeeding [6].

Energy metabolism in patients with renal failure has been studied, with conflicting results [7-14]. Studies have suggested that chronic kidney disease (CKD) is associated with hypometabolic state due to abnormalities in cell metabolism [10,11]. In contrast, a hypermetabolic state was frequently observed in AKI patients and associated with cause and severity [15]. The hypermetabolism may be present in AKI patients since AKI is a part of a more complex illness such as sepsis and not necessarily the direct consequence of renal failure per se [15-21]. Thus, it is unknown whether possible changes in energy metabolism observed in septic patients with AKI are directly related to AKI itself.

Given the lack of studies on energy metabolism in AKI patients, we decided to measure and compare the resting energy expenditure (REE) in septic patients with and without AKI using indirect calorimetry (IC). This study also aims to compare the REE estimated by the Harris-Benedict equation (HB) with that measured by IC.

Patients and Methods

A prospective, observational study was conducted from November 2013 to May 2015 in patients admitted to ICUs from a Brazilian University Hospital.

Patients 18 years of age or older who had sepsis according to "Survival Sepsis Campaign 2012 [22] and mechanically ventilated using of inspired oxygen (FiO_2) < 0.60 were included in the study. Exclusion criteria were patients with CKD stage 4 and 5 (creatinine clearance lower than 30 mL/min/1.73 m², estimated by the modification of diet in renal disease (MDRD) equation) [23].

Septic patients were divided into two groups according to presence or absent of AKI. AKI was defined using KDIGO 2012 criteria [24].

Variables previously reported to be associated with AKI, sepsis or energy metabolism were collected prospectively on each patient by review of the medical record: sex, age, the presence of comorbidities (diabetes, CKD, and hypertension), primary diagnosis, the a etiology of sepsis, prognostic score specific for AKI (ATN-ISS) [25], Sequential Organ Failure Assessment (SOFA) [26], use of vasoactive drug and neuromuscular blocking agents, serum creatinine and blood urea nitrogen levels, C reactive protein (CRP) and leukocytes.

The REE was estimated by HB equation [27] and measured by the IC within 72 hours after the diagnosis of sepsis and seven days after the initial measure. IC was performed using QUARK RMR (Cosmed, Rome, Italy). The calorimeter was calibrated before each use. The protocol required that patients be inactive and undisturbed for 30 minutes prior to testing and for 30-minute duration of the data collection. It is recommended that patients achieve steady state during testing. Steady state was defined as a variability of < 10% in the measurements of oxygen consumption and carbon dioxide production, and< 5% in the respiratory quotient from minute to minute. The REE was also estimated using HB formula and injury factor for sepsis as suggested by Long et al. [28].

Patient height was measured when possible, or it was considered the value documented in the medical record at the time. Weight was measured using calibrated hospital scales in most patients or estimated using Chumlea formula [29].

The Ethics Committee of the Botucatu School of Medicine – UNESP approved this study (approved protocol number 322.535) with a waiver of informed consent given its observational nature.

Statistical analysis

The sample size calculated was 61 patients considering standard deviation 200 kcal, estimated maximum error de 50 kcal in critically ill patients and p value =0.05.

Data analysis was performed using SAS for Windows (version 9.2: SAS Institute, Cary, NC, USA, 2012). Results were expressed as mean and standard deviation or median and interquartile range. The chi-square test was used to compare categorical variables. We used ANOVA to compare parametric variables of clinical, laboratory and nutritional data. For non-parametric variables, the *Mann-Whitney test* was used. Variables with significant univariate associations (p<0.10) were candidates for multivariable analysis, which was performed using stepwise variable selection. Repeated measures analysis using the mixed procedure was used for the evolutional REE. For all tests, a p-value of <0.05 was considered statistically significant.

Results

Sixty-eight septic patients admitted to ICU were evaluated. Mean age was 62.49 ± 16.6 years, 64.7% were male, 88.24% were Caucasian, SOFA was 9.81 ± 2.35, shock septic was the classification of sepsis more frequent (64.71%), lung was the main site of infection (70.6%) and comorbidities were present in 82.85% of patients. The measured REE was 1857 (1308-2261.5) kcal, while the estimated REE was 1449 (1255.5-1677.5) kcal. AKI was present in majority of patients (63.2%) and mortality was high (77.94%). Most of AKI patients was KDIGO stage 3 (60.5%), 30.2% were KDIGO2 and only four patients were

KDIGO 1 (9.3%). Nine patients needed renal replacement therapy and all of them were treated with intermittent hemodialysis. A comparison of baseline characteristics between those who did and did not develop AKI is shown in Table 1.

AKI group had higher SOFA (11.0±1.73 vs. 7.76±1.79, p<0.0001), CRP (p=0.0107), comorbidities (p=0.0179) and mortality (p=0.046). The groups were similar in gender, age and site of infection. In multivariable regression analysis, comorbidities (OR: 0.07; CI95%: 1.0-1.8) and SOFA (OR: 0.32; CI95%: 0.1-0.5) were identified as predictors of AKI (Table 2).

The Table 3 shows the comparison between estimated and measured REE in both groups of patients. Septic patients without

Table 1: Patients demographics and clinical characteristics (n=68) according to presence of AKI.

Variables	Septic patients (n=68)	AKI septic patients (N=43)	Non-AKI septic patients (N=25)	P
Age (years)	62.49±16.60	65.28±14.50	57.68±19.05	0.07
Male sex (%)	44 (64.71)	27 (62.79)	17 (68.0)	0.66
Race (%) Caucasian	60 (88.24)	38 (88.37)	22 (88.0)	0.91
Sepsis classification (%) Septic shock Sepsis Sepsis	44 (64.71) 24 (35.29)	26 (60.47) 17 (39.53)	18 (72.0) 7 (28.0)	0.41
Site of infection (%)				
Pulmonary	48 (70.59)	26 (60.47)	22 (88.0)	0.0857
Abdominal	14 (20.59)	11 (25.58)	3 (12.0)	0.079
Others	6 (8.82)	6 (13.95)	-	0.13
SOFA score*	9.81±2.35	11.0±1.73	7.76±1.79	<0.001
Presence Comorbidities (%) Hypertension Diabetes Mellitus Dyslipidemia Obesity	56 (82.85) 42 (61.76) 18 (26.47) 13 (19.11) 8 (11.76)	39 (90.7) 31 (72.09) 15 (34.88) 10 (23.25) 6 (13.95)	17 (68.0) 11 (44.0) 3 (12.0) 3 (12.0) 2 (8.0)	0.017 0.024 0.097 0.15
Ventilation mode (%) Controled Spontaneous	54 (79.41) 14 (20.59)	36 (83.72) 7 (16.28)	18 (72.0) 7 (28.0)	0.2491
FiO$_2$	35.97±9.49	35.84±9.59	36.20±9.50	0.8805
Use of vasoactive drugs (%)	50 (73.53)	34 (79.07)	16 (64.0)	0.1744
Use of sedatives (%)	34 (50.0)	21 (48.84)	13 (52.0)	0.5000
Use of antibiotics (%)	65 (95.59)	41 (95.35)	24 (96.0)	0.6967
Presence of fever (%)	46 (67.64)	29 (67.44)	17 (68.0)	0.5906
Blood Urea Nitrogen (mg/dl)	62.82±38.46	75.28±29.32	3.72±17.50	<0.001
Creatinine (mg/dl)	2.35±1.68	3.22±1.51	0.84±0.32	<0.001
CRP (mg/dl)**	29.27±15.72	32.94±14.63	22.98±15.82	0.0107
Leukocytes (mm³)	16392.81± 8761.79	17226.63± 9240.82	14992± 7872.42	0.3163
Outcomes (%) Death	53 (77.94)	38 (88.37)	15 (60.0)	0.046

*Sequential Organ Failure Assessment Score; **Acute Kidney Injury; *** C Reactive Protein reactive, FiO$_2$ fraction of inspired oxygen.

AKI (n =25) and with AKI (n = 43) had measured REE significantly higher than estimated one (1855.0 kcal (1636.75-2052.75) vs. 1551.0 (1349.0 -1719.25), p = 0.007 and 1868.0 kcal (1219.5-2364 75) vs. 1388.0 kcal (1254.0-1665.5), p = 0.026, respectively). The HB equation without using injury factor was not precise and underestimated the REE in 16.4% in septic patients without AKI and in 25.7% in septic patients with AKI.

However, when injury factor was used, the measured REE was significantly lower than estimated one in both groups. Measured and estimated REE were 1855 (1636.75 – 2052.75) vs 2467.2(1322-2213.8), p<0.001 in non-AKI group and 1868.0 (1219.5 – 2364.75) vs. 2370.63(1456-2451), p<0.001 in AKI group. Thus, the HB equation using injury factor was not precise and overestimated the REE in 33% in septic patients without AKI and in 26.9% in septic patients with AKI.

There was no significant difference between the two groups (with and without AKI) in measured and estimated REE (p = 0.6268 and 0.6360, respectively). This suggests that AKI does not affect the REE septic patients.

There was no significant difference in evolutional REE (day 1 vs. day 7) in general septic population (1845.955 ± 658.273 kcal vs. 1809.545 ± 755.083 kcal, p = 0.865) and after patients were divided into AKI (1873.5±718.43 vs.1610.5±629.98, p=0.706) and non-AKI groups (1795.833±557.734 vs. 1915 ±756.215, p=0.76) (Table 4).

Discussion

This study described and compared the REE estimated by the HB equation and measured by IC in septic patients who developed and did not develop AKI during ICU stay. Its results indicate that HB equation does not agree well with energy expenditure measured by IC in critically ill patients and that AKI itself apparently has no direct effect on energy metabolism of septic patients.

The measured REE was higher than the estimated one in general septic population and in groups that developed and did not developed AKI. The equation HB without using injury factor was not precise and underestimated the REE in both groups: septic patients without and with AKI.

Due to the inaccuracy of this equation, the correction factor was applied. However, when injury factor was used, the measured REE was statistically lower than the estimated one in all groups. Thus, the equation HB using injury factor was not precise and overestimated the REE in both groups: septic patients who did not develop AKI and in that developed AKI.

Similar results have been observed in previous studies [30-33]. Coletto et al. [30], reported in septic patients that HB equation underestimated the REE in 7.6% and when the injury factor as used, the REE was overestimated in more than 50%. In a systematic review, Frankenfield et al. [31], reported the results of an evidence analysis of the accuracy of metabolic rate calculation methods. HB equation had mean differences between measured resting metabolic rate and predicted values ranging from 250 to 900 kcal/ day. A review study conducted by Walker and Heuberger suggests not to use the

Table 2: Multivariable analysis for AKI risk (n=68).

Factors	OR	CI 95%	p
Site of infection	0.4	0.09 – 1.7	0.2284
Presence of comorbidities	0.07	1.0 – 1.8	0.0327
CRP*	0.94	0.88 – 1.0	0.0620
SOFA score **	0.32	0.1 – 0.5	0.0002

Note: OR: odds ratio; CI95%: confidence interval of 95%; p: statistical significance
* C Reactive Protein reactive; **Sequential Organ Failure Assessment Score.

Table 3: Anthropometric characteristics and resting energy expenderd of septic patients admitted to intensive care unit according to presence of AKI.

Variables	Septic patients (n=68)	AKI septic patients (n=43)	Non-AKI septic patients (n=25)	P
Weight (Kg)	76.74±25.40	77.23±26.35	75.88±24.17	0.83
Height (cm)	157.82±35.23	160.87±27.05	152.58±46,25	0.35
BMI (Kg/m²)*	27.83±8.59	28.04±7.97	27.48±9.55	0.72
Measured REE (kcal)**	1857 (1308-2261.5) [a]	1868 (1219.5-2364 75) [b]	1855 (1636.75-2052.75) [c]	0.63
Estimated REE (kcal)	1449 (1255.5-1677.5)	1388 (1254.0-1665.5)	1551 (1349.0 -1719.25)	0.63
Estimated REE using IF (kcal)	2283.2(1308-2261.5)	2370.63(1456-2451)	2467.2(1322-2213.8)	0.59

* Body Mass Index; ** Resting Energy Expenditure;
[a] Different from estimated REE using HB formula without and with injury factor, p<0.001
[b] Different from estimated REE using HB formula without and with injury factor, p=0.007 and < 0.001 respectively.
[c] Different from estimated REE using HB formula without and with injury factor, p=0.026 and < 0.001 respectively.
IF: injury factor.

Table 4: Evolutional resting energy expenderd (day 1 vs day 7) in septic patients according to presence of AKI.

	After seven days		
	measured REE D1 (kcal)	measured REE D7 (kcal)	P
Séptic patients (n=22)	1845.955 ±658.273	1809.545±755.083	0.865
AKI* septic patients (n=16)	1873.5±718.43	1610.500±629.98	0.706
Non-AKI septic patients (n=6)	1795.833±557.734	1915.000 ±756.215	0.762

*Acute Kidney Injury, *REE: rest energy expenditure.

HB equation with or without correction factors in critically ill AKI patients as it was found to be inaccurate and unreliable for ICU patient [32].

It may be argued that inaccurate predictions are expected because the HB equation was developed long ago and based on data from healthy volunteers. Others equations **as** the Ireton-Jones, Penn state and Faisy have been developed from REE measurements of hospitalized and critically ill patients, and dynamic variables as body temperature and minute ventilation that reflect the metabolic state of the patient. Although they are intended to critically ill patients, several studies have found these formulas have poor agreement with measured REE by IC [33,34].

Boulatta et al. [33], evaluated energy expenditure equations in 365 hospitalized patients. They found there were poor accuracy between REE measured by IC and REE predicted by the HB, Mifflin, Penn State and the Ireton-Jones equations. In all cases, the predictive equations underestimated measured REE.

Kroos et al. [34], evaluated the REE in 927 critically ill patients, including 401 obese patients. They also found there were poor agreement between REE measured by IC and REE predicted by the HB, American College of Chest Physicians, Mifflin, and the Ireton-Jones equations. In all cases, except using Ireton-Jones, the predictive equations underestimated measured REE.

We recently have published the paper "Poor Agreement between Predictive Equations of Energy Expenditure and Measured Energy Expenditure in Critically Ill Acute Kidney Injury Patients " that aimed to determine if six different predictive equations for estimated REE accurately reflect the requirements of AKI patients. We included in this prospective and observational study AKI patients AKIN-3 assessed by IC. Bland–Altman, intra class correlation coefficient and precision (percentagem of predicted values within 10% of measured values) were performed to compare REE by equations with REE measured by IC. None of these equations accurately estimated measured REE in severe AKI patients and most of them underestimated energy needs [35].

Our study agrees with review studies that also suggest that none of these equations has sufficient accuracy and agreement with measured REE in critically ill patients and should not replace the use of IC33. Using universal prediction equations to critical ill AKI patients, errors of prediction can occur and lead to overfeeding or underfeeding if they are used to guide the feeding regimen of these patient [36].

Using this data set, we also have demonstrated that there was no significant difference between the groups of septic patients who developed and did not developed AKI. This suggests that AKI does not affect the energy metabolism of septic patients. Similar results were observed by Schneeweiss e cols [35]. It was the only study that evaluated the REE also in AKI patients. In that study, energy metabolism was measured by IC in 86 patients with AKI and chronic kidney disease (CKD) and in 24 control subjects. In AKI patients with sepsis, the REE was increased ($p < 0.05$). In other groups with renal failure (AKI without sepsis, CKD with conservative treatment or hemodialysis, and severe untreated azotemia) the REE was not different from those of control subjects. The authors concluded that renal failure has no influence on energy expenditure as long as septicemia is absent.

Others studies agree with our results that suggest the hypermetabolism may be present in AKI patients since AKI is a part of a more complex illness such as sepsis and not necessarily the direct consequence of renal failure per se. suggesting that AKI does not influence the energy metabolism of septic patients [15-21].

There was no significant difference in evolutional REE (day 1 vs. day 7) in general septic population and after patients have been divided into AKI and non-AKI groups. Different results were observed by Vermeij et al. [37], who investigated if only a daily measure of REE could be extrapolated for the whole length of stay in the ICU. The authors noted that there were variations higher than 31% for the same patient, although the daily average is close to the average seven-day study.

Some limitations should be recognized. First, we did not examine others predictive equations currently used in practice such as Mifflin, Penn State and the Ireton-Jones equations. However, the HB equation that we evaluated contain clinical information readily available to practitioners, making it clinically useful equation. Second, we did not have information about treatments that might influence energy expenditure and carbon dioxide production, including type of nutrition and energy intake, catecholamine, neuromuscular blocking agents, and opioids. Finally, we studied a select population of patients, our findings may not be generalizable to all AKI, or critically ill patients.

Despite limitations, this is the largest study to report that predictive HB equation does not accurately estimate REE in critically ill septic patients and that possible changes in energy metabolism observed in septic AKI patients are not directly related to AKI itself. Our findings suggest that the REE measured by IC was significantly higher than that estimated by the HB equation in both septic with and without AKI and that the HB equation using injury factor also was not precise and overestimated the REE. The lack of difference in REE between the septic patients with and without AKI suggests that AKI does not influence the REE of septic patients and that possible changes in energy metabolism observed in septic AKI patients are not directly related to AKI itself.

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