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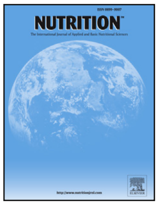

Applied nutritional investigation

Prognostic value of respiratory quotients in severe polytrauma patients with nutritional support

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ABSTRACT

Objective: The association between energy metabolism and prognosis in polytrauma patients has not yet been defined. The aim of this study was to describe energy metabolism and analyze the prognostic value of respiratory quotient (RQ) and nonprotein respiratory quotient (npRQ) in fasting polytrauma patients (fPP) and polytrauma patients with nutritional support (nsPP).

Methods: Twenty-two polytrauma patients (before and after parenteral nutrition administration) and 22 healthy controls (after overnight fasting) were examined on day 4 (median) after admission to the intensive care unit. To evaluate energy expenditure in nsPP and resting energy expenditure in fPP and controls with RQ and npRQ in all groups, we used indirect calorimetry. With regression analysis, the descriptive models of intensive care unit (ICU) length of stay (LOS) and mechanical ventilation time (VT) were derived.

Results: RQ and npRQ were significantly lower in fPP than in controls ($P < 0.05$ and $P < 0.01$, respectively) and in nsPP ($P < 0.05$). In nsPP, relationships between RQ or npRQ and the ICU LOS or mechanical VT were demonstrated ($P < 0.0001$, $r = -0.78$ for RQ and VT; $P < 0.0001$, $r = -0.78$ for npRQ and VT; $P < 0.001$, $r = -0.69$ for RQ and LOS; $P < 0.001$, $r = -0.72$ for npRQ and LOS).

Conclusions: RQ and npRQ parameters measured by indirect calorimetry in polytrauma patients with parenteral nutrition on the fourth day of ICU stay related to clinical outcomes such as duration of mechanical ventilation and ICU LOS.

Introduction

Polytrauma and critical illness generally are frequently associated with a state of malnutrition caused by both hypermetabolism and inadequate intake of energy and protein [1,2]. Kubrak and Jensen [3] described that the prevalence of malnutrition was 13% to 78% in acute care patients between 1996 and 2005. Kvale et al. [4] reported that 40% of patients loose >10 kg of body weight during the period directly after admission to the intensive care unit (ICU). It has been shown that nutrient deficiency correlates with a prolonged ICU/hospital length of stay (LOS) and is strongly associated with increased morbidity and mortality among critically ill patients [2,5–7]. However, the relation between energy metabolism

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and prognosis in polytrauma patients is not well known. The gold standard for determining energy and nutritional requirements is indirect calorimetry [8–12]. Although it is usually used to adjust the appropriate nutritional support composition, it also could have other uses. Studies in patients with various pathologic states, such as sepsis [13], hepatocellular carcinoma [14], nonalcoholic fatty liver disease [15], and liver cirrhosis [16,17], have already described respiratory quotient (RQ) or nonprotein respiratory quotient (npRQ) as a prognostic marker. However, to our knowledge this has not yet been described in polytrauma patients. The aim of this study was to characterize energy metabolism focusing on RQ and npRQ and their association with indirect prognostic markers such as length of mechanical ventilation and ICU LOS.

Material and methods

Patients

This was a prospective observational single-center pilot study. Twenty-two polytrauma patients (15 men and 7 women) admitted to the ICU 1 department of University Hospital in Hradec Kralove, Czech Republic between 2015 and 2017, together with 22 healthy controls (15 men and 7 women) with similar anthropometric characteristics were included. The clinical characteristics of the participants are shown in Table 1. Since 2015, the rescue service has brought in 2730 injured patients. Of these patients, 557 were polytraumatized with an injury severity score (ISS) >15. Of the polytrauma patients, only those with the highest ISS and with the most severe injuries were chosen. The chosen patients had at least two injuries (in most cases these were head injuries and fractures of the extremities or pelvis), the majority was ventilated, and all had undergone volume resuscitation due to shock. All patients underwent physical examination, sonography, computed tomography scanning, and blood tests. None of examined patients died while in the hospital. The main exclusion criteria were an inspired oxygen content >0.5 (patients on a ventilator), air leaks through chest drains (patients on a ventilator), inhaled nitric oxide therapy, diuresis <500 mL/d, continuous renal replacement therapy, age >85 or <18 y, irreversible circulatory shock, diabetes mellitus, pregnancy, elective admissions, or ability to eat.

In the polytrauma patients, all calorimetric examinations were performed as a part of therapeutic preventive care. No treatment and administration of nutritional support were affected; therefore, it was granted to waive informed consent. The treatment was standard according to the established practice of the ICU department. The study protocol strictly adhered to all provisions of the Declaration of Helsinki and was approved by the Ethics committee of the University Hospital in Hradec Kralove.

Anthropometric parameters

Anthropometry, including measurements of height and weight, was carried out. For the patients, height was estimated by measurement of lower leg length from the top of the patella with knee flexed at 90 degrees [18]. Height for the controls was measured with a stadiometer to the nearest 0.5 cm. Patients' weight was estimated by a specially calibrated bed scale with great attention to accuracy (to the nearest 0.1 kg). The InnerScan-Body Composition Monitor (Tanita Corporation, Japan) was used to measure weight of control participants to the nearest 0.1 kg (participants wore only their underwear). Weight and height were subsequently used to calculate body mass index [19] and body surface area (BSA) [20].

Table 1
Characteristics of patients and controls

	Polytrauma patients (n = 22) Median (25% percentile; 75% percentile)	Controls (n = 22) Median (25% percentile; 75% percentile)
Age (y)	44.5 (29.8; 59)	48.0 (27; 61)
Male/female (n)	15/7	15/7
Height (cm)	172 (165.8; 180)	178.1 (169; 185)
Weight (kg)	92.5 (74.6; 105)	85.2 (77.2; 93.8)
Body mass index (kg/m^2)	29.8 (28.4; 32.9)	27.2 (22.5; 30.2)
ISS	34 (22; 41.5)	—
Ventilation time (h)	157.5 (53.8; 400.5)	—
ICU length of stay (d)	12 (5.5; 37.3)	—

ICU, intensive care unit; ISS, injury severity score.

Indirect calorimetry

Energy metabolism was analyzed by indirect calorimetry (Vmax Series, V6200 Autobox, SensorMedics Corporation, Yorba Linda, CA, USA). Participants were at rest for ≥30 min before the assessment. All controls were examined after overnight (12-h) fasting. Patients' metabolism was analyzed during the first week of ICU stay (median day of examination was day 4)—first after 4 h of stopping nutritional support administration, and then after ≥4 h of parenteral nutrition administration. On average, the daily nutritional support recorded from patient documentation had the following composition: 18 ± 5.7 kcal/kg of energy (protein calories included), 1.8 ± 0.6 g/kg of carbohydrates, 0.7 ± 0.2 g/kg of lipids, and 1 ± 0.5 g/kg of proteins.

Oxygen consumption per minute (VO_2) and carbon dioxide production per minute (VCO_2) were measured by indirect calorimetry. Urine samples were collected 24 h before the measurement and urinary nitrogen concentration, characterizing protein metabolism, was determined by a standard kinetic ultraviolet assay (Roche/Hitachi 917 Analyzer, Roche Diagnostics, Indianapolis, IN, USA) at University Hospital. From the obtained parameters, resting energy expenditure (REE; for controls and fasting patients), energy expenditure (EE; for patients with nutritional support), RQ, and npRQ were calculated with the manufacturer's standard computer programs (V_{max} Series). EE and REE were calculated by the Weir equation [21]. This equation applies a correction for nitrogen expenditure (NE). NE was calculated as the sum of urinary urea nitrogen and nonurea nitrogen from feces, skin, and miscellaneous, predicted from the weight [22]. RQ and npRQ were calculated from VO_2 and VCO_2 (npRQ also from NE) [23]. The predicted REE was evaluated using the Harris-Benedict equation (REE_{HB}) [24] from weight, height, and age. The ratios of EE to EEHB and REE to REE_{HB} as a percentage were used for expression of the metabolic state, and were classified according to the following criteria: hypometabolism <90%; normometabolism between 90% and 110%; and hypermetabolism >110%.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA). Data distributions were evaluated with D'Agostino and Pearson omnibus normality test. According to the data distribution, the clinical and calorimetric data between the monitored groups were compared by the paired *t* test, the Wilcoxon test, the unpaired *t* test, or the Mann–Whitney test. Spearman test evaluated correlations between observed parameters. To develop descriptive models of indirect prognostic markers (ICU LOS and ventilation time [VT]), linear regression analysis was used. Statistical significance was defined as $P < 0.05$.

Results

Energy metabolism

The calorimetric and biochemical characteristics of the participants are shown in Table 2.

Polytrauma patients with nutritional support (nsPPs) had significantly higher VO_2 than controls. However, there was no statistically significant difference when comparing fasting patients with controls, or patients with and without nutritional support together. VCO_2 was significantly higher in nsPPs than in fasting polytrauma patients (fPPs). No significant difference between patients (both fPPs and nsPPs) and controls was found. When comparing EE or REE respectively, there were differences only between nsPPs and controls, specifically in kcal/d and in daily kcal/m^2. Significantly higher rates of nitrogen excretion were observed in both patient groups when compared with healthy controls. There was no statistically significant difference between glucose levels in fPPs and nsPPs. This was probably caused by insulin administered in combination with nutritional support (average dosage 20 IU/d).

The predicted REE did not differ significantly between patients with or without nutritional support and controls. The measured EE was significantly higher in nsPPs than REE in healthy controls ($P < 0.05$). In polytrauma patients without nutritional

Table 2
Calorimetric and biochemical data

	Controls (n = 22) Median (25% percentile; 75% percentile)	fPP (n = 22) Median (25% percentile; 75% percentile)	nsPP (n = 22) Median (25% percentile; 75% percentile)
Urine nitrogen (g/d)	15.69 (10.40; 18.67)	23.56 (17.44; 29.25)[*]	24.70 (18.11; 30.50)[*]
VO_2 (L/min)	0.27 (0.24; 0.31)	0.28 (0.23; 0.36)	0.31 (0.25; 0.38)[†]
VCO_2 (L/min)	0.20 (0.18; 0.22)	0.20 (0.16; 0.24)	0.23 (0.19; 0.27)[‡]
RQ	0.76 (0.70; 0.80)	0.67 (0.60; 0.77)[†]	0.74 (0.68; 0.79)[§]
npRQ	0.75 (0.67; 0.79)	0.61 (0.50; 0.72)[‖]	0.71 (0.60; 0.78)[§]
EE (kcal/d) measured	1820 (1656; 2063)	1871 (1549; 2379)	2053 (1690; 2493)[†]
REE (kcal/d) predicted	1712 (1548; 1965)	1861 (1528; 2050)	1861 (1528; 2050)
EE (%)	103.90 (97.34; 118.60)	106.30 (95.85; 118.7)	113.70 (102.90; 129.60)
EE/kg (kcal/kg/d)	21.80 (18.76; 23.00)	22.86 (19.36; 24.61)	22.52 (20.56; 25.88)
EE/BSA (kcal/m^2/d)	910.80 (796.60; 988.60)	937.90 (855.10; 1070)	1007 (928; 1152)[‖]
Glycemia (mmol/L)	–	6.40 (5.70; 7.50)	7.20 (6.00; 7.70)

BSA, body surface area; EE, energy expenditure; fPP, fasting polytrauma patients; npRQ, nonprotein respiratory quotient; nsPP, polytrauma patients with nutritional support; REE, resting energy expenditure; RQ, respiratory quotient; VCO_2, carbon dioxide production per minute; VO_2, oxygen consumption per minute.

[*] $P < 0.0001$ vs control.

[†] $P < 0.05$ vs control.

[‡] $P < 0.01$ vs fasting polytrauma patients.

[§] $P < 0.05$ vs fasting polytrauma patients.

[‖] $P < 0.01$ vs control.

Table 3
Distribution of examined groups according to their metabolic state

	Controls (n = 22)	fPP (n = 22)	nsPP (n = 22)
Hypometabolism, n (%)	3 (13.6)	3 (13.6)	1 (4.5)
Normometabolism, n (%)	11 (50)	10 (45.5)	8 (36.4)
Hypermetabolism, n (%)	8 (36.4)	9 (40.9)	13 (59.1)

fPP, fasting polytrauma patients; nsPP, polytrauma patients with nutritional support.

support, the measured REE was also higher, but not significantly. The measured EE was also significantly increased compared with the predicted REE in nsPPs ($P < 0.01$). However, it was not increased significantly either in controls or in polytrauma patients without nutritional support (Fig. 1). In contrast to npRQ and RQ (given below), EE or REE (in any units) did not correlate with length of mechanical ventilation or ICU stay. There also was no difference either in EE or in REE between patients on ventilator and spontaneously breathing patients in both groups (with or without nutritional support).

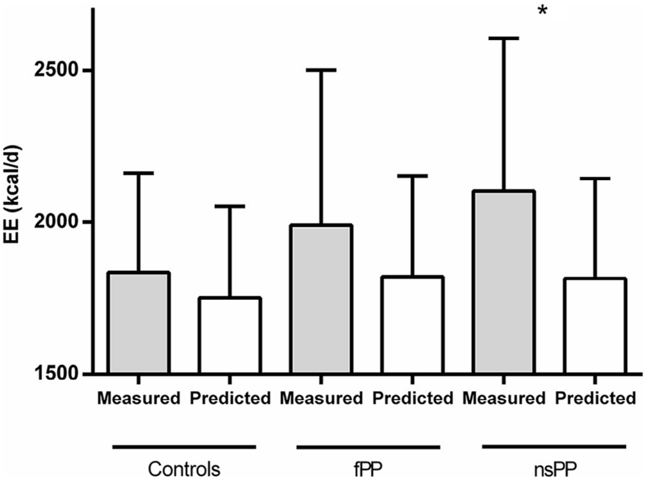

Fig. 1. Measured REE in controls and fPPs and EE in nsPPs versus predicted REE. Values are expressed as mean ± SD. EE, energy expenditure; fPP, fasting polytrauma patients; nsPP, polytrauma patients with nutritional support; REE, resting energy expenditure. *$P < 0.01$ versus predicted REE; paired *t* test.

When comparing the percentage of patients in the hypo-, normo- and hypermetabolic states (Table 3), the control group was more or less the same as the fPP group. nsPPs were more hypermetabolic (59.1 versus 36.4% in controls) and less hypometabolic (4.5 versus 13.6% in controls).

Both, RQ and npRQ were significantly lower in polytrauma patients without nutritional support than in controls ($P < 0.05$ for RQ, $P < 0.01$ for npRQ; Fig. 2) and in nsPPs ($P < 0.05$ for both RQ and npRQ; Fig. 2). However, there was no significant difference in RQ or npRQ when comparing nsPPs with controls. Both RQ and npRQ were higher in spontaneously breathing patients than in mechanically ventilated patients in both nsPP and fPP ($P < 0.01$).

Effects of energy metabolism on the ventilation time and ICU LOS of polytrauma patients

A correlation analysis was made between indirect prognostic markers (length of ICU stay and VT) and parameters obtained from indirect calorimetry (Table 4). This correlation analysis demonstrated that for nsPP, RQ, and npRQ are independent significant parameters relating to the ventilation time and ICU LOS. In contrast, these two parameters did not correlate significantly to ventilation time in fPPs; and for ICU LOS, the significance was much smaller than in the nsPPs. Using regression analysis (Fig. 3), the following descriptive models for mechanical VT and ICU LOS were derived:

$$VT = -1818 \times RQ + 1558.9 \tag{1}$$

$$VT = -1133 \times npRQ + 1010.5 \tag{2}$$

$$LOS = -178.53 \times RQ + 153.34 \tag{3}$$

$$LOS = -113.56 \times npRQ + 101.08 \tag{4}$$

No relationship between RQ or npRQ and ISS was found.

Discussion

Due to the catabolism and hypermetabolism after trauma, malnutrition is frequent in polytrauma patients [1,2,25], is an

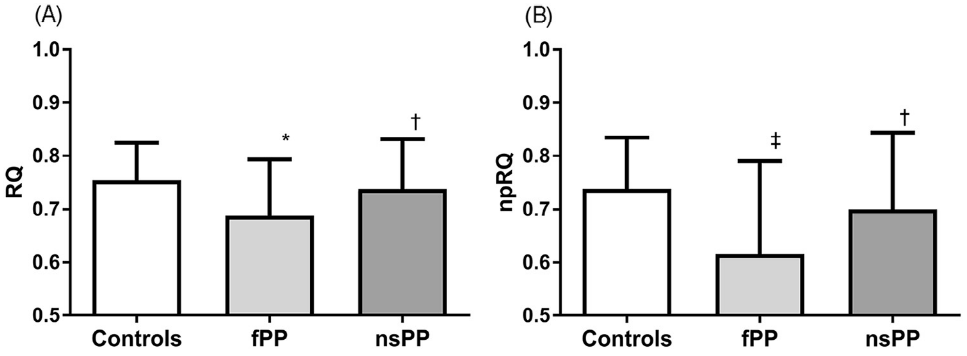

Fig. 2. The RQ (**A**) and npRQ (**B**) in controls and patients with (nsPP) or without (fPP) nutritional support. Values are expressed as mean ± SD. $^*P < 0.05$ versus controls; paired *t* test; $^†P < 0.05$ versus fPPs; $‡P < 0.01$ versus controls; unpaired *t* test. fPP, fasting polytrauma patients; npRQ, non-protein respiratory quotient; nsPP, polytrauma patients with nutritional support; RQ, respiratory quotient.

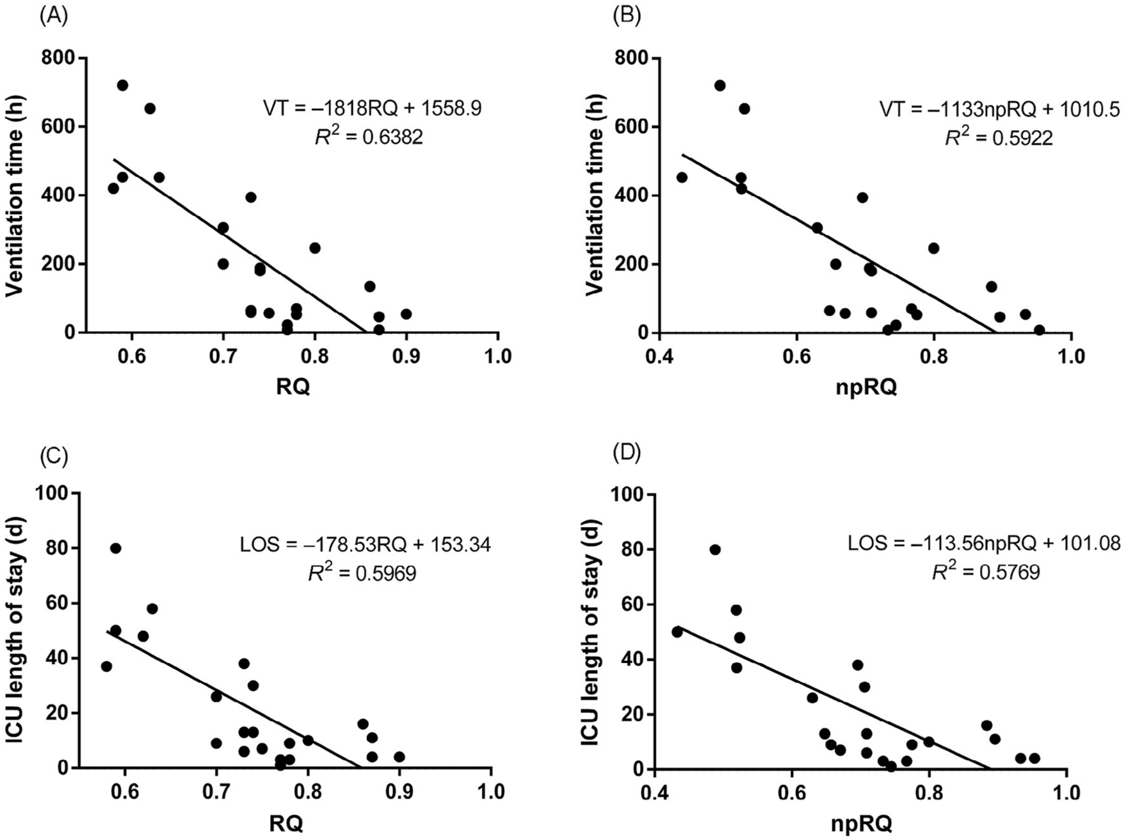

Fig. 3. Linear regression analysis of (**A**) ventilation time and RQ ($r = –0.78$, $P < 0.0001$), (**B**) ventilation time and npRQ ($r = –0.78$, $P < 0.0001$), (**C**) ICU LOS and RQ ($r = –0.69$, $P < 0.001$), and (**D**) ICU LOS and npRQ ($r = –0.72$, $P < 0.001$) in polytrauma patients after nutritional support administration. ICU, intensive care unit; LOS, length of stay; npRQ, nonprotein respiratory quotient; RQ, respiratory quotient; VT, ventilation time.

Table 4
Correlation analysis between indirect prognostic markers and respiratory quotients

	Ventilation time (h)		Length of ICU stay (d)	
	P value	*R*	*P* value	*R*
RQ (fPP)	0.118	–0.344	0.019	–0.496
npRQ (fPP)	0.077	–0.385	0.017	–0.502
RQ (nsPP)	1.623×10^{-5}	–0.783	3.468×10^{-4}	–0.693
npRQ (nsPP)	2.138×10^{-5}	–0.777	1.806×10^{-4}	–0.716

fPP, fasting polytrauma patients; ICU, intensive care unit; npRQ, non-protein respiratory quotient; nsPP, polytrauma patients with nutritional support; RQ, respiratory quotient.
Nonparametric Spearman correlation.

independent risk factor for morbidity and mortality, and prolongs hospital LOS [2,5–7]. However, nutritional support may at least in part prevent this sequence [25]. Although there have been many studies focusing on the relation between energy malnutrition and prognosis in polytrauma patients, little is known about the prognostic value of energy metabolism in these patients. In the present study, we evaluated the energy metabolism in polytrauma patients without and with nutritional support after physician administration and examined prospectively its association with the indirect prognostic markers (ICU LOS and VT). To the best of our knowledge, this is the first study focusing on the prognostic value of RQ or npRQ in polytrauma patients.

In general, EE and npRQ (which represents the ratio of glucose and fat utilization by excluding the participation of protein) are the main factors used to evaluate energy metabolism based on indirect calorimetry.

With respect to EE, it is commonly believed that the daily energy expenditure of critically ill patients (not just in polytrauma) exceeds the normal basal metabolic rate by about 50%. However, it has been proven that the REE or EE of many critically ill patients is normal both before and during nutritional support [26]. In the present study, nsPPs had a significantly higher measured EE than the predicted REE (median 13.7% higher) and these patients also had a significantly increased measured EE compared with the REE of control group (about 12.8%) and the REE of fPPs (about 109.7%). In patients without nutritional support, there was no statistically significant difference either between predicted and measured REE, or in measured REE compared with controls. This indicates that nutritional support was one of the factors affecting EE in the polytrauma patients. This conclusion also was supported by the comparison of observed groups according to their metabolic states. Surprisingly, the group of fasting controls and the group of patients without nutritional support were more or less the same (the same percentage of hypometabolic patients and a very similar percentage of patients in hypermetabolism). Meanwhile, the nsPP group had more hypermetabolic patients (59.1 versus 36.4%) and fewer in a hypometabolic state (4.5 versus 13.6%) than controls. These results again support the generally known fact that nutritional support has a thermogenic effect [27], which also has been described in critically ill patients [28–30].

In the present study, RQ and npRQ were significantly lower in the fPP group than in fasting controls. It is generally agreed that enhanced lipid oxidation and reduced glucose oxidation is responsible for the decrease in RQ in these patients [31,32]. This phenomenon is explained by insulin resistance caused by the acute stress response [31,33–36]. This phenomenon was not observed in the nsPP group (there was no difference between nsPP and controls); however, the RQ and npRQ of these patients were significantly higher than in those without nutritional support. This could be probably caused by a nutritional support readministration (especially with glucose), which may counteract enhanced lipolysis and gluconeogenesis from amino acids.

With respect to the relationship between RQ or npRQ and ICU LOS or VT, patients with higher RQ or npRQ spent significantly less time in the ICU or on mechanical ventilation ($P < 0.0001$, $r = -0.78$ for RQ and VT; $P < 0.0001$, $r = -0.78$ for npRQ and VT; $P < 0.001$, $r = -0.69$ for RQ and ICU LOS; $P < 0.001$, $r = -0.72$ for npRQ and ICU LOS). This corresponds with other studies [13–17] concerned with a variety of pathologies, which have described that npRQ or RQ decreases as the severity of the disease increases. Thus, this observation can be interpreted to mean that RQ or npRQ reflects the severity of the polytrauma. This fact could be supported by a study, which compared RQ between septic and nonseptic patients [37]. In this study, the septic patients had a significantly lower RQ than nonseptic patients ($P < 0.05$). Our RQ data (0.74 ± 0.09) seem to be much lower than those in this study (0.99 ± 0.26). The fact that we selected the most severe injuries for the present study and that the patients received less glucose per day (338.8 ± 105.5 kcal/m^2) than in the mentioned study (795 ± 530 kcal/m^2) [37], might be responsible for the lower RQ. Evidence for a relationship between disease severity and RQ also was seen in injured patients examined shortly after arrival in an accident and emergency department. Although those with minor or moderately severe injuries had an RQ (0.86) very similar to that of healthy controls with a mixed diet, those with severe injuries had a low RQ (0.78) [31,32]. On the other hand, in the present study, there was no correlation between RQ or npRQ and ISS.

It is important to mention, that in patients without nutritional support, neither RQ nor npRQ were significant factors relating to VT; for ICU LOS, the significance was much lower than in the nsPP group. This could be explained by the fact that some patients are able to use more carbohydrates (they have higher RQ and npRQ and recover faster). When the nutritional support is administered to these patients, we can recognize them (according to higher npRQ or RQ). When it is not, the fasting patients without carbohydrate input cannot use carbohydrates as an energy source, even if they would be able to (they have none available), thus the RQ or npRQ remains low.

This study had some limitations. Because it was done at a single center, the results may not be generalizable to other ICUs. However, this ICU admits patients with a wide range of diseases and illness severity, and is one of the best in Czech Republic. The medical care was provided according to established practice and the newest guidelines, and due to the observational nature of the study, the care delivery procedures were not affected. We admit that the ICU LOS is an inaccurate parameter for patient prognosis determination. Nevertheless, patients spending more time in the ICU are usually those with more severe complications and poorer repair capacity and quality of life. We also know that RQ could be affected by more than nutritional support. For example, RQ could be influenced by hyper- or hypoventilation or buffering of an acid–base disturbance. Nevertheless, it has been proven that when these processes persist and the body equilibrates, this effect of RQ displacement is lost. The RQ and EE also could be affected by the metabolism of pharmacologic agents [38]. For the treatment of our patients, the same standard treatment procedures were used according to the type of disability of individual parts of their body. The median day of calorimetric examination was the fourth day of ICU stay. On this day, the majority of the patients were under a similar degree of sedation. Due to the fact that our patients were treated similarly, we can compare them with each other. For REE prediction, we used the Harris-Benedict equation. The opinions on this equation are not consistent; however, it is a part of our calorimeter manufacturer's software. What is more, it has been shown that this equation could be used in critically ill patients [39,40], and it is still widely used all round the world. The final study limitation is the number of patients included. Since the *R* values of correlation analysis were so conclusive, we expect increased proof in a larger sample of patients. From a statistical point of view, the given number of patients was sufficient. The small cohort was due to the limited number of patients with such severe injuries and high ISS score at the University Hospital in Hradec Kralove, Czech Republic during 3 y. For the same reason, studies examining such patients are relatively rare. Regardless, further study is definitely needed.

Conclusion

Due to the strong association between RQ and npRQ with clinical outcomes such as VT or ICU LOS in nsPPs, indirect calorimetry could have a new clinical application.

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