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Indicators of lean body mass catabolism: emphasis on the creatinine excretion rate

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Summary

Background: The major stress response to critical illness leads to a catabolic state and loss of lean body mass.

Aims: To test whether an increased rate of creatinine excretion might provide unique and timely information to monitor cell catabolism; to relate this information to balances of cell constituents (nitrogen, potassium, phosphate and magnesium); to evaluate the effectiveness of nutritional therapy to reverse this catabolic process.

Design: Prospective observational study.

Methods: Children with severe traumatic brain injury admitted to the paediatric critical care units of The Hospital for Sick Children, Toronto, Canada and Hospital das Clínicas, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil were studied. Complete 24 h urine collections were obtained for measurement of creatinine excretion rate and daily balances of nitrogen, potassium, phosphate and magnesium.

Results: Seventeen patients were studied for 3–10 days. On Day 1, all had negative balances for protein and phosphate. Balances for these intracellular constituents became positive when protein intake was $\geqslant 1$ g/kg/day and energy intake was $\geqslant 50\%$ of estimated energy expenditure ($P < 0.0001$). Creatinine excretion rate was positively correlated with the urea appearance rate ($r = 0.60$; $P < 0.0001$), and negatively with protein balance ($r = -0.45$; $P < 0.0001$). Sepsis developed in four patients; before its clinical detection, there were negative balances for all intracellular markers and an abrupt rise in the excretion of creatinine.

Conclusions: Negative balances of intracellular components and an increase in rate of creatinine excretion heralded the onset of catabolism.

Introduction

The stress response to major trauma produces a catabolic state. The depletion of lean body mass may lead to respiratory failure, decreased immune function and increased morbidity and mortality.[1,2] Therefore, adequate nutritional support should be fundamental for the care of critically ill patients. By supplying adequate quantities of protein and energy, nitrogen balance can be improved.[3] On the other hand, the detection of a negative nitrogen balance when nutritional therapy has been adequate may be an early sign of the presence of a catabolic stimulus such as sepsis.[4]

Catabolism causes the release of amino acids from endogenous proteins, which if oxidized, yield

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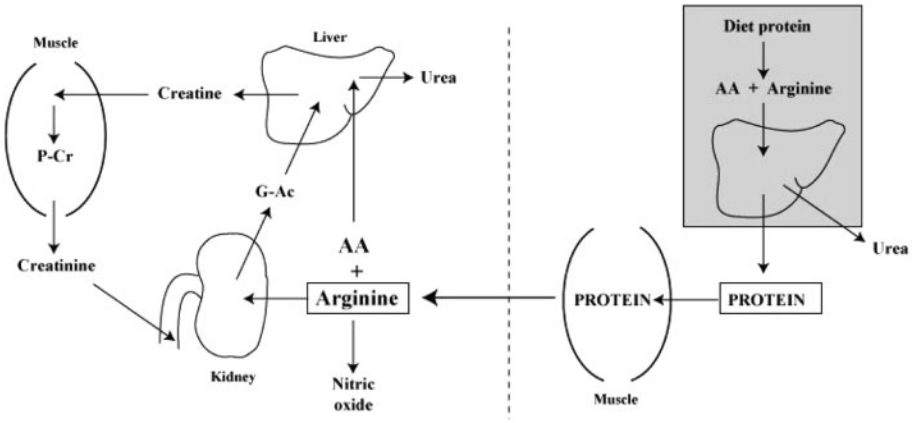

Figure 1. Overview of the biochemistry of arginine. The phosphocreatine (P-Cr)/arginine cycle is shown in the left portion of the figure. It begins with the degradation of P-Cr in skeletal muscle, producing creatinine, which is excreted in the urine. To replenish muscle P-Cr, arginine must be present in the '*systemic*' circulation, and this requires hydrolysis of endogenous proteins. This arginine is converted to guanidinoacetate (G-Ac) in the kidney; G-Ac is converted to creatine in the liver; the uptake of creatine by muscle completes the cycle. The fate of dietary proteins is shown on the right. After digestion, the absorbed amino acids (including arginine) are delivered to the liver via the '*portal*' blood where they are converted initially to newly synthesized proteins. Many of these proteins enter the '*systemic*' blood and virtually all of the remaining arginine is converted to urea by hepatic arginase. Hence, there is very little free arginine from dietary protein that enters the '*systemic*' circulation. In a catabolic state, there will be an increased rate of hydrolysis of endogenous proteins with the release of arginine, which raises the concentration of arginine in the '*systemic*' circulation. Of greater importance, the high arginine concentration may lead to an increased synthesis of nitric oxide. This high arginine concentration may be responsible for an increased excretion of creatinine.

urea as the major nitrogen end-product.[5] In addition, one might also find the release of other intracellular constituents (potassium, phosphate, magnesium) with a predictable stoichiometry.[6] There is also evidence of increased rate of excretion of creatinine in patients with traumatic injury;[7,8] this might reflect a higher rate of release of arginine into the systemic circulation (Figure 1).[9] Moreover, the use of creatinine appearance as a marker of catabolism has potential implications for the dangers of this process because a higher concentration of arginine may lead to an increased rate of synthesis of nitric oxide,[10] an agent that might have important consequences for haemodynamics.[10,11] Thus, our first aim was to determine whether negative balances of intracellular constituents could be markers for cell catabolism in critically ill children. We also wished to test whether there was a rise in the rate of creatinine appearance during a catabolic episode, and to determine whether its time course could lead to an earlier recognition of this catabolic state. In addition, we aimed to evaluate the effectiveness of nutritional therapy by following changes in balances and the rate of excretion of creatinine over time.

Patients and methods

This study was approved by the Institutional Research Ethics Boards of The Hospital for Sick Children (HSC), Toronto, Canada and Hospital das Clínicas, Faculty of Medicine of Ribeirão Preto, University of São Paulo (USP), Brazil and informed consent was obtained from the patients' parents. Children with severe traumatic brain injury (Glasgow Coma Scale $\leqslant 8$) admitted to the paediatric critical care units of HSC and USP were eligible for this prospective observational cohort study. The exclusion criteria were the presence of acute renal failure and extensive skeletal muscle injury.

Patients were treated using the same protocol in both units.[12] All patients were intubated and mechanically ventilated throughout the study period; all received sedatives (midazolam or lorazepam) and analgesics (morphine or fentanyl) with or without neuromuscular blockers (pancuronium, rocuronium or vecuronium). Core body temperature was monitored by oesophageal probes and hyperthermia (>37.5°C) was treated aggressively with antipyretics and cooling with thermal blankets. Sepsis, septic shock and systemic inflammatory response syndrome were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria.[13] Nosocomial pneumonia was defined according to the Centres for Disease Control criteria.[14] Urinary catheters were inserted in all patients as part of their routine care. Attending physicians made all decisions concerning nutritional support, independent of the study.

Complete 24 h urine collections were obtained from all patients. Daily balances of potassium, phosphate and magnesium in millimole per kilogram per day were calculated by subtracting the amounts excreted in urine and drainage fluids (gastric, thoracic and external ventricular drainage) from all inputs by intravenous and enteral routes. The electrolyte concentrations in drainage fluids were estimated based on data from the literature;[15] we emphasize that these volumes were <5% of the urine values in every case. To calculate nitrogen balance, the urea that should be produced from the complete oxidation of the administered protein was compared to the quantity of urea excreted plus any additional urea that was retained in body water (called the rate of appearance of urea).[16] If the rate of appearance of urea exceeded its potential synthesis from exogenous protein, nitrogen balance was assumed to be negative; the converse is also true (see equations below).

$$\begin{aligned}
\text{Nitrogen balance} &= \text{Urea from protein intake} \\
&\quad - \text{Urea appearance} \\
\text{Urea appearance} &= \text{Urea}_{\text{urine}} + \Delta\text{pool size of urea} \\
\text{Urea}_{\text{urine}} &= [\text{Urea}_{\text{urine}}] \times \text{Volume}_{\text{urine}} \\
\Delta\text{ pool size of urea} &= (([\text{Urea}_{\text{plasma}}]_{\text{final}} \\
&\quad - [\text{Urea}_{\text{plasma}}]_{\text{initial}}) \\
&\quad \times \text{Total body water}) \\
&\quad + (\text{H}_2\text{O balance} \\
&\quad \times [\text{Urea}_{\text{plasma}}]_{\text{final}})
\end{aligned}$$

(Total body water was assumed to be two-thirds of body weight)

Since 6.25 g of protein contains 1 g of nitrogen and 1 mmol of urea is equivalent to 60 mg of urea and 28 mg of nitrogen, protein balance was calculated as grams per kilogram per day as follows:

$$\begin{aligned}
\text{Protein balance} = [&(\text{Urea balance (g/day)} \\
&\times (28/60) \times 6.25)/\text{weight(kg)}]
\end{aligned}$$

Total energy and protein daily intakes were calculated based on information obtained from patients' charts. Protein from blood products (albumin) was not included in our calculations. Total energy intake was expressed as a percentage of the estimated energy expenditure (%EEE) based on the Holliday–Segar formula.[17] Creatinine excretion was expressed as milligrams per kilogram per day. Average values for creatinine excretion in children were calculated by the following formula: $15.4 + 0.46 \times \text{age (years)} \pm 3.4$ (standard error of the mean), in milligrams per kilogram per day.[18]

The concentration of creatinine in blood and urine was measured by a colorimetric assay. Urea was determined by enzymatic assay. Potassium was measured by flame photometry; phosphate and magnesium were measured by spectrophotometry.

Statistical analysis

Data are expressed as median (range). Comparisons between groups were made using Fisher's exact test for categorical data and Mann–Whitney U-test for continuous variables. Correlation between variables was analysed by Spearman test. Analyses were made using GraphPad Prism 4.0 (San Diego, CA). A *P*-value of <0.05 was considered significant.

Results

The demographic data are provided in Table 1. Seventeen patients (13 males) with severe traumatic brain injury were enrolled in this study; nine (53%) had multiple trauma. Their median age was 6 years (range 2–14 years) and their median weight was 20 kg (range 13–60 kg). Patients were studied within the first days following admission to the paediatric critical care unit for a median time of 5 days (range 3–10 days, total days of balance measurements was 88 days). In addition to sedatives and analgesics, 13 patients (76%) received neuromuscular blockers for 2–8 days (median 4 days). None of the patients was treated with barbiturate coma or hypothermia. During the study period, 14 patients received enteral nutrition only, two received enteral and parenteral nutrition and one patient received parenteral nutrition only. Time to initiation of nutritional support ranged from 1 to 5 days (median 2 days).

On Day 1, all patients had negative balances for protein (median –0.9 g/kg; range –1.6 to –0.2 g/kg) and phosphate (median –0.6 mmol/kg; range –1.9 to –0.07 mmol/kg). Potassium (median –1.8 mmol/kg; range –6.1 to 0.5 mmol/kg) and magnesium (median –0.08 mmol/kg; range –0.1 to 0.5 mmol/kg) balances were negative in all but one patient; these latter patients had received intravenous fluids with a high concentration of potassium and magnesium, respectively.

Over the study period, protein balances became positive (for 1–3 days; median 2 days) in 10 patients while seven patients had persistently negative daily balances for protein. Anabolism was associated with a higher protein intake (median 1.1 g/kg/day; range 0.7–2.2 g/kg/day) compared to catabolism (median 0.1 g/kg/day; range 0–1.8 g/kg/day) ($P < 0.0001$). Energy intake was also higher during days of anabolism compared to days of catabolism (median 60% EEE; range 35–83% EEE vs. 13.5%

Table 1 Demographic data

Patient	Age (year)	Gender	Weight (kg)	Study time (days)	Type of nutrition	Days with anabolism	Type of trauma
1	10	M	25	5	Enteral	None	TBI
2	5	M	20	4	Enteral + Parenteral	Day 4	TBI, pulmonary and cardiac contusion
3	4	M	20	4	Enteral	Days 2, 3	TBI
4	14	M	60	10	Enteral + Parenteral	Days 4, 5, 10	TBI
5	8	M	35	6	Enteral	Days 5, 6	TBI, knee fracture
6	5	F	18	4	Parenteral	Days 2, 4	TBI
7	6	M	25	6	Enteral	None	TBI, clavicle fracture
8	4	F	18	5	Enteral	Days 2, 3, 5	TBI
9	2	M	15	3	Enteral	None	TBI, pulmonary contusion, tibia fracture
10	7	M	18	3	Enteral	None	TBI, pulmonary contusion, hip and elbow fractures
11	3	F	15	5	Enteral	Day 5	TBI, scalp laceration, pulmonary contusion, clavicle fracture
12	11	M	60	6	Enteral	None	TBI
13	2	M	13	5	Enteral	Days 4, 5	TBI
14	5	F	20	5	Enteral	Day 5	TBI, scalp laceration, hemothorax
15	10	M	27	4	Enteral	Day 3	TBI
16	13	M	35	6	Enteral	None	TBI, tibia and fibula fractures
17	12	M	50	7	Enteral	None	TBI, lower limb blunt trauma

M, male; F, female; TBI, traumatic brain injury.

EEE; 0–128% EEE) ($P<0.0001$). On days with anabolism, balances were greater compared with those on days with catabolism for potassium (median 0.5 mmol/kg; range –1.3 to 1.3 mmol/kg vs. –0.7 mmol/kg; –6.1 to 1.4 mmol/kg), phosphate (median 0.4 mmol/kg; range –0.4 to 1.3 mmol/kg vs. –0.3 mmol/kg; –1.9 to 0.6 mmol/kg) and magnesium (median 0.2 mmol/kg; range –0.1 to 0.4 mmol/kg vs. –0.06 mmol/kg; –0.4 to 0.5 mmol/kg) ($P<0.0001$).

There was a significant positive correlation between protein intake and balances for protein ($r=0.63$; $P<0.0001$), potassium ($r=0.44$; $P<0.0001$), phosphate ($r=0.66$; $P<0.0001$) and magnesium ($r=0.61$; $P<0.0001$) (Figure 2). There was also a significant positive correlation between energy intake and balances for protein ($r=0.57$; $P<0.0001$), potassium ($r=0.46$; $P<0.0001$), phosphate ($r=0.71$; $P<0.0001$) and magnesium ($r=0.62$; $P<0.0001$) (Figure 3). Of importance, positive balances for phosphate and magnesium occurred with protein intake between 0.5 and 1 g/kg/day and energy intake between 25% and 50% of EEE, when most daily balances for protein were still negative.

The rate of excretion of creatinine correlated positively with the urea appearance rate ($r=0.60$; $P<0.0001$) and negatively with protein balance ($r=–0.45$; $P<0.0001$) (Figure 4). In all patients, the concentrations of creatinine in serum were within the normal range for age.[19] Interestingly, there was a surprisingly high rate of creatinine excretion (>30 mg/kg/day) in those patients who had the largest negative balances for protein. Figure 5A illustrates protein balance (g/kg) and creatinine excretion (mg/kg) every 12 h in a patient who received low amounts of protein (<0.2 g/kg/day) and calories (<15% EEE) throughout the study period. It is of great interest that on the day that protein balance became less negative, the rate of creatinine excretion declined towards the expected range (at 60 h) and both of these trends reversed over the subsequent 36 h.

Over the study period, four patients had nosocomial pneumonia and developed sepsis; at that time, each had negative balances for protein and other intracellular markers along with a parallel increase in the excretion of creatinine despite receiving increasing amounts of protein and calories (Table 2 and Figure 5B).

The median length of stay in the paediatric critical care unit was 8.5 days (range 5 to 22 days) for patients who had anabolism and 7 days (range 5 to

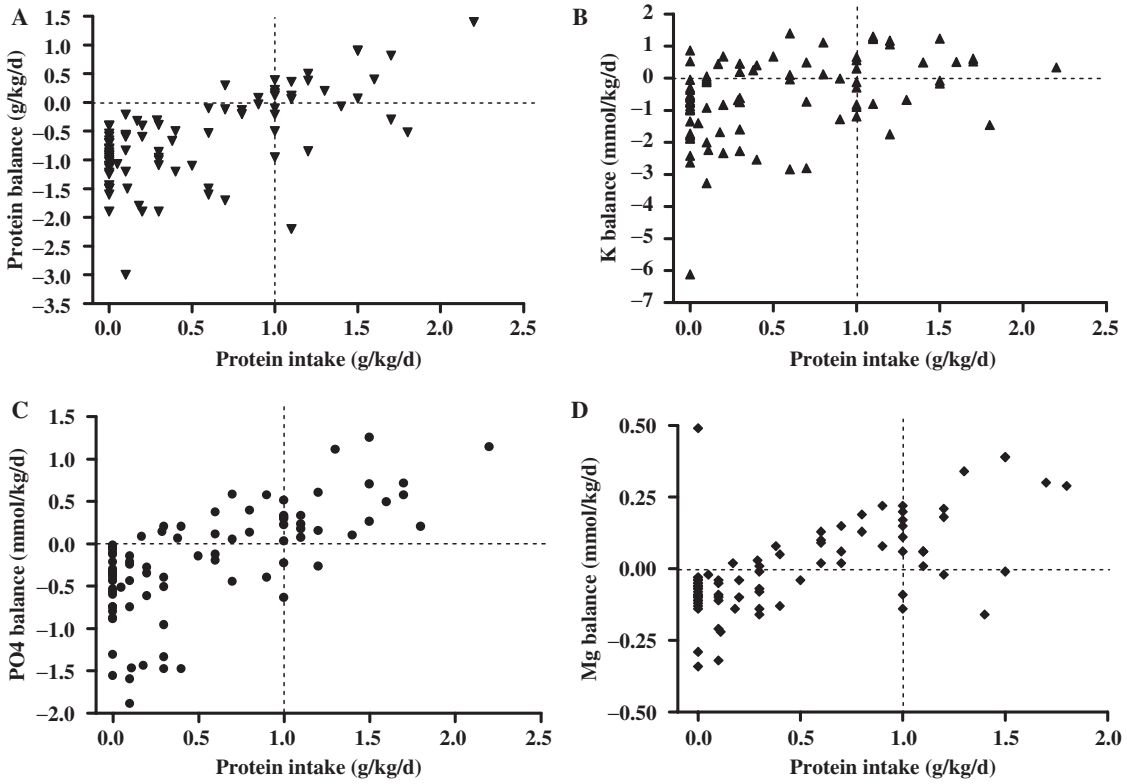

Figure 2. Effect of protein intake on daily balances. The balance data for protein in g/kg/day (**A**), potassium (K) in mmol/kg/day (**B**), phosphate (PO_4) in mmol/kg/day (**C**) and magnesium (Mg) in mmol/kg/day (**D**) are shown for different levels of protein intake. All the points with negative balances of protein, K, PO_4 and Mg when protein intake was >1 g/kg/day represent data from patients who developed sepsis.

22 days) for those who had only catabolism ($P = 0.81$). All patients who had anabolism survived, while one of seven patients who had only catabolism died of sepsis ($P = 0.41$).

Discussion

A relatively homogeneous population of patients with severe traumatic brain injury was studied to evaluate markers of protein catabolism and the efficacy of nutritional support on the metabolic response to injury. All patients had negative balances for nitrogen and phosphate, and all but one had negative balances for potassium and magnesium in the initial 24 h after trauma. The latter three negative balances strongly suggest that this catabolism represents loss of lean body mass. While it has been recommended that children undergoing major traumatic injury receive the resting energy expenditure multiplied by a stress factor and two times the Recommended Dietary Allowances (RDA) of protein,[4,12] in our study, the administration of $\geqslant$1g/kg/day of protein and $\geqslant$50% of calories based on the EEE calculated by the Holliday–Segar formula[17] was associated with anabolism. Nevertheless, we emphasize that all patients were intubated, mechanically ventilated and sedated, and most received neuromuscular blockers over the study period, which might have decreased their nutritional requirements.[20]

One novel aspect of our balance study was that positive balances for phosphate and magnesium preceded the positive balance for protein (Figure 3). This time course likely reflects the need to synthesize RNA before protein synthesis. On the other hand, balance for potassium was the least reliable index to monitor catabolism in the early phase after injury, which may be due to the fact that an adrenergic surge might lead to a shift of potassium into muscle cells.[21] Another advantage of balance data is that a new catabolic stress could be diagnosed in 4 out of 17 patients even earlier than catabolism became evident at the bedside. The basis for this catabolic response was sepsis, as confirmed by additional investigations. Notwithstanding, there are important limitations to the use of balance data. First, although urinary urea nitrogen is assumed to constitute 80 to 90% of the total urinary nitrogen, nitrogen excretion may be underestimated in situations with increased excretion of non-urea forms of nitrogen, such as ammonium, resulting in a

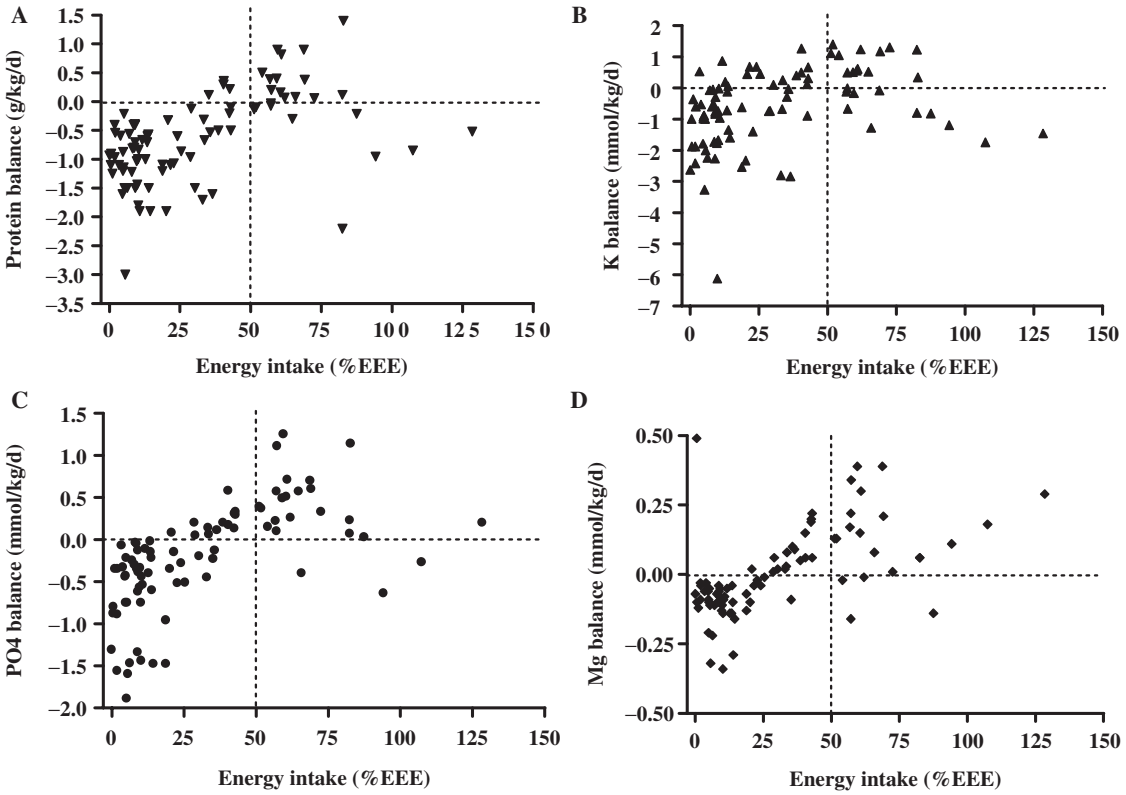

Figure 3. Effect of energy intake on daily balances. The balance data for protein in g/kg/day (**A**), potassium (K) in mmol/kg/day (**B**), phosphate (PO_4) in mmol/kg/day (**C**) and magnesium (Mg) in mmol/kg/day (**D**) are shown for different levels of energy intake expressed as percentage of the estimated energy expenditure (%EEE). All the points with negative balances of protein, K, PO_4 and Mg when energy intake was >50% of the estimated energy expenditure represent data from patients who developed sepsis.

false-positive nitrogen balance.[22] Second, there are technical difficulties associated with the complete collection of urine. Third, balance data represent events in the 'preceding' 24 h so there is a delay before the diagnosis of catabolism could be made with these data. Fourth, and most important, balance data do not provide information about the absolute rate of catabolism because they only indicate the difference between rates of anabolism and catabolism. In fact, it may be more important to know the rate of catabolism because when endogenous proteins are hydrolysed, their constituent amino acids are released into the 'systemic' circulation. Moreover, if one of these amino acids (e.g. arginine) were converted into a product with potentially untoward effects (e.g. nitric oxide, Figure 1), it would be important to recognize this process as early as possible.

The results of the present study support the impression that the rate of creatinine appearance may be an indicator of endogenous protein catabolism.[7,8,23] Nevertheless, the importance of this relationship has received little emphasis to date, perhaps because the linkage between creatinine excretion and a catabolic state was not appreciated. In fact, it was suggested that this relationship could be due to a methodological issue as a result of the excretion of non-creatinine chromogens that react with picric acid to produce falsely high values for creatinine.[24] On the other hand, our data provide an opportunity for a novel advance, as there was both a very 'early' and a 'marked' increase in creatinine excretion rate 'coincident' with the onset of protein catabolism (Figure 5). Furthermore, there is evidence that this relationship could have physiological importance, because in patients who have undergone major traumatic injury, there was a direct relationship between the rate of excretion of creatinine and the rate of appearance of 3-methylhistidine,[8] which reflects the absolute rate of endogenous protein hydrolysis.[8,23]

The source of urinary creatinine is the non-enzymatic conversion of phosphocreatine to creatinine.[24] Each day, close to 2% of phosphocreatine in skeletal muscle is converted to ~20 mg or 200 μmol of urinary creatinine per kilogram body weight.[24]

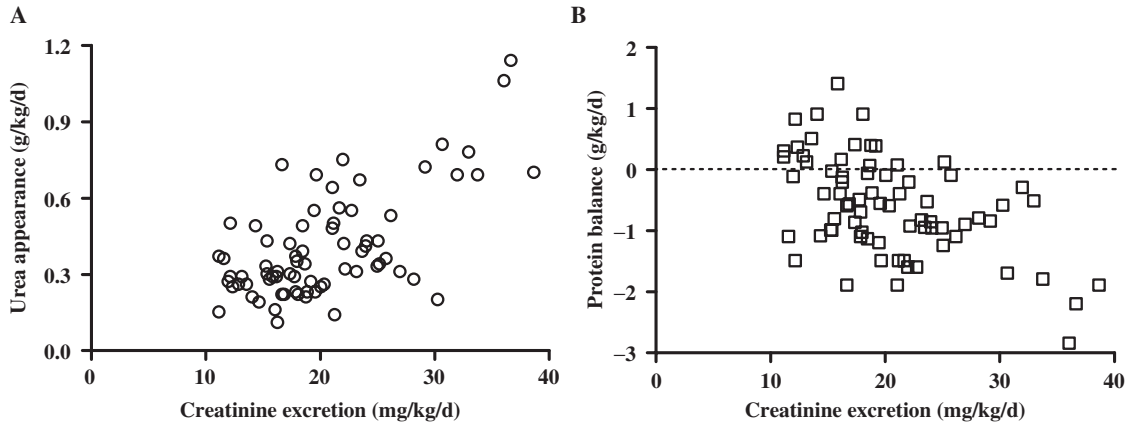

Figure 4. Relationship between urea appearance and the rate of excretion of creatinine. (**A**) The rate of excretion of creatinine in mg/kg/day is plotted on the *x*-axis and the rate of urea appearance in g/kg/day is shown on the *y*-axis. (**B**) The rate of excretion of creatinine in mg/kg/day is plotted on the *x*-axis and protein balance in g/kg/day is shown on the *y*-axis. All the points with creatinine excretion rates that exceed 30 mg/kg/day represent data in patients who had low protein and energy intake or sepsis.

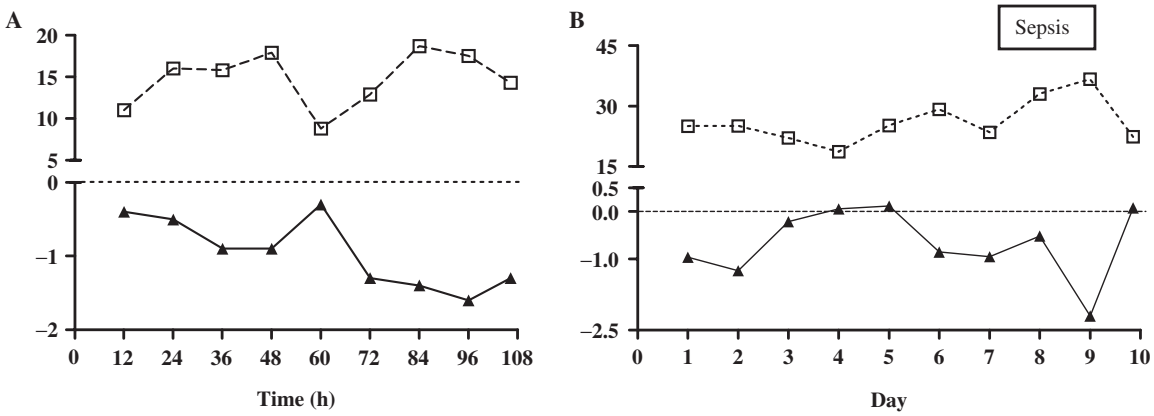

Figure 5. Relationship between protein balance and the rate of excretion of creatinine in a patient with a low intake of protein and energy, and a patient with sepsis. (**A**) Data are from patient #1 who received low amounts of protein (<0.2 g/kg/day) and calories (<15% of estimated energy expenditure) throughout the period of observation. Protein balance in g/kg are shown as solid triangles connected by a solid line and creatinine excretion in mg/kg is depicted as open squares connected by a dashed line. The mean creatinine excretion expected for his age is 20 mg/kg/day (or 10 mg/kg every 12 h). Of note, his balances of potassium, phosphate and magnesium were persistently negative during the entire period. (**B**) Data are from patient #4 in whom sepsis was diagnosed on Day 6 post-traumatic brain injury. Balances of protein in g/kg/day are shown as solid triangles connected by a solid line and creatinine excretion in urine in mg/kg/day is depicted as open squares connected by a dashed line. The mean creatinine expected for his age is 22 mg/kg/day. Of note, the peak of creatinine excretion was coincident with the most negative protein balance.

To achieve balance, this same quantity of phosphocreatine must be synthesized; this requires the catabolism of 1 arginine per creatine synthesized (Figure 1).[25] We speculate that endogenous protein catabolism may cause a higher rate of excretion of creatinine due to a rise in arginine concentration in the 'systemic' circulation. Moreover, an increased concentration of arginine into the 'systemic' circulation may result in a higher production of nitric oxide, which has a major vasodilatory effect.[10,11] Indeed, there is evidence that the development of acute protein-energy malnutrition in the paediatric critical care unit contributes to haemodynamic instability.[26]

There should be a marked difference in the concentration of arginine in the 'systemic' circulation, depending on whether its source is dietary or endogenous protein (Figure 1). For when arginine is delivered to the liver, its major fates are protein synthesis and conversion to urea while little free arginine reaches the systemic circulation.[10] In contrast, catabolism of endogenous proteins causes a high concentration of arginine in the 'systemic' circulation,[27] where its major fate is catabolism by

Table 2 Data on patient#4 who developed sepsis on Day 6 post-traumatic brain injury

Day	K balance	PO_4 balance	Mg balance	Protein intake	Energy intake
1	−2.4	−0.89	−0.09	0	1.9
2	−0.4	−0.35	−0.12	0	1.1
3	−0.8	0.03	−0.14	1	88
4	1.3	0.33	0.01	1.1	73
5	1.2	0.23	0.06	1.1	83
6	−1.8	−0.27	0.18	1.2	107
7	−1.2	−0.64	0.11	1	94
8	−1.5	0.20	0.29	1.8	128
9	−0.8	0.07	0.06	1.1	83
10	−1.3	−0.40	0.08	0.9	66

Balances of potassium (K), phosphate (PO_4) and magnesium (Mg) (all in mmol/kg/d), and intakes of protein (g/kg/d) and energy (% estimated energy expenditure) over the study period.

renal arginase to produce creatine to replace the daily loss of phosphocreatine. Nevertheless, owing to avid renal re-absorption of creatine, there is very little creatine excreted unless its plasma level rises markedly; this may occur if there is extensive injury to skeletal muscle.[7] Accordingly, there are three possible causes of high concentrations of arginine levels: a very rapid rate of catabolism of proteins of endogenous origin, a slower rate of protein synthesis in skeletal muscle and/or reduced renal or hepatic arginase activity. Hence, sepsis, failure to provide adequate nutritional support, and reduced renal or hepatic function may lead to hyperargininaemia and possibly a poorer outcome in patients in a critical care setting.

There are several potential strategies that may help to decrease the concentration of arginine in the 'systemic' circulation. In our study, the supply of both protein (at least 1 g/kg/day) and a source of calories (at least 50% of the EEE) were usually sufficient to induce a positive balance of protein and return high rates of excretion of creatinine to control values. Of great importance, provision of this nutritional support was not sufficient to cause anabolism or prevent a rise in the rate of appearance of creatinine in patients who became septic. Nevertheless, these indicators of catabolism were no longer present once therapy for sepsis was effective.

Limitations and contingencies

We emphasize that we designed a prospective observational study to compare methods to detect the earliest appearance of a catabolic response in patients who present to hospital after major trauma. An important goal was to examine whether the rate of appearance of creatinine over short time periods could reflect the rate of endogenous protein catabolism. To avoid potentially confounding issues, patients with major soft tissue (skeletal muscle) injury or renal failure were excluded; hence whether the results reported are valid in these later populations will need to be evaluated in future studies. Moreover, creatinine should be measured using a specific enzymatic assay to examine a possible role for non-creatinine chromogens. In addition, the concentration of arginine in systemic blood and exhaled nitric oxide in catabolic patients will also need to be evaluated.

Concluding remarks

Although balance data continue to be the gold standard to detect catabolic responses in patients in a critical care setting, an important emphasis should be directed towards the concentration of arginine in the 'systemic' circulation; this can be achieved by measuring the rate of creatinine appearance. Our data suggest that when balances are examined, a positive balance for phosphate provides the earliest information to detect a switch from catabolism to anabolism. If the catabolic response occurs later in the course of the illness (after Day 3), especially if nutritional support is adequate, an increased rate of creatinine excretion and/or a marked decrease in the anabolic trend as reflected by balances of intracellular constituents, should strongly suggest that there is a new catabolic stress; this was a very early sign of sepsis in our patients. In addition, the rate of excretion of creatinine can be a very convenient marker of lean body catabolism because changes in its rate of excretion were large, creatinine is easy to measure, and its measurement only requires timed urine samples which can be collected for a period <24 h. Because the dietary supply of amino acids may drive the metabolism of arginine to protein

synthesis in the liver, enteral nutritional support may decrease the availability of arginine for the synthesis of nitric oxide, which could result in an improved haemodynamic state of critically ill patients, and thereby, help to provide a better outcome. We emphasize that the response to nutritional support should be evaluated in individual patients, because it is unlikely that a 'one-size-fits-all' will be optimal. Notwithstanding, there should be guidelines. In our population, supplying 1 g/kg/day of protein and 50% of their EEE was an adequate starting point.

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