CLINICAL INVESTIGATION

Protein and Nitrogen Metabolism Changes Following Closed Head Injury or Cardiothoracic Surgery in Pediatric Patients

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OBJECTIVE We compared markers of protein metabolism between children who had a controlled injury and an acute traumatic event. Significant protein catabolism occurs after acute severe injury. During surgery the injury is controlled and the degree of subsequent catabolism may be blunted.
METHODS This was a prospective, unblinded observational study in 10 children 2 to 12 years old with a closed head injury (CHI) and an admission Physiologic Stability Index of ≥ 10 and in 10 children who underwent elective cardiothoracic surgery (CTS). Nutrient intake, nitrogen balance, serum albumin and prealbumin, urinary 3-methylhistidine excretion, and 3-methylhistidine to creatinine ratios were evaluated on days 1, 2, 3, 4, and 10 after injury.
RESULTS Nutrient intake was similar in both groups on study days 1–4 and did not meet estimated needs. By day 10, 7 patients in the CTS group and 2 patients in the CHI group had been discharged home. The 3 CTS patients were still in the ICU while the 8 hospitalized CHI patients had been transferred to the floor. Compared to the CTS group, nitrogen balance in the CHI group was lower on day 1. On day 10, nitrogen balance and prealbumin were greater in the CHI group than in the CTS group, consistent with recovery and increased nutrient intake.
CONCLUSIONS Markers of protein metabolism follow similar patterns after CTS or CHI in children. However, markers of protein metabolism indicate more severe catabolism soon after injury in CHI.

KEYWORDS: acute injury, cardiovascular surgery, head injury, pediatrics, protein metabolism

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INTRODUCTION

Classically, the response to acute injury was described using the terms "ebb and flow."[1] During the ebb phase, metabolic responses are geared toward maintaining perfusion of vital organs. After this initial response, the flow phase ensues with increasing metabolic rate and generalized catabolism, characteristic of the flow phase. Many of these responses are due to the release of various cytokines and secre-

ABBREVIATIONS: CHI, closed head injury; CTS, cardiothoracic surgery; GCS, Glasgow Coma Scale; ICU, intensive care unit; PRISM, Pediatric Risk of Mortality; PSI, Physiologic Stability Index; TUN, total urine nitrogen; UUN, urine urea nitrogen

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Table 1. Demographic Data in Closed Head Injury and Cardiothoracic Surgery (Patients Admitted to the Pediatric Intensive Care Unit)

	Closed Head Injury (n = 10)	Cardiothoracic Surgery (n = 10)	P Value
Age,* yrs	7.2 ± 3.0	4.5 ± 3.2	NS
(range)	(4–12)	(2–12)	NS
Weight,* kg	26.4 ± 9.5	18.3 ± 16.4	NS
Gender, male	8	4	NS
PSI	17 ± 5	6.1 ± 4.6	< .05
Prealbumin (mg/dL)*	16.1 ± 3.4	15.2 ± 2.9	NS
Albumin (g/dL)*	3.5 ± 0.6	3.0 ± 0.3	.055

**mean ± SD*
PSI, Physiologic Stability Index

tion of hormones that are age- and/or disease related.[2-5] The metabolic consequence of these stress responses on visceral proteins, nitrogen balance, and other indicators of catabolism after acute injury in children remains unclear.

We evaluated protein metabolism after a cardiothoracic surgical procedure and after an acute closed head injury in children. Our hypothesis was that the effects on protein metabolism would be less severe in those undergoing a controlled procedure than in those who experienced an acute severe trauma. The objectives were to evaluate Physiologic Stability Index (PSI) scores, albumin and prealbumin plasma concentrations, nitrogen balance, and urinary 3-methylhistidine excretion beginning within 24 hours of injury and on days 1, 2, 3, 4 and 10 to characterize differences between the two groups.

MATERIALS AND METHODS

Children from 2 to 12 years of age who either underwent elective cardiothoracic surgery that required cardiopulmonary bypass with an estimated cross-clamp time of > 30 minutes (n = 10) or who presented with a closed head injury with a PSI score of ≥ 10 (n = 10) were eligible for inclusion. Patients in the cardiothoracic surgery group were enrolled prior to the surgical procedure. This study was approved by the University's Institutional Review Board, and informed consent was obtained from the parent or guardian prior to patient enrollment.

Demographic data collected included age, weight, gender, diagnosis, and routine laboratory assessments. In the cardiothoracic surgery group baseline samples were collected pre-operatively, and measurement of plasma albumin and prealbumin (transthyretin) concentrations, and a 24-hour urine collection for nitrogen balance, creatinine, and 3-methylhistidine was performed. PSI score, a measure of severity of acute illness that evaluates 34 variables in 7 physiologic systems (e.g., cardiovascular, respiratory, neurological assessment including Glasgow Coma Scale (GCS) score, hematological, renal gastrointestinal, and metabolic) was determined on all study days.[6]

In the closed head injury group, baseline albumin and prealbumin concentrations were obtained on admission to the intensive care unit (ICU). For both groups, the study day 1 PSI score was obtained from parameters determined beginning at the time of ICU admission until 0800 the next day, and the most aberrant assessments were used for scoring. PSI scores during the subsequent study periods consisted of the most aberrant assessments during the 24-hour period from 0800 to 0800. All kilocalorie (kcal), protein, and fluid intakes and outputs were quantified for each study period. Carbohydrate kcal from all parenteral and enteral sources including fluid infusions and diluent used for medications were included. Protein intake included both enteral and parenteral nutrition.

At 0800 on study days 1, 2, 3, 4, and 10, blood was obtained for albumin and prealbumin concentration determination. The institution's general chemistry laboratory measured serum albumin concentrations using the bromocresol green colorimetric method. Prealbumin was assessed by the investigators in duplicate using radial immunodiffusion (M-Partigen Prealbumin Kit, Behring Diagnostics, Inc.) according to manufacturer's recommendations.

Table 2. Patient clinical characteristics

Closed Head Injury		Cardiothoracic Surgery	
Pt#	Diagnosis	Pt#	Diagnosis
1	Hit in head by brick, depressed skull fracture	4	VSD repair
2	MVA, humoral and clavicular fractures	5	TOF, central shunt reconstruction
3	MVA, frontal lobectomy	6	VSD, ASD closure
7	PVA, subdural hemorrhages, femur fracture, pulmonary contusion	9	ASD repair
8	MVA, small puncture hemorrhage	10	PDA ligation, subaortic membrane resection
12	MVA, pelvic and femoral fractures	11	Fontan (Blalock Taussig shunt)
16	MVA, skull fracture, splenic trauma, pulmonary contusion	13	TOF, VSD patch, foramen ovale closure
17	MVA, c-spine subluxation, respiratory arrest	14	TOF, RVOT reconstruction
18	PVA, intraventricular hemorrhage, multiple fractures, pulmonary contusion	15	TGA, atrial baffle revision
19	MVA, skull fracture, temporoparietal epidural hematoma	20	VSD patch, RVOT reconstruction

ASD, atrial septal defect; MVA, motor vehicle accident; PDA, patent ductus arteriosus; PVA, pedestrian vehicle accident; RVOT, right ventricular outflow tract; TGA, transposition of the greater arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect

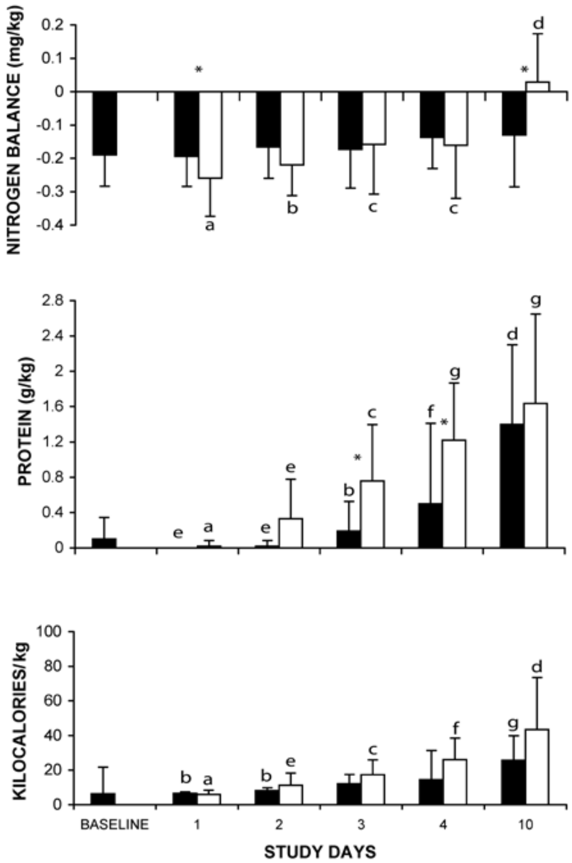

Figure 1. Nitrogen balance (top), protein (from enteral and parenteral sources) (middle), and kilocalorie (bottom) intakes following cardiothoracic surgery (■, n = 10) and closed head injury (□, n = 10) by study day in children from 2–12 years of age. * = between group difference, P < .05; within group differences (P < .05): a = different from days 3, 4, 10; b = different from day 10; c = different from days 1, 10; d = different from days 1, 2, 3, 4; e = different from days 4, 10; f = different from days 1, 2, 10; g = different from days 1, 2.

In both groups, a urine collection began upon admission to the ICU and continued until 0800 the following day. This was considered the study day 1 observation. Each subsequent study day's urine collection was pooled for a 24-hour period of time ending at 0800 the following morning. Urine was acidified with 6N hydrochloric acid and kept on ice in a closed container at 4°C during the collection period. Volumes for each collection period were quantified and an aliquot frozen in an airtight container at –70°C until analysis. Urine urea nitrogen (UUN) was measured using a modification of the Berthelot method (Sigma Diagnostics, St. Louis, MO). Total urinary nitrogen (TUN) was measured using Pyro-chemiluminescence with the Antek Nitrogen Analyzer (Houston, TX). Urine 3-methylhistidine was quantified using the Beckman 6300 amino acid analyzer. Preformed ammonia and creatinine concentrations were measured using quantitative colorimetric assays supplied by Sigma Diagnostics (St. Louis, MO) according to manufacturer's instructions.

Nitrogen balance was calculated using the formula: nitrogen balance (g/kg) = {[protein intake (grams / 6.25)] - total urinary nitrogen out (grams)}/weight (kg). Neither chest tube drainage nor protein from colloid infusions were included in the nitrogen balance calculation. No adjustment was made for insensible losses. Urinary 3-methylhistidine excretion (μmol/kg/day) was measured, and 3-methyl-

Table 3. Glasgow Coma Scale Scores in Children with Closed Head Injury by Study Day

	Admission (n = 10)	Day 1* (n = 10)	Day 2 (n = 10)	Day 3 (n = 10)	Day 4 (n = 10)	Day 10 (n = 8)
GCS† (range)	4.9 ± 1.3 (3–6)	6.9 ± 3.0 (4–14)	7.7 ± 3.7 (4–14)	8.4 ± 4.1 (5–15)	8.8 ± 4.5 (5–15)	9.3 ± 3.2 (6–15)

**Admission–Day 1*
† mean ± standard deviation
GCS, Glasgow Coma Score

histidine/creatinine ratio (µmol/mg) was calculated for each study observation.

Between group comparisons of demographic data were made using an unpaired t-test or Chi-square, as appropriate. Analysis of covariance with the post hoc Fisher's least significant difference test was used to determine within and between group differences during the observation periods. Correlation analysis (PSI with nitrogen balance, 3-methylhistidine excretion, and prealbumin) was done using Pearson correlation coefficient. A P value of ≤ .05 was considered significant for all tests. Data are presented as mean ± SD or median and range.

RESULTS

The demographic data comparing the two groups are shown in Table 1, and the admission characteristics of each patient are listed in Table 2. All patients in both groups completed the first four study periods in the ICU.

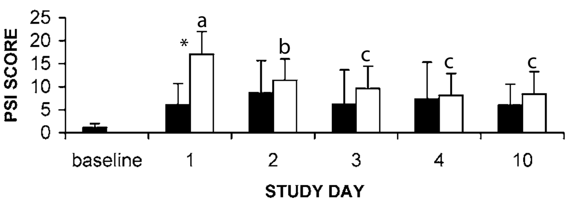

Figure 2. PSI scores following cardiothoracic surgery (■) and closed head injury (□) by study day in children from 2–12 years of age. * = between group difference, P < .05; within group differences (P < .05): a = different from days 2, 3, 4, 10; b = different from days 1, 10; c = different from day 1. PSI, Physiologic Stability Index.

The Glasgow Coma Scale scores in patients with closed head injury according to study day are shown in Table 3. Eight had an intracrainial pressure monitor placed upon admission. By day 10, 2 patients had been discharged home, and the remaining 8 who were no longer critically ill had been transferred to the neurosurgery floor.

In the cardiothoracic surgery group, 7 patients had been discharged home by day 10. The remaining 3 patients had a complicated post-operative course and remained in the ICU; one of these had congestive heart failure preoperatively. Another experienced a full arrest upon arrival to the ICU, required extensive resuscitative efforts, and underwent a second procedure to explore the mediastinum on the following day. The third child had Down Syndrome and was still receiving inotropic support on day 10.

The percent of total urine nitrogen (TUN) as urine urea nitrogen (UUN) ranged from 66 ± 9% to 75 ± 12% in the head injury group and from 37 ± 34% to 64 ± 26% in the cardiothoracic surgery group. TUN excretion ranged from 352 ± 96 mg/kg on day 4 to 251 ± 103 mg/kg on day 10 in the head injury group and from 177 ± 109 mg/kg on day 2 to 286 ± 60 mg/kg on day 10 in the cardiothoracic surgery group. Protein (g/kg) and kcal/kg intakes and nitrogen balance are

Table 4. Albumin, Fresh Frozen Plasma, and Plasmanate Intakes (g/kg) and Number of Patients Receiving by Day In Cardiothoracic Surgery (CTS) Or Closed Head Injury (CHI) Patients

	Admission	Day 2	Day 3	Day 4	Day 10
CTS*	1.39 ± 1.1	2.62 ± 2.38	2.37 ± 2.23	1.55 ± 1.12	0
# of CTS patients	5	2	2	2	0
CHI*	0.72 ± 0.28	0	0	0.5	0.47 ± 0.05
# of CHI patients	3	0	0	1	2

**mean ± SD*
CHI, Closed Head Injury; CTS, Cardiothoracic Surgery

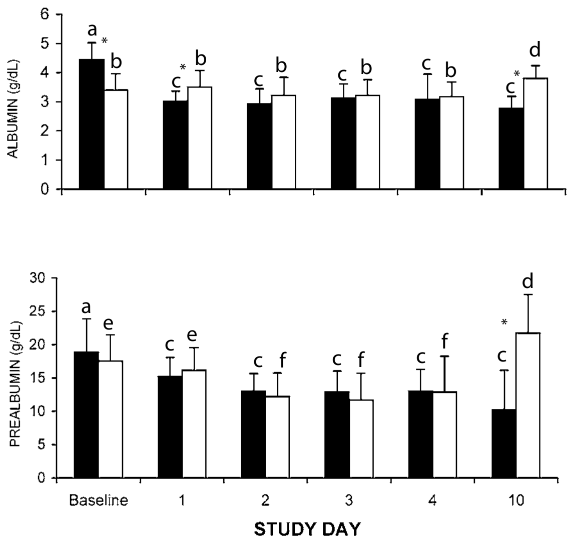

Figure 3. Prealbumin and albumin concentrations following cardiothoracic surgery (■) and closed head injury (□) by study day in children from 2–12 years of age. * = between group difference, P < 0.05; within group differences (P < .05): a = different from days 1, 2, 3, 4, 10; b = different from day 10; c = different from baseline; d = different from baseline and days 1, 2, 3, 4; e = different from days 2, 3, 4,10, f = different from baseline and days 1, 10.

compared in Figure 1. Both groups received < 50% of age-related protein and kcal requirements through study day 4. Colloid intakes (g/kg) and chest tube outputs (mL/kg) in the two groups are shown in Tables 4 and 5. Two of the cardiothoracic surgery patients had more than one chest tube; the child with congestive heart failure had a pleural and a mediastinal chest tube postoperatively, and the child who experienced a full arrest had 3 chest tubes in place on days 1, 2, and 3.

PSI scores for each study day are compared in Figure 2. Within group PSI score did not differ for any study day in the cardiothoracic surgery group. However, in the closed head injury group PSI score was higher on study day 1 than on any other study day and in two children was > 20. A between group difference was noted on day 1 when the PSI score was lower in the cardiothoracic surgery group. PSI scores did not correlate with nitrogen balance, 3-methylhistidine excretion, or prealbumin concentration. The responses of prealbumin and albumin are shown in Figure 3. Concentrations of both were near normal at the initial assessment in both groups. On day 10, prealbumin was normal (21.7 ± 5.8 mg/dL) in the head injury group (n = 7) and was significantly higher than in the 3 patients remaining in the cardiothoracic surgery group (10.3 ± 5.9 mg/dL). The urinary 3-methylhistidine excretion and 3-methylhistidine to creatinine ratio data are depicted in Figure 4.

The head injury patients were hospitalized for 42.2 ± 32 days (range 5 to 114), while the cardiothoracic surgery patients had an average hospitalization length of 10.9 ± 8.1 days (range 5 to 29) (P < .02). Five of the head injury patients were discharged home; one with no apparent deficits, one with a seizure disorder, two with mild neurological deficits, and one with severe deficits. Four were discharged to rehabilitation units or long-term care facilities. The disposition of one patient was unknown. While 3 surgery patients had postoperative complications, all were eventually discharged home.

DISCUSSION

This the first study to serially evaluate and compare markers of nitrogen and protein metabolism in stressed children after a controlled surgical procedure and an acute traumatic injury. These two different types of patients were chosen expecting that the head injured patients would be more catabolic throughout the study period than the cardiothoracic surgery patients.

During the first four study days, both groups of children experienced very similar physiologic instability; all measurements reflected profound catabolism and were similar in direction. While the early response to injury was stereotypic in both groups, the closed head injury group had a more negative nitrogen balance on day 1 and a greater urinary 3-methylhistidine excretion on days 1, 2, and 3. The day 10 observations in the head injury group were reflective of recovery. However, the 3 hospitalized children in cardiothoracic surgery group had developed complications, and markers of protein metabolism continued to reflect catabolism despite modest nutrient intakes.

The relationship between severity of illness scoring systems and nitrogen excretion and other markers of protein metabolism is highly variable.[6-9] PSI and Pediatric Risk of Mortality (PRISM) scores correlated with oxygen consumption and TUN excretion in 12 critically ill children up to 7 years of age, some with infection.[6] On the other hand, PRISM score did not

Table 5. Chest Tube Placement and Output In Children with Cardiothoracic Surgery or Closed Head Injury

	Admission–Day 1	Day 2	Day 3	Day 4
Cardiothoracic Surgery				
Patients with CTs (n)	10	10	6	3
Total CTs (n)	11†	13‡	9‡	6‡
CT output (mL/kg)*	19 ± 19.1	29.6 ± 52.5	21.3 ± 37	22.3 ± 23.2
Closed Head Injury				
Patients with CTs (n)	2	3	2	2
Total CTs (n)	2	3	2	2
CT output (mL/kg)*	1.5 ± 1.2	0.3 ± 0.4	0.2 ± 0.2	0.4 ± 0.5

**mean ± SD*
†one patient had 2 CTs
‡one patient had 2 CTs, one patient had 3 CTs
CT, chest tube

correlate with resting energy expenditure in 21 children with systemic inflammatory response syndrome and sepsis.[7] The Injury Severity Score and protein metabolism were not correlated in 19 pediatric trauma patients,[8] and the Therapeutic Intervention Scoring System score did not correlate with nitrogen balance in 19 critically ill children receiving parenteral nutrition.[9] Similarly, we found no correlation between PSI scores and any of the parameters of nitrogen metabolism that were evaluated.

Prealbumin concentration is a sensitive indicator of surgical stress and was noted to rapidly increase to normal in otherwise healthy children undergoing a minor surgical procedure.[10] In our study, the preoperative prealbumin concentration in the cardiothoracic surgery group was at the low end of the normal range (18 to 40 mg/dL) perhaps due to the difficulties in achieving adequate nutrient intake during chronic illness. The head injured patients, who presumably were well nourished prior to injury, had prealbumin concentrations near the lower end of the age related normal value shortly after ICU admission. This finding indicates rapid consumption and/or decreased hepatic synthesis of this relatively short half-life visceral protein following serious injury. The three cardiothoracic surgery patients who were critically ill had low prealbumin concentrations on day 10. This was due to continued stress, only modest nutrient intake, or due to dilution since they were also receiving crystalloid and colloid during this time.

Urinary 3-methylhistidine excretion is a sensitive indicator of skeletal muscle catabolism in adults[11] and is useful in children.[12-15] Duffy et al. enrolled critically ill children with either infection or trauma on days 3–5 after admission and measured urinary 3-methylhistidine excretion on days one, two, three, and five after initiation of parenteral nutrition.[13] Urinary 3-methylhistidine excretion ranged from 6–11 μmol/kg/day on day one of parenteral nutrition and decreased to 2–3 μmol/kg/day by parenteral nutrition day five during recovery.[13] Similarly, urinary 3-methylhistidine excretion in the closed head injury group we studied was 11.4 ± 5.6 μmol/kg/day on day one, and it steadily decreased with recovery to 4.9 ± 2.6 μmol/kg/d on day 10, somewhat greater than had been previously reported. The three critically ill cardiothoracic surgery patients had increased 3-methylhistidine excretion throughout the study, probably reflective of ongoing catabolism related to the development of complications.

Relating 3-methylhistidine to creatinine using a μmol/mg ratio evaluates protein catabolism per unit of lean body mass.[11,15] Gunel reported that the 3-methylhistidine to creatinine ratio was similar in protein fasted, healthy adults (0.16) and in unstressed adults with short bowel syndrome (0.18).[11] Similar to adults,[11] the ratio in healthy growing premature infants was generally < 0.2, while infants who were stressed or had inadequate intake was > 0.2.[15] In our patients, this ratio was > 0.2 on every study day in both groups. The difference between the groups noted on day 3 was due to an aberrant 3-methylhistidine ratio in one cardiothoracic surgery patient whose creatinine excretion was surprisingly low.

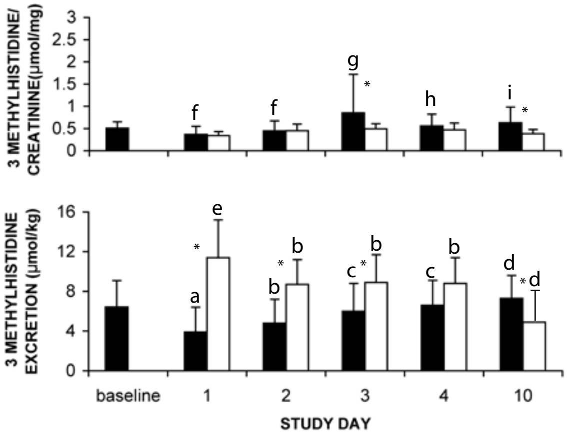

Figure 4. 3-methylhistidine excretion and 3-methylhistidine to creatinine ratio following cardiothoracic surgery (■) and closed head injury (□) by study day in children from 2–12 years of age. * = between group difference, $P < .05$; within group differences ($P < .05$), a = different from days 3, 4, 10; b = different from day 10; c = different from days 1, 10; d = different from days 1, 2, 3, 4; e = different from days 2, 3, 4, 10; f = different from days 3, 10; g = different from days 1, 2, 4; h = different from day 3; i = different from days 1, 2.

Seashore et al. reported that ten children who had a closed head injury and who were treated with steroids had an average TUN excretion of 256 ± 24 mg/kg/day [SEM]) compared to 172 ± 29 mg/kg/day in nine children with closed head injury who did not receive steroids.[16] These investigators averaged TUN excretion over four days, thus any changes that may have occurred with recovery from injury cannot be appreciated.[16] In a separate study, children with meningogoccal sepsis who did not receive steroids had similar nitrogen excretion in the first and second 24 hours of admission—271 mg/kg and 251 mg/kg, respectively.[17] The closed head injury group in our study had nitrogen excretion that was similar to the previous studies in children with meningococcal sepsis and in children with a closed head injury who received steroids. While two children in the head injury group did receive steroids, nitrogen balance was similar to the other 8 who did not. TUN excretion tended to be greatest on day 4 and lowest on day 10 after injury in our CHI group. In the 3 cardiothoracic surgery children who remained critically ill, TUN excretion tended to be greater on day 10 and is likely reflective of continued stress due to the development of complications.

Hammarquist reported that in adults, nutritional intervention does not appear to modify the muscle protein catabolism pattern that occurs after stress.[18] In neonates, however, Duffy et al. reported that nitrogen balance was improved and protein catabolism decreased when protein intake was increased.[12] We found that nitrogen balance remained negative during the first four days after injury in both groups of essentially unfed patients. By day 10, nitrogen balance was slightly positive in the recovering head injury patients who were receiving modest amounts of nutrition substrate and is suggestive of recovery. On the other hand, nitrogen balance on day 10 remained negative in the cardiothoracic surgery group despite nutrient intake that was similar to the head injured group. These findings are similar to those previously reported after traumatic or surgical injury or during infection in parenterally alimented children.[13]

CONCLUSION

In the critically ill child, there is a period of either reduced production or increased consumption of visceral proteins, or both, and increased peripheral protein catabolism that persists for at least 4 days but subsides by the 10th post injury day with recovery and refeeding. Finally, PSI scores and the indicators of protein synthesis or catabolism did not correlate in our patients.

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