Metabolic Changes Associated with Malnutrition in the Patients with Multiple Organ Failure

Jiro SATO, Hideo INABA, Hiroyuki HIRASAWA and Tadanobu MIZUGUCHI

To clarify the metabolic changes associated with malnutrition in the patients with multiple organ failure (MOF), we measured energy expenditure, nitrogen excretion, nonprotein respiratory quotient (NPRQ), caloric intake, and cumulative caloric balance (CCB) in 20 MOF patients (12 survivors and 8 non-survivors). The non-survivors exhibited significantly greater cumulative caloric deficit than the survivors. Metabolic activity tended to decline to normal in the survivors as organ failures were overcome. In the non-survivors, on the contrary, regardless of large caloric deficit hypermetabolism persisted and characteristically followed by the sudden decrease in metabolic activity at the time immediately prior to death. Compared to the survivors, the non-survivors generally exhibited poorer response in metabolic activity and greater NPRQ change to the altered amount of caloric intake. It seemed that protein sparing effect by increased caloric intake was preserved in both the survivors and the non-survivors only with CCB above −5 times basal energy expenditure. These results suggest that persistent hypermetabolism and poor metabolic response to nutritional support are partly responsible for existing organ failures and poor outcome in MOF patients. (Key words: metabolic activity, caloric balance, hypermetabolism, respiratory quotient)

(Sato J, Inaba H, Hirasawa H, et al.: Metabolic changes associated with malnutrition in the patients with multiple organ failure. J Anesth 7: 276–286, 1993)

The development in indirect calorimetry has enriched our knowledge of the energy metabolism and the nutritional management in critically ill patients[1,2]. It is well recognized that not only inadequate caloric intake but also glucose overload produce harmful influences on the pathology in critically ill patients. Malnutrition may cause anergy, high vulnerability to infection, retarded wound healing, and other complications[3,4]. Excessive glucose intake over caloric requirement, on the other hand, may produce fatty infiltration of liver[5,6] or make the patients difficult to be weaned from mechanical ventilation by increasing CO_2 production[7,8]. There have been many studies which demonstrate

Departments of Anesthesiology, and Emergency and Critical Care Medicine, Chiba University School of Medicine, Chiba, Japan

Address reprint requests to Dr. Sato: Department of Anesthesiology, Chiba University School of Medicine, 1-8-1 Inohana, Chuow-ku, Chiba, 263 Japan

Table 1. Criteria for organ failures

organs	criteria for diagnosis
cerebral	Glasgow coma scale $< 5+T$ or 7
pulmonary	respiratory index $(A\text{-}aD_{O_2}/Pa_{O_2}) > 3.0$
cardiac	poor response to inotroic agents
hepatic	total bilirubin > 5 mg·dl^{-1}, serum GOT > 100 IU·l^{-1}, and GPT > 100 IU·l^{-1}
gastro-intestinal	bleeding requiring blood transfusion of more than 500g
renal	BUN > 50 mg·dl^{-1} and serum creatinine > 3 mg·dl^{-1}
coagulopathy	satisfying three or more of the following criteria: platelet $< 80,000$ /mm^3, FDP > 40 μg·ml^{-1}, fibrinogen ≤ 150 mg·dl^{-1} prothrombin time > 15 sec, or obvious bleeding tendency.

the metabolic changes following sepsis, trauma, burn, and surgical stress[9–12]. Although these illnesses are known to produce high susceptibility to organ systems failure, it is still remained controversial how the energy metabolism responds to nutritional management in MOF patients[13].

Once MOF develops in critically ill patients, nutritional management is influenced and often limited by other treatments such as maintaining cardiovascular stability or normalization of body fluid composition and electrolytes. In the patients with cardiac or renal failure, for example, a large intake of calorie and nitrogen inherently leads to significant amount of water load. Those patients, therefore, may require frequent hemodialyses to remove the excessive water, which may result in unstable hemodynamics during hemodialyses. Thus, it is occasionally difficult to administer adequate amount of nutrients to MOF patients. Although there have been many studies which demonstrate general influences of undernutrition on the patients with cancer or other chronic illnesses[14–16], such investigations on the MOF patients are still not abundant. Therefore, the aim of this study is to investigate the effect of undernutrition on the energy metabolism during the course of MOF by measuring energy expenditure, nitrogen excretion, NPRQ, caloric intake, and cumulative caloric balance in the MOF patients.

Subjects and Methods

The study was conducted on 20 postoperative patients with MOF (mean age of 54, ranging from 32 to 74 years old, 12 males and 8 females). All the patients were treated in our intensive care unit (ICU). Their primary diseases were esophageal cancer in 8, gastrointestinal cancer in 4, hepatobiliary cancer in 5, and other diseases in 3 patients. The failures of organ systems were determined using the criteria shown in table 1, and MOF was diagnosed when two or more organ systems were simultaneously counted as the failing organs. The factors precipitating MOF were sepsis or severe infection in 15 cases, hemorrhage in 4 cases, and hypoxia in 1 case.

All the patients received nutritional support by intravenous hyperalimentation using the fluid containing glu-

cose, amino acids and other elements. The hyperalimentation supplied the daily caloric intake of more than 700 kcal with calorie-to-nitrogen ratio less than 300. Indirect calorimetry and other metabolic measurements were performed on a daily basis until the patients recovered and discharged from the ICU (survivors), or died in the ICU (non-survivors). No uniform intervention for the nutritional management was made from the results of these measurements.

Minute oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$, $ml \cdot min^{-1}$ in STPD) were measured every morning using a metabolic computer (Engstrom EMC®, Stockholm). $\dot{V}O_2$ and $\dot{V}CO_2$ were measured every minute for 30–60 min at the steady state, then the running averages with a window length of 15-min were computed and finally the stable values were taken as the $\dot{V}O_2$ and the $\dot{V}CO_2$ for further analysis. All the measurements were performed when all the following conditions were satisfied; 1) on or after the second postoperative day, 2) neither quality nor quantity of nutrients had been changed from at least eight hours before the initiation throuogh to the end of the measurement, 3) lipid emulsion had not been administered for the same period, 4) no blood purification had not been performed for the same period, and 5) the systolic blood pressure had remained over 100 mmHg for the period.

Urinary output (UO, $l \cdot day^{-1}$), urinary urea nitrogen (UUN, $g \cdot l^{-1}$), and blood urea nitrogen (BUN, $g \cdot l^{-1}$) were measured. In this study, nitrogen excretion (N-OUT, $g \cdot day^{-1}$) was defined as the sum of the urinary nitrogen excretion (UO × UUN × 6/5) and the daily change in the urea nitrogen in the body water (ΔUN). ΔUN was calculated using Allen's formula[17] in which the amount of the body water was assumed to be 60% of the body weight. On the day when a blood purification was performed, BUN was additionally measured both 2 hours before and after the blood purification to estimate the 24-hour change in BUN (see the calculation detail in APPENDIX). N-OUT values were normalized with the unit of $mg \cdot kg^{-1} \cdot day^{-1}$. As implicitly specified in the measurement condition, the indirect calorimetry was performed before blood purification was initiated on the days when blood purification was indicated.

Energy expenditure (EE, $kcal \cdot day^{-1}$) and NPRQ were computed using the algorithm of Westenskow et al.[2,18]. Intravenous amino acid was not considered as the exogenous caloric source. Basal energy expenditure (BEE, $kcal \cdot day^{-1}$) was calculated by Harris-Benedict formulas[19]. The metabolic activity and the sufficiency of caloric intake were defined as EE/BEE and CAL-IN/EE, respectively. The daily caloric balance (CAL-IN minus EE) was summed up from day to day starting on the day of the ICU admission. The running sum divided by BEE was defined as the cumulative caloric balance (CCB). The CCB was classified into three grades of nutritional status: 1) greater than −5 × BEE (overnutrition or minimal malnutrition), 2) −5 to −10 × BEE (moderate undernutrition), and 3) lower than −10 × BEE (severe malnutrition).

In the patients who had finally exhibited CCB lower than −10 × BEE, the serum concentrations of retinol binding protein and prealbumin were measured by a radial immunodiffusion (Partigen®, Behringer Institut) for the assessment of the protein synthetic capability of liver.

The correlation between EE/BEE and other parameters were examined by a least square linear regression method. The statistical difference be-

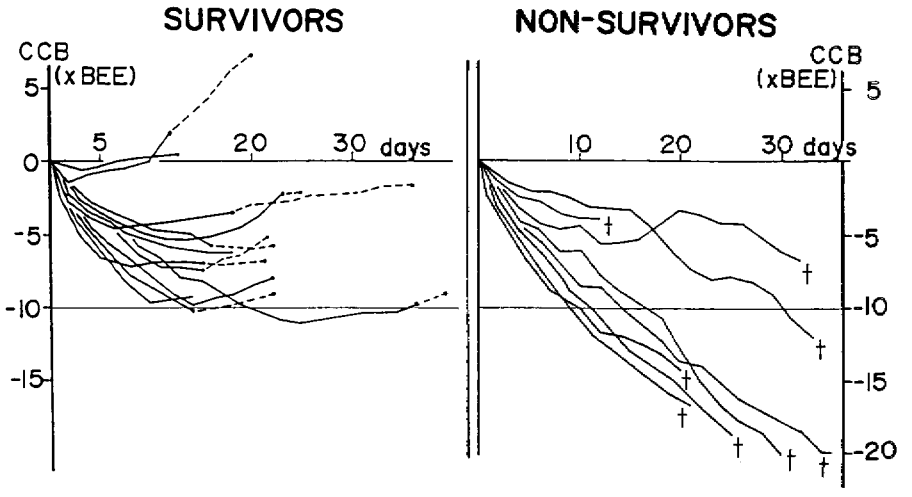

Fig. 1. Sequential changes in the cumulative caloric balance (CCB) in 20 MOF patients: the 12 survivors (left panel) and the 8 non-survivors (right panel). The CCB is expressed as a multiple of basal energy expenditure (BEE). Solid lines represent the change during MOF and dashed line the change during the recovery period from MOF (i.e. with no or one organ failure).

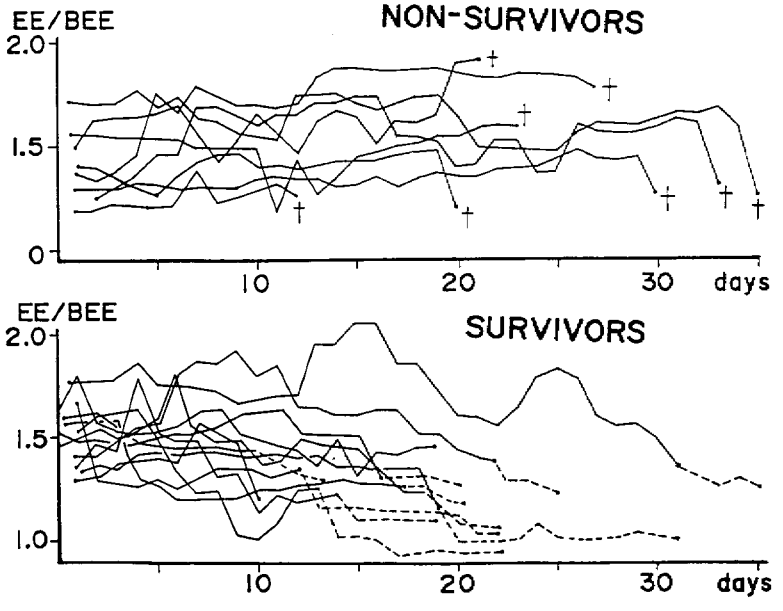

Fig. 2. Sequential changes in metabolic activity in 20 MOF patients: the survivors (top panel) and the non-survivors (bottom panel). The line types are same as in figure 1. Notice that the metabolic activity gradually declined during the recovery period in the survivors whereas the non-survivors sustained high metabolic activity followed by a sudden fall immediately before death.

tween two regression lines was tested by an analysis of covariance. The other differences between the survivors and the non-survivors were evaluated by a

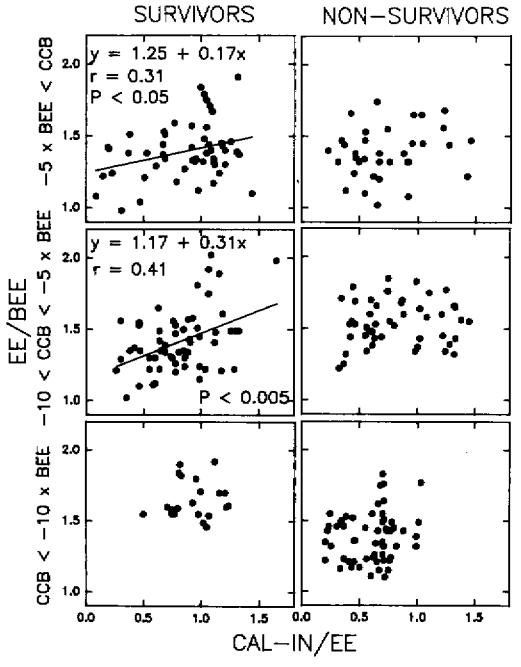

Fig. 3. Correlation between CAL-IN/EE and EE/BEE: $-5 \times BEE < CCB$ (top panel), $-10 < CCB < -5 \times BEE$ (middle), and $CCB < -10 \times BEE$ (bottom). Significant positive correlations were found in the survivors with CCB above $-10 \times BEE$.

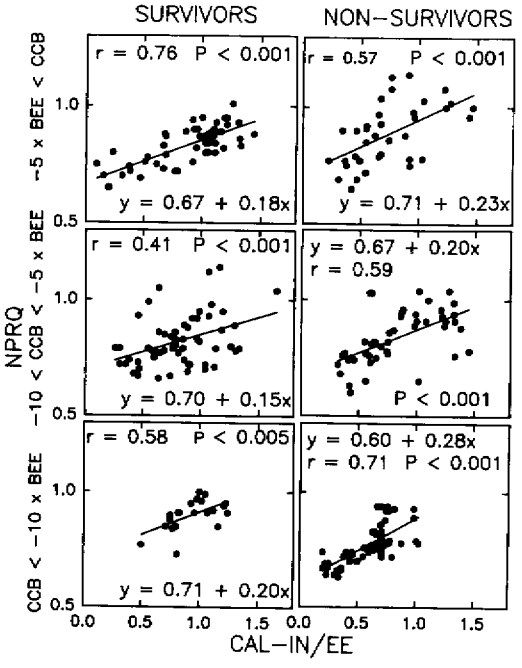

Fig. 4. Correlation between CAL-IN/EE and NPRQ: $-5 \times BEE < CCB$ (top panel), $-10 < CCB < -5 \times BEE$ (middle), and $CCB < -10 \times BEE$ (bottom). Significant positive relationship was found at any stage of CCB in both the survivors and the non-survivors. The slopes of the regression lines were significantly greater in the non-survivors than in the survivors at $CCB > -5 \times BEE$ (top) and at $CCB < -10 \times BEE$ (bottom).

non-paired T test. *P* values of less than 0.05 were considered significant. The values in the text were expressed as the mean ± SD.

Results

The sequential changes in CCB are presented in figure 1. The CCB was almost negative in both the survivors and the non-survivors throughout the courses. In the non-survivors (right panel), the CCB rapidly decreased. Six out of the eight non-survivors exhibited the severe negative balance below $-10 \times BEE$. In the survivors (left panel), on the other hand, the initial decrease in the CCB tended to be followed by CCB increase. The positive CCB was achieved in the two survivors by the day of discharge from the ICU. The CCB of the survivors on the day of the discharge ($-4.0 \pm 4.2 \times BEE$) was significantly greater than that of the non-survivors on the day of death in the ICU ($-13.8 \pm 6.2 \times BEE$).

As demonstrated in figure 2, the metabolic activity in the survivors tended to decline as some of the organ failures were overcome (lower panel), while the non-survivors sustained high metabolic activity until the time immediately prior to their death (upper panel).

Significant correlations were observed between EE/BEE and CAL-IN/EE when CCB was higher than $-10 \times BEE$ in the survivors whereas no significant correlation was found at any

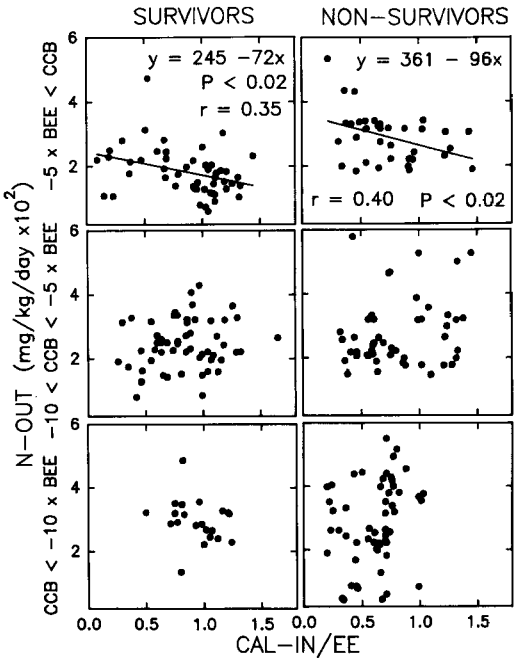

Fig. 5. Correlation between CAL-IN/EE and N-OUT: $-5 \times$ BEE $<$ CCB (top panel), $-10 <$ CCB $< -5 \times$ BEE (middle), and CCB $< -10 \times$ BEE (bottom). Significant negative correlations were found in the survivors and the non-survivors both with CCB of greater than $-5 \times$ BEE.

grade of CCB in the non-survivors (fig. 3).

Figure 4 demonstrates a positive relationship between CAL-IN/BEE and NPRQ at any grade of CCB in both the survivors and the non-survivors. The slope of the regression line was significantly greater in the non-survivors than in the survivors when CCB was greater than $-5 \times$ BEE or less than $-10 \times$ BEE, indicating that the NPRQ change in response to altered caloric intake was greater in the non-survivors.

Figure 5 shows the correlations between CAL-IN/EE and N-OUT. The significant negative correlations were obtained at CCB over $-5 \times$ BEE in both the survivors and the non-survivors.

Figure 6 illustrates positive relationships between the serum concentrations of rapid turnover proteins and CCB.

Discussion

In this study, we showed that undernutrition was one of the common features of MOF patients and that the non-survivors exhibited larger caloric deficit than the survivors. Furthermore, we demonstrated that the metabolic changes which occurred presumably in response to the altered amount of caloric intake were considerably different between the survivors and the non-survivors.

The patients with cumulative caloric deficit greater than $10 \times$ BEE (CCB below $-10 \times$ BEE) exhibited poor outcome. This observation is in good agreement with the report of Bartlett et al.[13] which showed that critically ill patients burdened with more than 10,000 kcal of cumulative caloric deficit were claimed high susceptibility to the development of severe organ failures and consequently poor outcome. It may be that in the present study the caloric deficit seen in the non-survivors was mainly produced by limited caloric intake in order to reduce total fluid intake in the patients with renal failure, unstable hemodynamics or the patients requiring large blood transfusion. The sustained hypermetabolism, however, might certainly augment this caloric deficit by widening the gap between energy expenditure and caloric intake. Although both the survivors and the non-survivors presented hypermetabolism at the initial stage of MOF, the metabolic activity tended to decline as organ failures were sequentially overcome in the survivors (fig. 2). It is characteristic, in contrast, that hypermetabolism persisted in the non-survivors until their death, then followed by the sudden decrease in metabolic activity. This is in accord

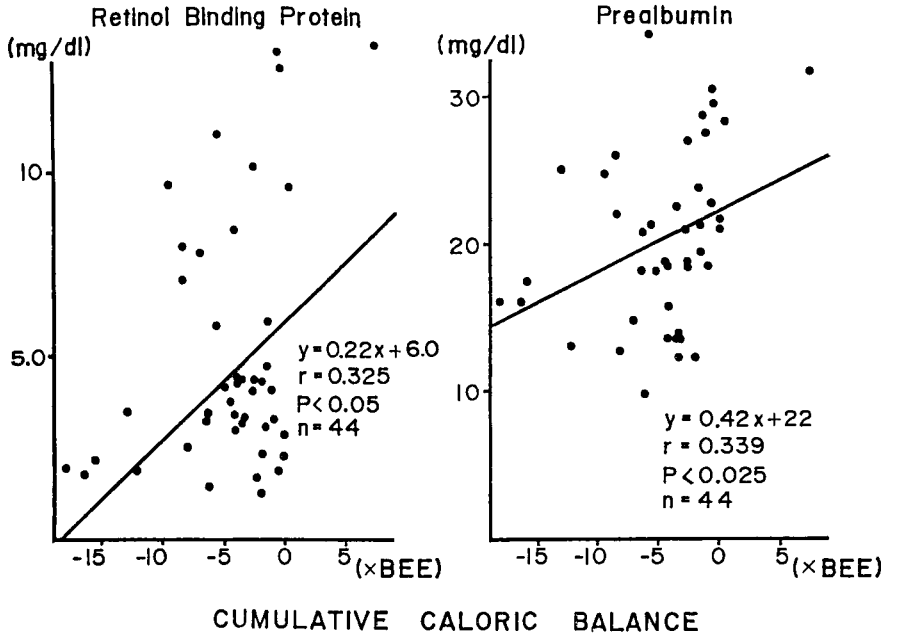

Fig. 6. Correlations between rapid turnover proteins and CCB: retinol binding protein (left panel) and prealbumin (right panel).

with the reports that the metabolic activity increased in proportion to surgical or traumatic stress, infection, and fever[20,21] and that the metabolic activity in critically ill patients reflected the severity of illness assessed by APACHE II score[22]. These arguments suggest that undernutrition in the MOF patients is in close relation to their persistent hypermetabolism. Therefore, treating the underlying organ failures, per se, could be one of the important metabolic interventions by reducing caloric demand.

It is generally accepted that the increase in caloric intake induces the increase in metaboic activity in depleted non-stressed patients who attempt to acclimatize metabolic environment by changing basal energy expenditure[16]. In the present study, however, this positive relationship between caloric intake and metabolic activity could be found only in the survivors without severe cumulative caloric deficit (fig. 3). Astiz et al.[23] and Dahn[24] found that the delivery-dependent oxygen consumption in tissues was present in wider range of oxygen delivery in septic patients than healthy subjects. This may be applied to our results and a possible speculation is as follows. The survivors were generally in the condition of delivery-independent oxygen consumption so that they could increase $\dot{V}O_2$ as the amount of energy substrate increased. On the contrary, the non-survivors' oxygen consumption was dependent on the oxygen delivery, therefore, they could not increase $\dot{V}O_2$ in response to the increased caloric intake unless the oxygen delivery to tissues was not regained. Dahn et al.[25] demonstrated the presence of splanchnic ischemia produced by the mismatching between splanchnic blood flow and oxygen demand. Bihari et al.[26] found substantial oxygen debt introduced by the infusion of prostacyclin in critically ill patients with respiratory failure. These suggest that not the total amount of oxygen output

from the cardio-respiratory system but the amount of oxygen which actually reaches to the metabolic tissues takes a key role in maintaining the adequate metabolic response to increased caloric intake[24,27]. In this sense, it might not be helpful solely to administer enough calorie which meets energy expenditure. In addition, the maintaining adequate blood supply to the metabolic organs may be an essential measures to furnish those organs with sufficient amount of oxygen[28,29].

There was a significant positive correlation between NPRQ and CAL-IN/EE at any level of CCB in both the survivors and the non-survivors. The change in NPRQ may give us an indirect but a useful insight into energy substrates oxidized. One considerable finding in the NPRQ vs. CAL-IN/EE relationship is that NPRQ either greater than 1.0 or smaller than 0.707 was not exceptional (fig. 4). These could not be achieved by the oxidation of essential energy sources – glucose, fat and amino acids since the respiratory quotients for the three are 1.0, 0.707 and 0.82, respectively. Giovanini et al.[30] suggested in critically ill patients that impaired glucose oxidation and subsequent fatty degeneration in liver might occur as the result of the relative ischemia, or by endotoxin and chemical mediators involved in host defence. The greater increase in NPRQ with incremental CAL-IN/EE seen in the non-survivors might imply this possibility since the lipogenesis from glucose has RQ of 9.0 (much higher than unity). Askanazi et al.[31] reported that a large dose of glucose did not suppress net fat oxidation in hypermetabolic patients as did in non-stressed depleted patients. Thus, MOF patients may fail to utilize the incremental dose of glucose as an energy source but consume it for fat synthesis. Fat synthesis is an ineffective way of energy production which may lead to further caloric deficit in hypermetabolic patients. In this case, the effort to attain positive caloric balance may result in further metabolic derangement.

Clowes et al.[32,33] proposed the considerable role of a cleavage product of Interleukin 1 in increased protein mobilization from skeletal muscle in septic or traumatic patients. Cerra et al.[34] demonstrated that autocannibalism of muscle mass was little influenced by either glucose or amino acid support in the absence of the control of septic process. These arguments might hold our patients with moderate or severe cumulative caloric deficit. The negative correlation between CAL-IN/EE and N-OUT, however, was found in both the survivors and the non-survivors only with no or mild caloric deficit. This may suggest that protein sparing by increased caloric intake might be preserved in the patients before sustaining large caloric deficit.

The synthesis of the rapid turnover proteins, which are produced in liver, decreased with the development of malnutrition. Not the malnutrition in itself but the organ failures, particularly hepatic failure, may be responsible for the reduced protein synthesis, since hepatic failure was almost always present at the stage of severe caloric deficit. This deteriorated synthesis of the proteins might be in charge of immuno-incompetence or delayed wound healing. Our results might agree with the results of Clowes et al[33]. They found that the amino acid mobilization *in vivo*, determined by central plasma clearance rate of amino acid, was correlated with hepatic protein synthesis *in vitro*, and that it was greatly depressed in septic patients who were going to die of overwhelming infection.

In summary, the study suggests that the persistent hypermetabolism may produce malnutrition by broadening

the difference between energy expenditure and caloric intake in MOF patients. Malnutrition may occur in the process of organ failures and, in turn, the organ failures may aggravate malnutrition by barring the nutritional support[35]. The nutritional support with adequate calorie and amino acid, therefore, may be the only logical solution. If fluid intake is limited because of renal failure, unstable hemodynamics, or blood transfusion, etc., continuous hemofiltration may be an effective measures for full nutritional support[36–38]. In patients who fail the metabolic response to nutritional support, however, full nutritionall intake may be ineffective or even harmful. Then maintaining sufficient blood flow to the metabolic organs may be helpful to prevent relative ischemia or oxygen debt – tissue hypoxia, for example, using dopamine[24,27–29] or vasodilators[28].

APPENDIX:

Calculation of ΔUN on a day of blood purification:

Allen's formula is

$$\Delta UN = (BUN2\text{–}BUN1) \times \text{body weight} \times 0.6,$$

where BUN1 and BUN2 are BUN measured in the mornings of the day and the next day, respectively. However we cannot use this formula to calculate ΔUN on the days when any form of blood purifications is performed, since a significant amount of UN is removed from the body through blood purifications. The alternative we adopted is to assume that the rate of UN production is constant throughout a day and to estimate 24-hr ΔUN from BUN changes in the periods when blood purifications are not performed on.

Suppose that a blood purification started X+2 hours after the measurement of BUN1 and ended Y+2 hours before the measurement of BUN2, and that the values of BUN were A and BX hours after BUN1 measurement and Y hours before BUN2 measurement, respectively. The 24-hour change in BUN of the day, ΔBUN, is,

$$\Delta BUN = \frac{(BUN2\text{–}B) + (A\text{–}BUN1)}{X + Y} \times 24,$$

Therefore,

$$\Delta UN = \Delta BUN \times \text{body weight} \times 0.6.$$

(Received Apr. 15, 1992, accepted for publication Oct. 26, 1992)

References

1. Hunker FD, Bruton CW, Hunker EM, et al: Metabolic and nutritional evaluation of patients supported with mechanical ventilation. Crit Care Med 8: 628–632, 1980
2. Westenskow DR, Cutler CA, Wallace WD: Instrumentation for monitoring gas exchange and metabolic rate in critically ill patients. Crit Care Med 12:183–187, 1984
3. Rhoads JE: The impact of nutrition on infection. Surg Clin North Am 60:41–47, 1980
4. Gross RL, Newberne PM: Role of nutrition in immunologic function. Physiol Rev 60:188–291, 1980
5. Sheldon GF, Petersen SR, Sanders R: Hepatic dysfunction during hyperalimentation. Arch Surg 113:504–508, 1978
6. Rowlands BJ, MacFyden BV, DeJong P, et al: Monitoring hepatic dysfunction during intravenous hyperalimentation. J Surg Res 28:471–478, 1980
7. Askanazi J, Rosenbaum SH, Hyman AI, et al: Respiratory changes induced by the large glucose loads of total parenteral nutrition. JAMA 243:1444–1447, 1980
8. Askanazi J, Weissman C, Rosenbaum SH, et al: Nutrition and the respiratory system. Crit Care med 10:163–172, 1982
9. Siegel JH, Cerra FB, Coleman B, et al: Physiological and metabolic correlation in human sepsis. Surgery 86:163–193, 1979
10. Abbott WC, Echenique MM, Bistrian BR, et al: Nutritional care of the trauma patient, Surg Gynecol Obstet 157:585–597, 1983
11. Turner WW, Ireton CS, Hunt JL, et al: Predicting energy expenditures in burned patients. J Trauma 25:11–16,

1985
12. Kinney JM, Long CL, Gump FE, et al: Tissue composition of weight loss in surgical patients I. Elective operation. Ann Surg 168:459–474, 1968
13. Bartlett RH, Dechert RE, Mault JR, et al: Measurement of metabolism in multiple organ failure. Surgery 92:771–779, 1982
14. Hansell DT, Davies JWL, Burns HJG, et al: The oxidation of body fuel stores in cancer patients. Ann Surg 204:637–642, 1986
15. Lindnark L, Eden E, Ternell M, et al: Thermic effect and substrate oxidation in response to intravenous nutrition in cancer patients who loose weight. Ann Surg 204: 628–636, 1986
16. Kinney JM: Energy metabolism, in Surgical Nutrition. Edited by Fischer JE. Boston, Little Brown and Co, 1983, pp. 97–126
17. Allen PC, Lee HA: A Clinical Guide to Intravenous Nutrition. Oxford, Blackwell Scientific Publication, 1964, pp. 144–166
18. Bursztein S, Saphar P Glaser P, et al: Determination of energy metabolism from respiratory function alone. J Appl Physiol 42:117–119, 1977
19. Harris JA, Benedict FG: Biometric Studies of Basal Metabolism in Man. Washington DC, Carnegie Institute of Washington Publication, Publication Number 297, 1919
20. Blackburn GL, Bistrian BR, Maini BS, et al: Nutrition and metabolic assessment of the hospitalized patient. J Parent Ent Nutr 1:11–22, 1977
21. Lanschot JJB, Feenstra BWA, Looijen R, et al: Total parenteral nutrition in critically ill surgical patients: fixed vs tailored caloric replacement. Intensive Care Med 13:45–51, 1987
22. Swinamer DL, Phang PT, Jones RL, et al: Twenty-four energy expenditure in critically ill patients. Crit Care Med 15:637–643, 1987
23. Astiz ME, Rackow EC, Falk JL, et al: Oxygen delivery and consumption in patients with hyperdynamic septic shock. Crit Care Med 15:26–28, 1987
24. Dahn MS: Visceral organ resuscitation. Perspectives in Critical Care 4:1–41, 1991
25. Dahn MS, Lange P, Lobdell K, et al: Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery 101:69–80, 1987
26. Bihari D, Smithies M, Gimson A, et al: The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. New Engl J Med 317:397–402, 1987
27. Shoemaker WC, Appel PL, Kram HB: Oxygen transport measurements to evaluate tissue perfusion and titrate therapy: Dobutamine and dopamine effects. Crit Care Med 19:672–688, 1991
28. Hasselgren PO, Biber B, Fornander J: Improved blood flow and protein synthesis in postischemic liver following infusion of dopamine. J Surg Res 34:44–52, 1983
29. Anghern W, Schmid E, Althaus F, et al: Effect of dopamine on hepatosplanchnic blood flow. J Cardiovasc Pharmacol 2:257–265, 1980
30. Giovanini I, Boldrini G, Castagneto M, et al: Respiratory quotient and patterns of substrate utilization in human sepsis and trauma. JPEN 7:226–230, 1983
31. Askanazi J, Carpentier YA, Elwyn DH, et al: Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg 191:40–46, 1980
32. Clows Jr. GHA, George BC, Villee Jr. CA, et al: Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. N Engl J Med 308:545–552, 1983
33. Clows Jr. GHA, Hirsch E, George BC, et al: Survival from sepsis; The significance of altered protein metabolism regulated by proteolysis inducing factor, the circulation cleavage product of interleukin 1. Ann Surg 202:446–458, 1985
34. Cerra FB, Siegel JH, Coleman B, et al: Septic autocannibalism: A failure of exogenous nutritional support. Ann Surg 192:570–580, 1980
35. Cerra FB: Hypermetabolism, organ failure, and metabolic support. Surgery 101:1–14, 1987

36. Bartlett RH, Mault JR, Dechert RE, et al: Continuous arteriovenous hemofiltration: Improved survival in surgical acute renal failure? Surgery 100:400–408, 1986
37. Mault JR, Dechert RE, Lees P, et al: Continuous arteriovenous filtration: Ann effective treatment for surgical acute renal failure. Surgery 101:478–484, 1987
38. Hirasawa H, Sugai T, Ohtake Y, et al: Energy metabolism and nutritional support in anuric multiple organ failure patients, Nutritional Support in Organ Failure. Edited by Tanaka T and Okada A. Amsterdam, Elsevier Scientic Publishers, 1990, 429–440