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INVESTIGATION OF INTERMEDIARY METABOLISM AND ENERGY
EXCHANGE FOLLOWING HUMAN TRAUMA(U) COLUMBIA UNIV NEW
YORK COLL OF PHYSICIANS AND SURGEONS J M KINNEY SEP 80

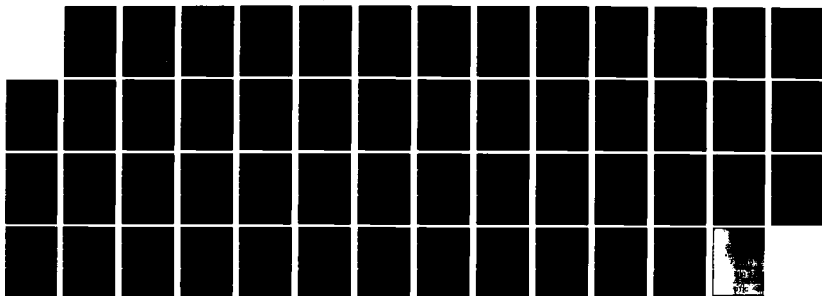
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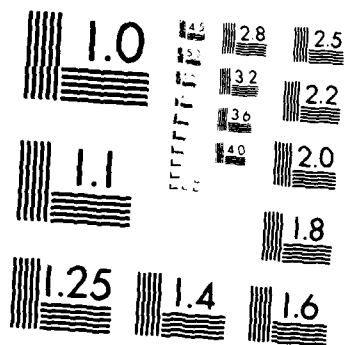
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Investigation of Intermediary Metabolism and Energy
Exchange Following Human Trauma

Annual Report

John M. Kinney, M.D.

September 1980

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DA-49-193-MD-2552

College of Physicians and Surgeons
Columbia University, New York, NY 10032

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM	
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER	
	AD A129829		
4. TITLE (and Subtitle)		5. TYPE OF REPORT & PERIOD COVERED	
Investigation of Intermediary Metabolism and Energy Exchange Following Human Trauma		Annual (1 Oct 79 - 30 Sept. 80)	
		6. PERFORMING ORG. REPORT NUMBER	
7. AUTHOR(s)		8. CONTRACT OR GRANT NUMBER(s)	
John M. Kinney, M.D.		DA-49-193-MD-2552	
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS	
College of Physicians and Surgeons Columbia University New York, NY 10032		62772A.3S162772A874.AA.124	
11. CONTROLLING OFFICE NAME AND ADDRESS		12. REPORT DATE	
US Army Medical Research and Development Command Fort Detrick, Frederick, Maryland 21701		September 1980	
		13. NUMBER OF PAGES	
		53	
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report)	
		Unclassified	
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	
16. DISTRIBUTION STATEMENT (of this Report)			
Approved for public release; distribution unlimited			
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)			
18. SUPPLEMENTARY NOTES			
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)			
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)			

PROGRESS REPORT

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Availability Codes	
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PUBLICATIONS

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- Michelsen CB, Askanazi J, Gump FE, Elwyn DH, Kinney JM, Stinchfield FE:
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replacement. J Trauma 19:29-32, 1979
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- Kinney JM: Indirect calorimetry - Application to clinical studies, in Kinney JM (ed): Assessment of Energy Metabolism in Health and Disease. Ohio, Ross Laboratories, 1980, p 42

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- Kinney JM: Calorie and nitrogen requirements in catabolic states, in Karran SJ, Alberti KGMM (eds): Practical Nutritional Support. Pitman Medical, Kent, England, 1980
- Kinney JM: Energy flow - A vital theme in injury and infection: The First Sir David Cuthbertson Lecture, in Schuberth O, Wahren J, Vinnars E (eds): Proceedings of an International Symposium on Parenteral and Enteral Nutrition, Stocholm, September, 1979 (In press, 1980)

PROGRESS REPORT

EFFECT OF NUTRITIONAL INTAKE ON LIMB SKELETAL MUSCLE COMPOSITION

Generalized weakness and fatigue are the most persistent consequences of injury and infection. The biochemical basis for the prolonged convalescence is unclear. However, even after elective operation, there is a period of 5 weeks to 3 months where the ability to work a full day without undue fatigue is impaired. In order to understand better the biochemical mechanisms underlying postoperative fatigue we have undertaken a study of muscle composition in injury, infection, starvation and convalescence utilizing the Bergstrom percutaneous biopsy technique. Our studies have included measurements of muscle, water and electrolytes, amino acids, high energy phosphates and glycolytic intermediates and glycogen. Data which was presented in preliminary form in our previous application is presented here only in summary form.

a) Muscle Water and Electrolytes

Our goals for this aspect of the muscle composition program have been: 1) to investigate the effect of injury on muscle water and electrolytes; 2) to determine whether the severity of the injury correlates with the changes observed; 3) to determine whether nutritional support has an effect on the changes observed. This study has been performed in collaboration with Drs. Bergstrom, Furst, and Vinnars.

a) Normal subjects do not show abnormalities of muscle composition after 4 days of bedrest or starvation. Therefore, the changes seen in postoperative patients can be ascribed to factors other than physical

activity or food intake.

b) Following major elective surgery there is increased Na^+ , Cl^- and extracellular water with no changes in intracellular water or electrolytes.

c) Following major trauma or burns there is increased Na^+ , Cl^- , extracellular water and decreased K^+ and Mg^{++} .

d) With sepsis complicating major trauma there is a further rise in extracellular water.

e) There is no observable effect of diet, during the first 4 postoperative days.

b) Muscle and Plasma Amino Acids

The metabolic response to trauma is usually associated with a negative nitrogen balance. The severity of the condition is usually reflected by the extent of negativity, which is largely the result of protein breakdown in muscle. This catabolic condition is thought to be associated with translocation of amino acids from muscle to viscera. However, when discussing plasma amino acid concentrations, it should be remembered that the largest pool of free amino acids is not in the extracellular space, but within muscle cells. A fundamental question is whether a unique pattern of free amino acids exists in muscle, which is distinctive for the disease or condition studied. The development of the percutaneous needle biopsy technique provides a safe method for quantitative measurement of the composition of human muscle under a variety of conditions. Using this technique, characteristic changes of muscle amino acids in

different catabolic states (uremia, diabetes, injury and immobilization) have been demonstrated suggesting that a unique pattern of muscle free amino acids appears to be characteristic for each condition.

Current developments have made it possible to support traumatized patients with energy sources and crystalline amino acids by intravenous means. Although many studies have been conducted in the amounts and proportions of nutrients (1 - 5) to be used in surgical patients, the optimal composition of the nutrition for an injured patient remains unclear. Our studies on muscle composition have been centered on patterns observed on bedrest, starvation, postoperative trauma, major accidental injury, sepsis and convalescence. These results have been published in detail and summarized briefly here.

The postoperative pattern of amino acids is characterized by elevated levels in muscle and plasma of the branched-chain amino acids; phenylalanine, tyrosine and methionine. There is a marked decrease in muscle glutamine and smaller decreases in the basic amino acids in both muscle and plasma. Muscle to plasma concentration ratios are increased for the neutral amino acids, decreased for glutamine and the basic amino acids and are unchanged for the acidic amino acids.

The patterns seen after hip replacement are almost identical to those seen after colectomy or accidental injury. To investigate the effect of parenteral nutrition on the patterns observed, three forms of postoperative nutrition were compared: a) 5% dextrose; b) 3.5% amino acids; c) 5% dextrose and 3.5% amino acids.

Normal volunteers on bedrest served as control subjects and received a) 5% dextrose or b) 3 - 5% amino acids. In the patients a muscle biopsy was performed preoperatively and on the morning of the fourth postoperative day. In the normal volunteers a biopsy was performed prior to and on the morning of the fourth day.

There was a marked rise in muscle and plasma levels of the branched-chain amino acids in both injury and semistarvation (Figures 1, 2). The rise in muscle exceeded the rise in plasma amino acids. In muscle there was essentially no effect of nutritional support on the pattern of amino acids observed in muscle. In the normal subjects amino acid infusions resulted in a marked increase in muscle amino acid levels as compared to 5% dextrose. The aromatic amino acids (Figures 3, 4) and methionine increased in muscle and plasma in both the postoperative patients and normal subjects at bedrest.

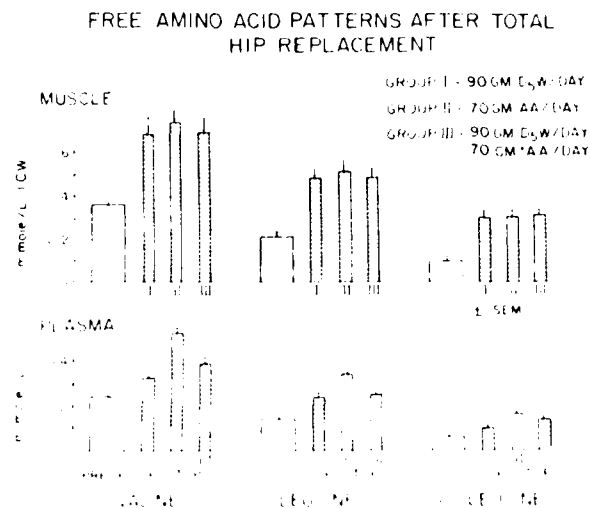


Fig. 1

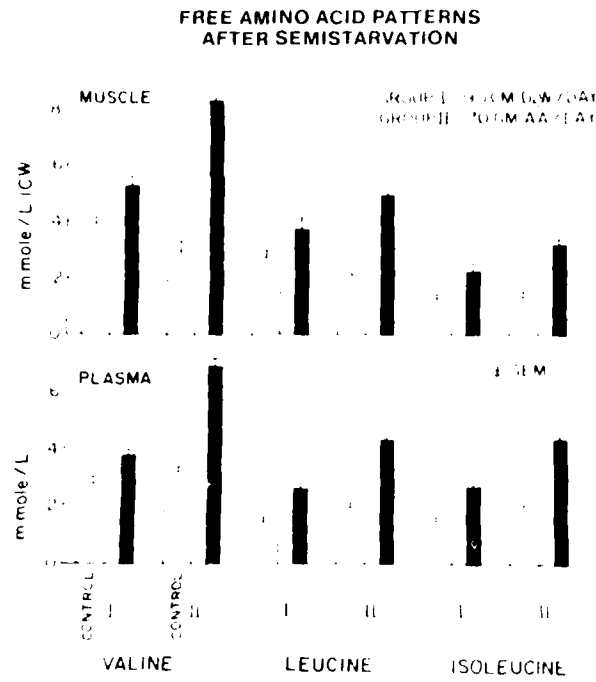


Fig. 2

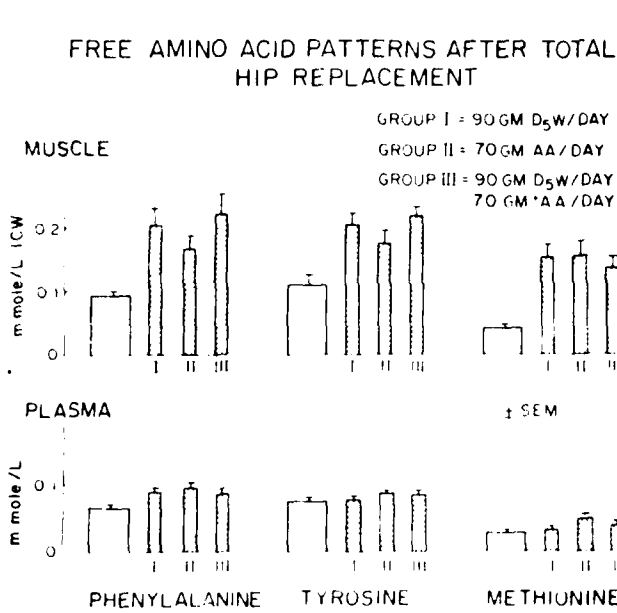


Fig. 3

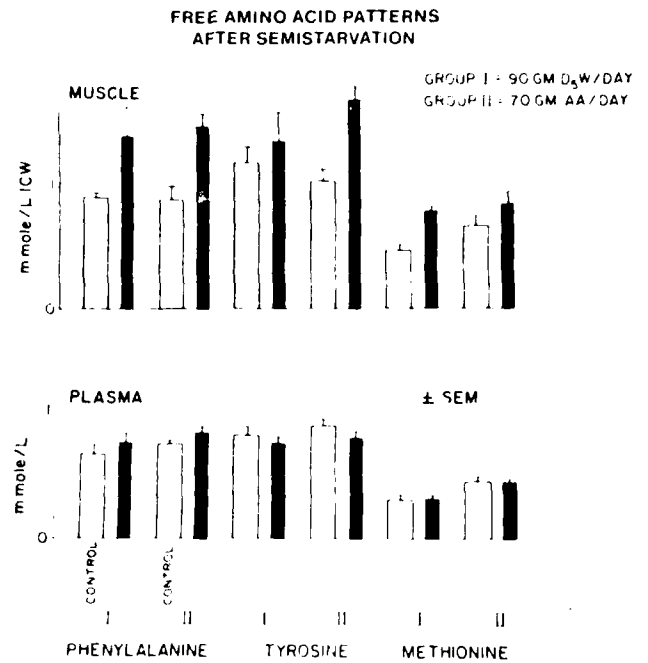


Fig. 4

Again, the rise in muscle exceeded the rise in plasma. There was no effect of nutritional intake on muscle or plasma levels in either group. Glutamine demonstrated a marked decrease in muscle concentration in the postoperative group (Figures 5, 6) which was unaffected by nutritional intake. In the normal subjects there was also a decrease in muscle glutamine but to a lesser degree than that seen in the patient group. Arginine, lysine and histadine decreased in muscle following total hip replacement but remained unchanged during bedrest plus semistarvation. (Figures 7, 8).

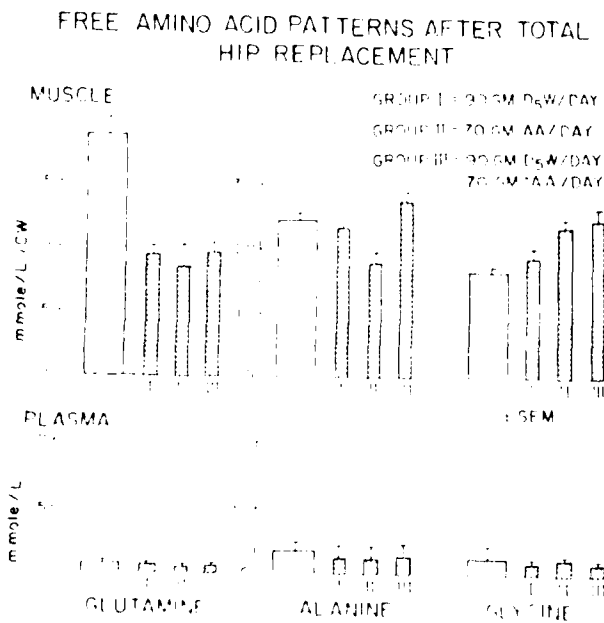


Fig. 5

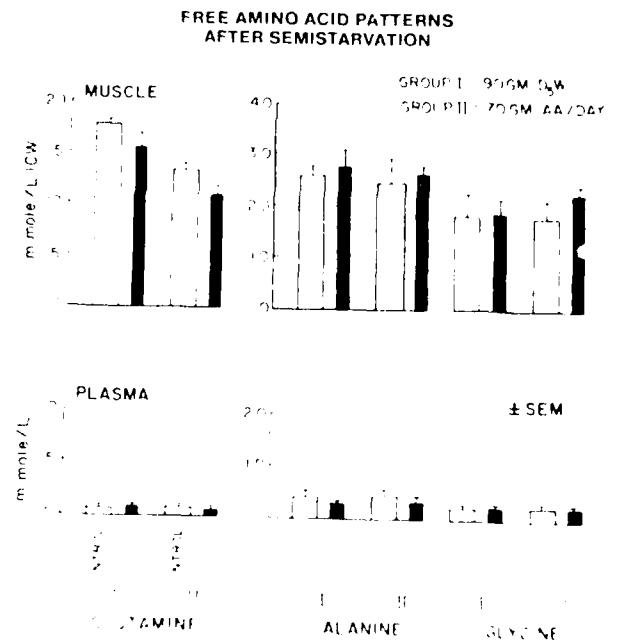


Fig. 6

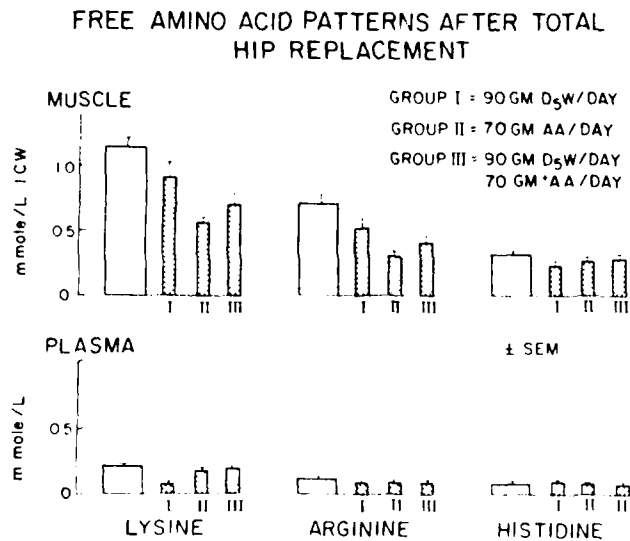


Fig. 7

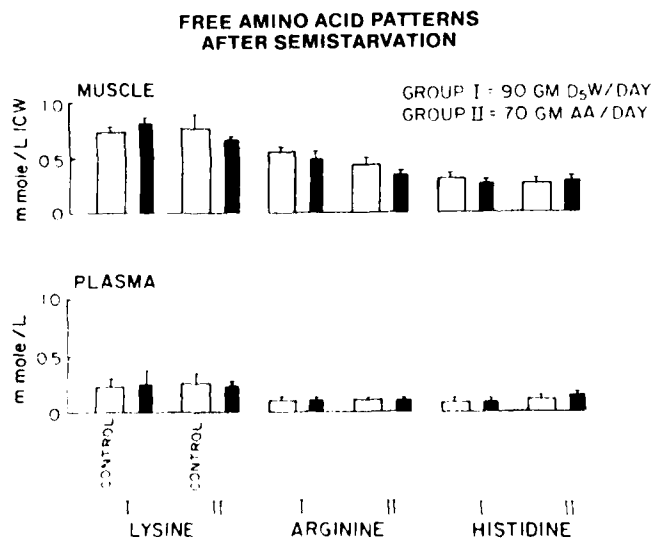


Fig. 8

The most striking finding of the present study was that the "pattern of trauma" is maintained irrespective of nutritional regimen, thus there was no major difference between the three postoperative groups. This would suggest that the hormonal milieu seen in the injury state causes changes in muscle which nutrition can affect in only minor ways. In contrast, infusions of amino acids caused marked elevations of the branched-chain amino acids in muscle in the normal subjects during bedrest plus semistarvation.

c) Muscle High Energy Phosphates

The metabolic response to injury is characterized not only by weight loss and negative nitrogen balance but also by resting hypermetabolism carbohydrate intolerance and increased mobilization of fat. High energy phosphates such as ATP and phosphocreatine (PC) are the immediate source of energy in muscle cells. The formation of ATP in cells requires energy derived from the oxidation of endogenous or exogenous derived fuels. The method of obtaining samples from muscle tissue by needle biopsy in man has opened new possibilities for studying intermediary energy metabolism in muscle tissue. The metabolic picture in certain experimental conditions such as dynamic and static exercise has been explored (6). There is, however, very little information available describing the cellular metabolic changes and energy levels in catabolic conditions. It has been reported that in severely ill patients there was an increase in muscle lactate, a decrease in the PC stores, and also a small decrease in the ATP and total adenine (TA)

pools. In patients with more prolonged severe diseases the biggest change was found in the ATP and TA pools. This decrease was as much as 50% for ATP (7, 8). Also, in patients with chronic obstructive lung disease and acute respiratory failure the concentrations of ATP and PC were low in intercostal and quadriceps muscle (9). As the patients responded to nutritional support and respiratory care the concentration of energy rich compounds in both muscle groups rose significantly.

We have studied changes in high energy phosphates of thigh muscle in varying degrees of resting hypermetabolism and the influence of nutritional support of the patterns observed. Eleven patients before and after total hip replacement were compared to those seen in major trauma and sepsis. All patients received 5% dextrose as nutritional support. High energy phosphates (Figures 9, 10 and 11) were not significantly changed in muscle after total hip replacement, or moderate injury, while lactate and pyruvate increased.

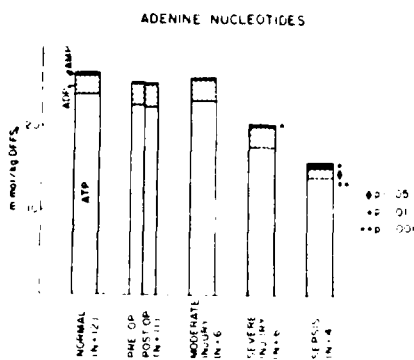


Fig. 9

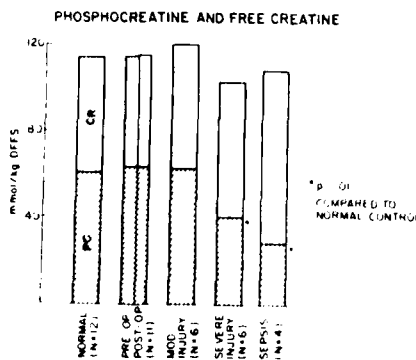


Fig. 10

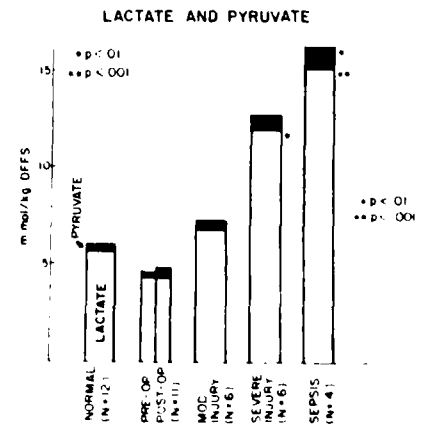


Fig. 11

Increased degrees of hypermetabolism, such as severe trauma and sepsis, were associated with a reduction of muscle ATP and PC, while AMP, free Cr, lactate and pyruvate rose. Alterations in the ATP-ADP-AMP in muscle suggest a low energy charge following severe trauma, especially if accompanied by sepsis. This suggests an imbalance between energy and energy generation. Actual energy generation may be heightened, but still inadequate to meet requirements. Tissue high energy levels may thus be the cellular express of the catabolic state.

The effect of glucose on the changes observed were investigated by a) studies of postoperative patients and normal subjects that received 70 gms/day amino acids alone for 4 days and b) administration of total parenteral nutrition containing 600 gms/day glucose. Figure 12 shows the relation of skeletal muscle ATP to injury in patients receiving 90 gms/day of glucose. Figure 13 also shows a proposed relationship between glucose intake, degree of injury, skeletal muscle ATP.

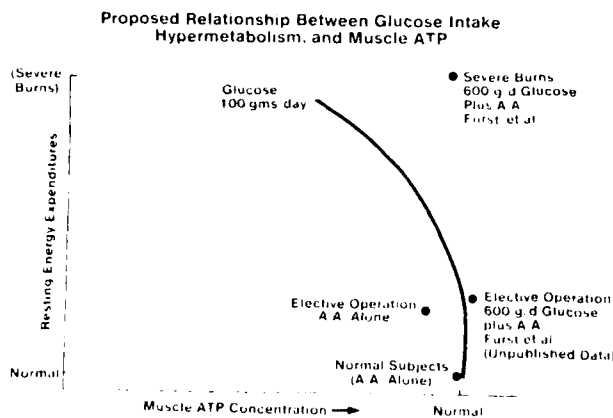


Fig. 12

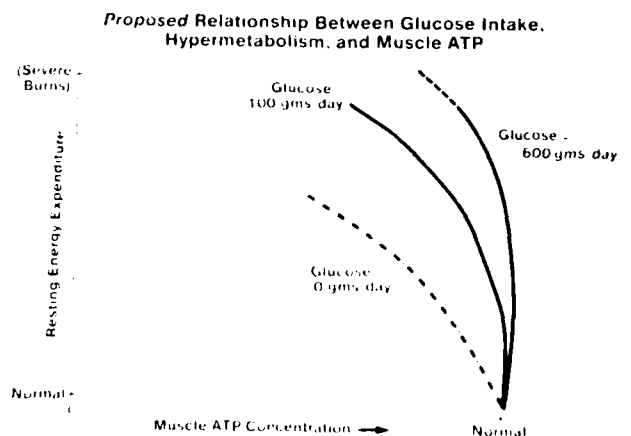


Fig. 13

It is suggested that for any given degree of injury there is a salutary effect of increasing glucose intake on skeletal muscle ATP. Similarly at any given level of glucose intake increasing injury is associated with a decreasing level of ATP. This proposed relationship is remarkably similar to the relationship between glucose intake, phosphocreatine and exercise level. An inverse relationship exists between phosphocreatine level and work load (10). At high work loads the PC concentration decreases rapidly to zero and the contractive capacity of the muscle ceases. When the glycogen store is decreased the PC level at a given work level is lower than when the same work load is carried out with the glycogen store intact.

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PROGRESS REPORT

EFFECTS OF NUTRITION ON METABOLIC DEMAND AND VENTILATORY RESPONSES

We have observed the development of respiratory distress (1) secondary to administration of parenteral nutrition containing amounts of glucose that exceed caloric equilibrium. A high carbohydrate load would be expected to be associated with increased CO_2 production as a combined result of oxidation and lipogenesis. However, as shown in Figure 1, the increased CO_2 production associated with an increased carbohydrate intake is a function of the patient's clinical status.

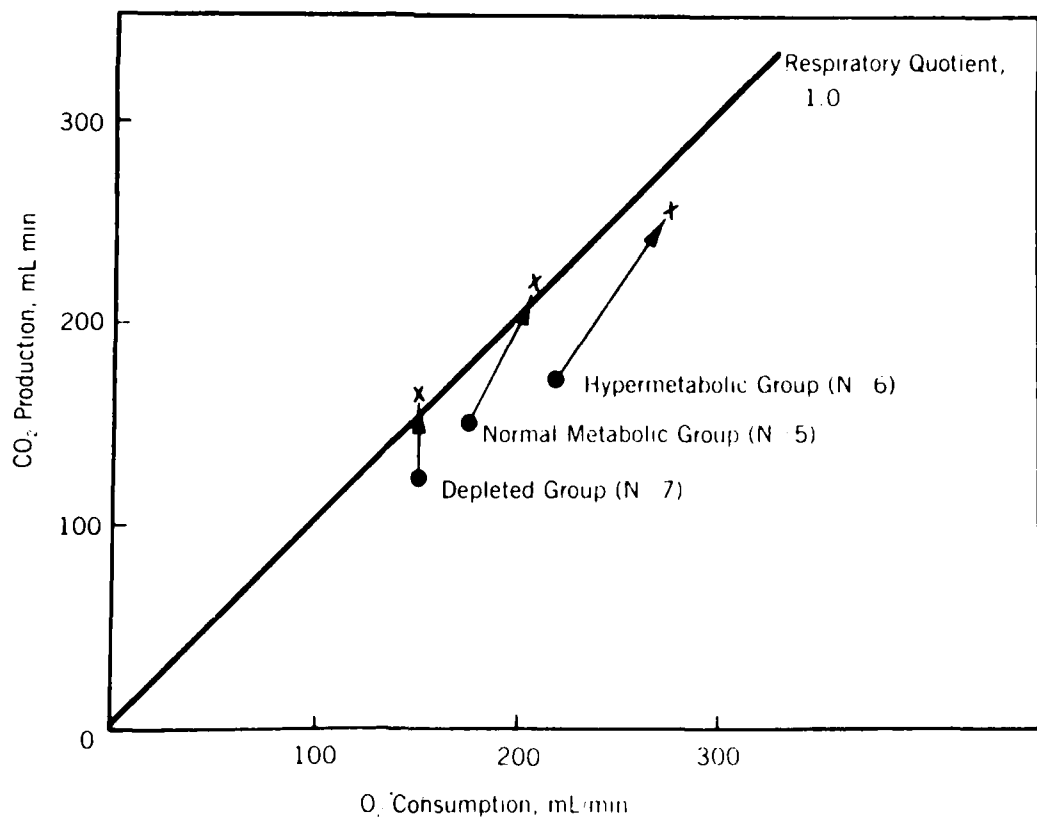


Fig 1.—Gas exchange prior to (circle) and during (X) total parenteral nutrition

Fig. 1

relating diet to skeletal muscle work performance has emphasized the beneficial effect of carbohydrate. This may not extend to the hyper-metabolic patient in whom fat seems to be a preferential fuel. In developing models for the study of nutrition and work performance, the clinical status of the patient must be carefully defined. These studies indicate that glucose loading in both the depleted and hypermetabolic patient is associated with increased ventilatory demands due to increased CO_2 production.

Since high glucose intakes given during administration of total parenteral nutrition (TPN) has been demonstrated to increase CO_2 production, we investigated the pulmonary and metabolic effects of substituting fat emulsions for glucose.

Changes in CO_2 production and O_2 consumption induced by TPN using either (a) glucose as the entire source of non-protein calories, or (b) fat emulsions as 50% of the non-protein calories, were analyzed in patients with either chronic nutritional depletion or acute illness secondary to injury and/or infection. In 5 patients with chronic nutritional depletion, shifting from the lipid to the glucose system caused a 20% ($p < .025$) increase in CO_2 production which resulted in a 26% increase in minute ventilation ($p < .01$) (Table I). This agrees with data collected on acutely ill patients in which those receiving the glucose system had a significantly higher CO_2 production than those receiving the lipid system (179 ml/min/m^2 vs 147 ml/min/m^2 , $p < .01$).

TABLE I
Gas Exchange and Breathing Patterns
In Five Nutritionally Depleted Patients

	V_{O_2} ml/min	$V_{C_{O_2}}$ ml/min	RQ	V_T ml	f CPM	V_E l/min	T_I sec.	Inspiratory Flow ml/sec.
<u>Lipid System</u>								
Mean \pm SD	198	173	.87	290	18.9	5.51	1.34	251
	± 52	± 46	± 0.02	± 75	± 3.6	± 1.9	$\pm .56$	± 121
<u>Glucose System</u>								
	206	208	1.00	379	21.7	7.48	1.17	309
Mean \pm SD	± 56	± 63	.03	99	± 3.6	± 2.6	± 2.9	± 117
% Change	+5%	+20%	+15%	-30%	+15%	+26%	-13%	+29%
P	.NS	.025	.001	NS	NS	.01	NS	.01

In both nutritionally depleted patients and acutely ill patients, the use of fat emulsions in moderate quantities resulted in a significant reduction in CO_2 production and hence in ventilatory requirements. Clinically, the increase in CO_2 production caused by administration of a large carbohydrate load could be a critical factor in the patient with marginal pulmonary reserve. Fat emulsions which are oxidized with an RQ of 0.7 could prove useful in providing nutritional support without undue respiratory stress.

We have recently begun a series of studies aimed at assessing the effect of nutritional support on ventilatory responses. The ventilatory response to carbon dioxide is assessed using our canopy

spirometry system and administering 2% and 4% carbon dioxide. Minute ventilation is measured and related to the arterial P_{CO_2} . The protocol for this study is shown in Figure 2.

Effect of Nitrogen Intake on Ventilatory Drive: Study Design

Studies performed 1) *prior to* and 2) following one week of TPN.

Formula for total parenteral nutrition:

Energy intake = $1.5 \times$ resting energy expenditure

Non-protein calories given as $\frac{1}{2}$ glucose + $\frac{1}{2}$ fat

Nitrogen intake either 7.5 mg/Kcal REE (low N) or
15 mg/Kcal REE (high N)

Each diet given for 1 week, initial diet randomly assigned

Prior to TPN all patients received 5% dextrose solution.

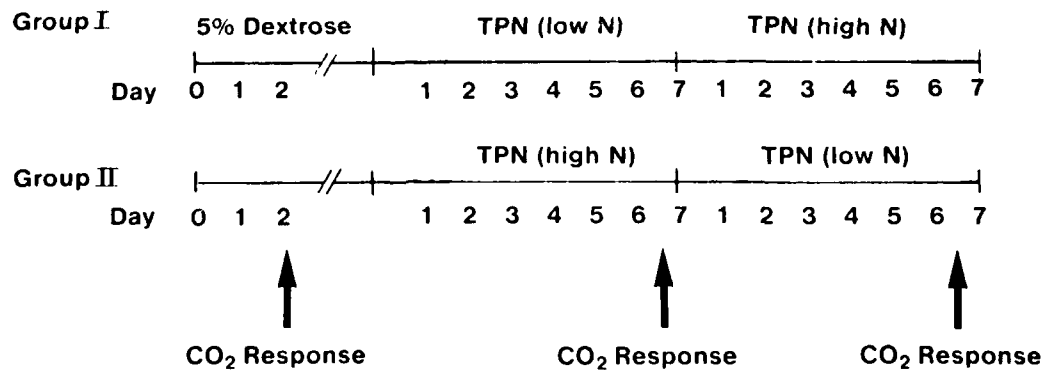


Fig. 2

The first 2 patients studied are illustrated in Figure 3. These results suggested that increased nitrogen intake enhanced ventilatory drive. The effect of protein intake on ventilatory drive appears to be related to the level of the intake and not the duration of administration. Pilot studies have demonstrated that this effect reaches a maximum at 24 hours.

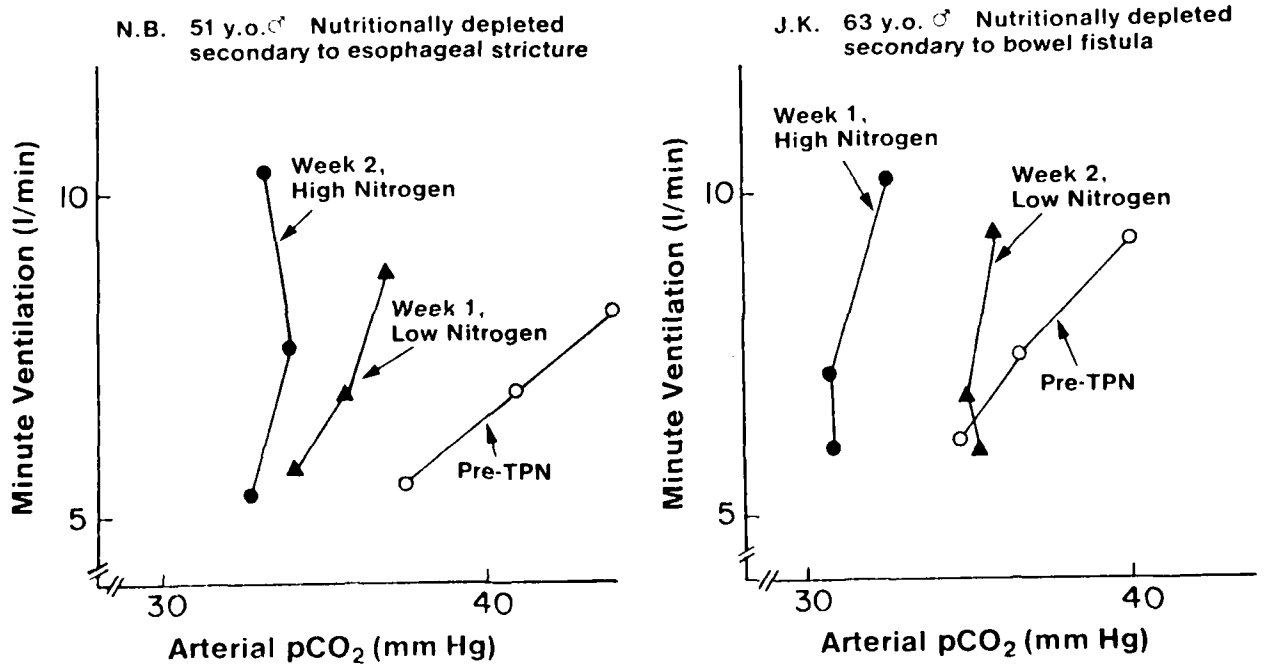


Fig. 3

Figure 4 shows the results of ventilatory responses in 6 depleted patients studied prior to and during administration of TPN.

Effect of Nitrogen Intake on Ventilatory Drive

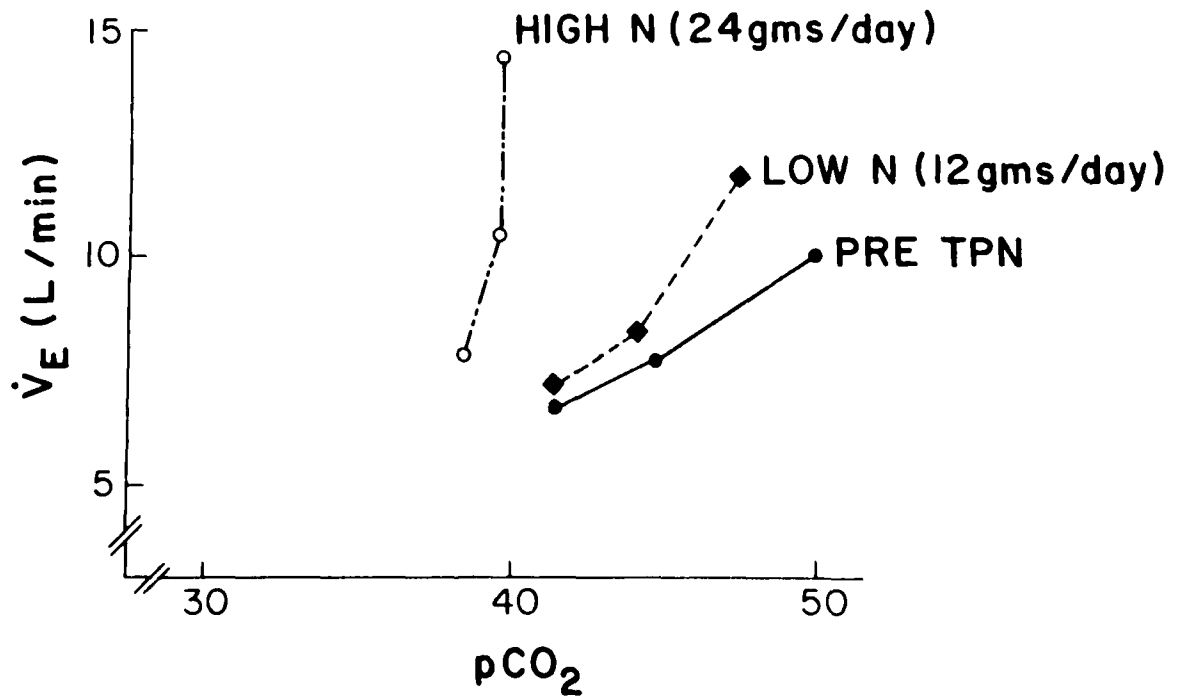


Fig. 4

These preliminary results suggest an increased sensitivity to carbon dioxide with increasing amino acid intake. Our previous results demonstrated that normal volunteers undergoing 6 days of semistarvation

in which 100 gms/day of glucose served as the sole source of calories was not associated with a fall in REE. If a direct relationship between expenditure and ventilatory drive exists as postulated by Doekel (6), then one would expect a fall in ventilatory drive in normal volunteers receiving 100 gms/day of glucose and a preservation of ventilatory drive in those receiving 70 gms/day.

**Parenteral Nutrition and Ventilatory Drive:
 Effect of 5% Dextrose and 3.5% Amino Acids
 in a Normal Subject**

Sequence of Studies

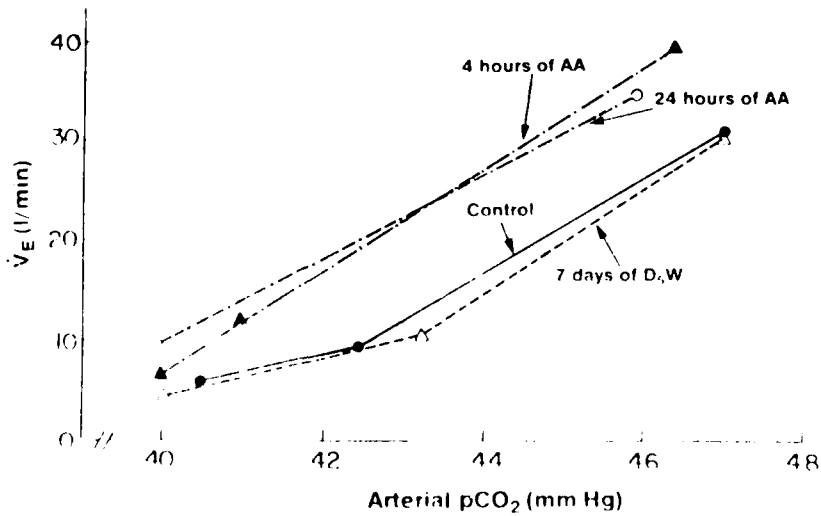
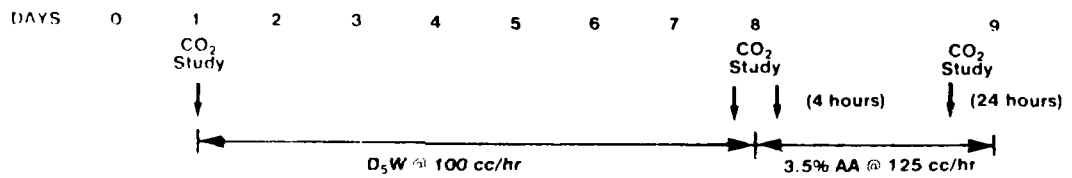


Fig. 5

We examined the effect of amino acid infusions on ventilatory drive in normal volunteers undergoing 7 days of semistarvation in which 100 gms/day of glucose served as the sole nutritional support. Using the canopy system, the ventilatory response to CO_2 was assessed in the postabsorptive state and considered the control run. The volunteers then underwent a 7 day period of semistarvation in which 100 gms/day of glucose was administered (via continuous infusion) as the sole source of nutritional support. The ventilatory response to CO_2 was assessed on day 7 following which an infusion of isotonic amino acids was started (70 gms/day). The ventilatory response to CO_2 was then assessed at 4 and 24 hours. Data for the first normal subjects is shown in Figure 5, on the previous page.

This demonstrates a slight fall in ventilatory responsiveness following 7 days of semistarvation. There is an abrupt increase in the ventilatory response to CO_2 at 4 hours. This effect persists for at least 24 hours.

Data for both normal subjects is shown in Table II on the following page and is expressed as the ratio of change in minute ventilation (V_E)/change in arterial P_{CO_2} (PaCO_2). A decrease in ventilatory drive (as measured by $\Delta V_E/\Delta \text{PaCO}_2$) is seen following semistarvation in both subjects.

(See Table II on the following page)

TABLE II

	Subject #1 $\Delta V_E / \Delta PaCO_2$	Subject #2 $\Delta V_E / \Delta PaCO_2$
Control	3.9	2.6
7 Days of 5% Dextrose	3.8	1.5
Following 4 hours of amino acid infusion	4.6	1.9
Following 24 hours of amino acid infusion	5.3	2.1

With administration of an amino acid infusion for 4 hours, there is an increase in ventilatory drive which persists for at least 24 hours.

As demonstrated in Figure 1, infusions of glucose and amino acids increase metabolic rate in hypermetabolic patients. We have recently observed a case in which the administration of TPN (glucose/amino acids), on the second day after surgery, to a 26-year-old male with multiple fractures resulted in a rise in rectal temperature from 37.6 to 39° C (Figure 6). Resting energy expenditure showed a sustained 23% increase when the nutritional intake was changed from 5% dextrose to TPN. This case demonstrates that the increased metabolic rate associated with administration of TPN in acutely injured patients may be associated with an increase in body temperature.

METABOLIC RESPONSES TO TPN (Glucose/AA)

26 y.o. ♂ - Multiple Fractures
PH 262-87-03
BSA = 2.07 m², Pred.
REE = 2035 kcal/day

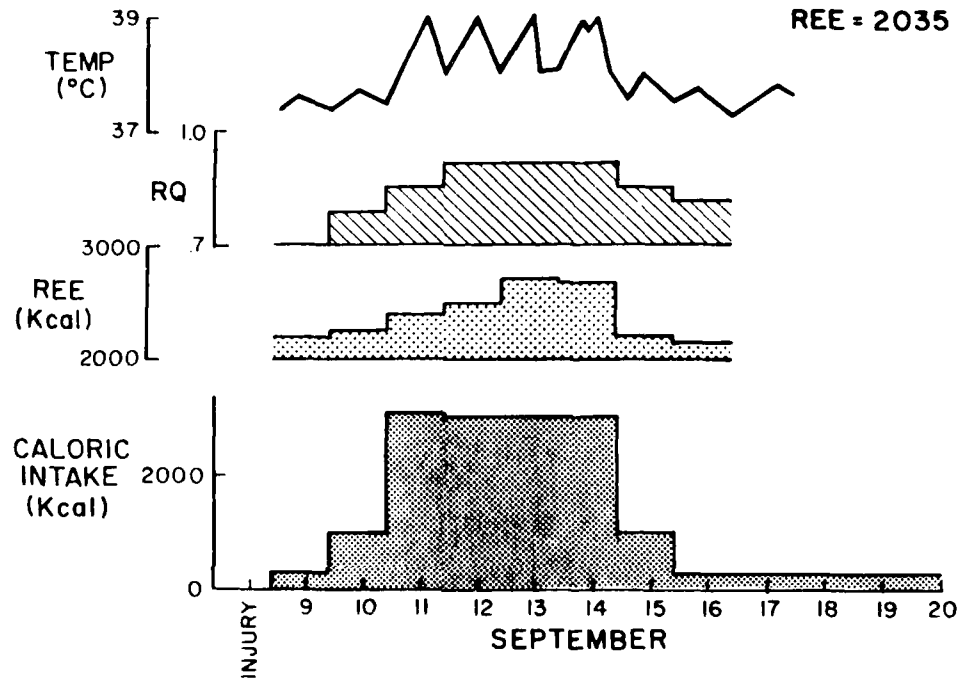


Fig. 6

Since making the observation in this case, we have confirmed this phenomenon in 10 patients undergoing cystectomy.

The problem of fever is often regarded exclusively in terms of infectious disease. However, there is a growing body of information, illustrated by this case, indicating that observations of body temperature has potential value in surgical care beyond its relation to infection (7). The increased body temperature in the case reported here may have been due to an alteration of normal cooling mechanisms (i.e., vasoconstriction of

the skin leading to impaired heat dissipation) or a resetting of central nervous system (CNS) control of body temperature due to glucose loading in an acutely injured patient. In either case, this demonstrates an alteration in heat metabolism in an injured patient because a similar increase in REE during exercise is not associated with an equivalent rise in temperature in normal subjects. It is not clear at the present time whether this phenomenon will prove to be of benefit in patients convalescing from major trauma.

An example of the influence of total parenteral nutrition composed of glucose and amino acids on minute ventilation and arterial P_{CO_2} when administered to a 30 year old male beginning 3 days after sustaining multiple gunshot wounds of the abdomen, is shown in Figure 7.

Effect of TPN (Glucose/AA) on Ventilatory Drive

Ex: 30 y.o. m with multiple GSW of abdomen
Study performed with 40% O_2 , administration of 2% CO_2

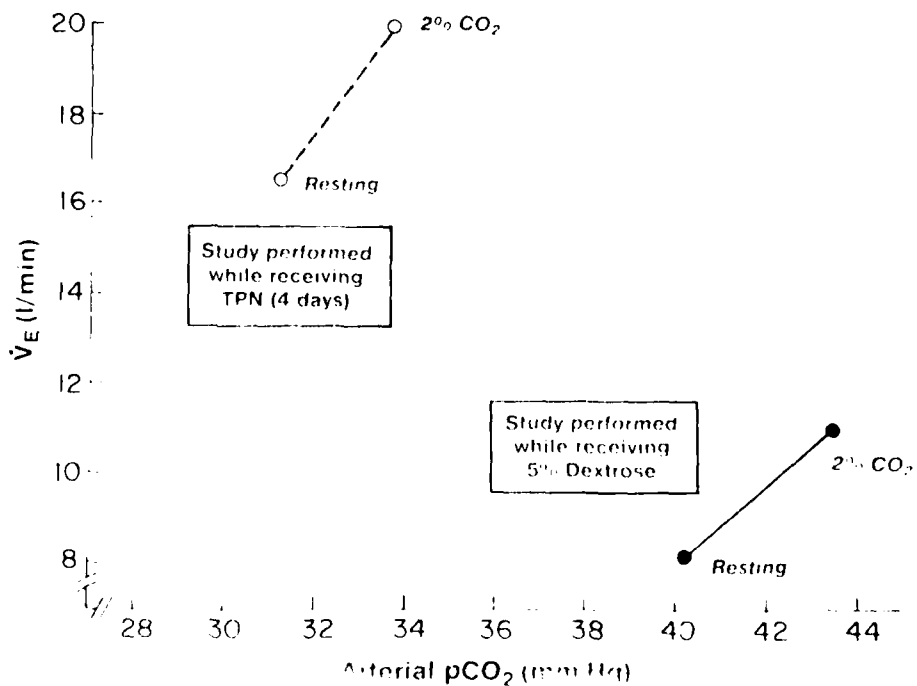


Fig. 7

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PROGRESS REPORT

REGIONAL METABOLISM IN INJURY, SEPSIS AND DEPLETION

The goals continue to be a systematic description of patterns of interorgan movements and regional metabolism of major substrates and hormones in both man and dogs subjected to trauma, sepsis or depletion. Although a variety of regional vascular beds of human, as well as animal, studies are included in the original application, the work in the current year has focused on the human splanchnic exchange. The more specific objectives of this phase of the work relate to the hepatic handling of nutrients in total parenteral nutrition (TPN) with special emphasis on the mechanisms of glucose intolerance in the presence of high carbohydrate loads; the utilization of endogenous fat, with and without, administration of lipid; and, most important of all, an effort to quantitate protein synthesis by the liver.

We have been able to improve our basic protocol which utilizes patients that need TPN who are either acutely injured, septic or depleted. Baseline measurements are made and then a catheter is passed into the hepatic vein under fluoroscopic control. This was originally done using a #7 French catheter, passed via an antecubital vein cut-down, and a catheter of this size had to be removed within a matter of hours. We now introduce a small catheter (smaller than a Swan-Ganz) percutaneously via the internal jugular and leave it in place for 3-4 days. This simple procedure

is repeated after a week of TPN so that we are now able to obtain control values and values during the initiation of TPN, as well as measurements on the 3rd, 4th and 8th day. Thus, the scope of the study has been greatly increased from the original protocol which relied on a single hepatic vein catheterization. We have also added the measurement of blood O_2 and CO_2 content so that we are able to determine the R.Q. of the liver (splanchnic bed) at different times prior to and after the start of TPN.

We are able to study about 1 patient per month and have studied 8 patients to date. Six of the patients were febrile and septic (resting metabolic expenditure 20% greater than the predicted value) and the other 2 were depleted (15% weight loss) with no hypermetabolism at rest. Total parenteral nutrition is administered as hypertonic glucose and amino acids. Energy intake is set at 1.5 x resting energy expenditure.

The 6 septic patients presented a similar picture and will be described together. With the onset of TPN the measured metabolic expenditure increased, as has been previously reported from our unit. In one patient who sustained an abdominal gunshot wound the expenditure started at 53% above predicted and rose to plus 86% after 6 days on fat-free TPN. Nitrogen balance was positive with a cumulative value of 44 grams over 6 days.

Important differences are noted when these measurements are

compared to values in depleted patients. As a rule the increases in metabolic expenditure after starting TPN are less marked and this was true in the 2 depleted patients that were studied. Furthermore, the non protein R.Q. almost always goes well above 1.0 on TPN indicating that glucose is being converted to fat. In the septic patients it is difficult to achieve net fat synthesis and the R.Q. usually approaches but does not exceed 1.0, while protein synthesis, as judged by nitrogen retention, is achieved with greater difficulty. We are in the process of analyzing the results of splanchnic exchange in these 8 patients in order to understand better the differences between septic and depleted patients.

Glucose exchange across the splanchnic bed has been previously studied in our laboratory but our original protocol has been modified and improved. We now include measurements of O_2 and CO_2 content of the arterial and hepatic venous blood samples. In this way splanchnic oxygen consumption and CO_2 production can be calculated before and during TPN where all non-protein calories were provided by glucose. This requires not only A-HV differences across the splanchnic bed but also a measurement of hepatic or splanchnic blood flow. We have continued to use continuous infusion of ICG for this purpose and utilize this flow measurement to quantitate splanchnic exchange of all the substrates involved in nutritional support. Glucose uptake averaged 198 ± 12 mg/min after a week on TPN in the 2 depleted patients but only 123 mg/min in the

1 septic patient whose study has been completed. This difference is also reflected in the higher blood sugar level in the septic patient although all patients on the study received a caloric intake of 1.5 times their measured resting energy expenditure.

The preliminary data on splanchnic gas exchange reveals an increase in oxygen consumption when TPN is started. Most of this is due to increased extraction of oxygen (the A-HV difference goes from 4.5 vol% to 10-12 vol%) rather than an increase in splanchnic blood flow. The highest extractions were noted in the septic patients.

When the human body is receiving a sufficient glucose intake for the non-protein respiratory quotient (V_{CO_2}/V_{O_2}) to be 1.0, it is commonly believed that all tissues are oxidizing glucose for fuel, i.e. that glucose is the preferred fuel by all tissues if it is available, including the small proportion of body tissues which depend upon glucose for glycolysis as a source of energy. The non-protein respiratory quotient of 1.0 should not be thought of as indicating the utilization of glucose throughout the body, but rather as a whole body measurement which represents a balance between fat oxidation (R.Q. = 0.71), glucose oxidation (R.Q. = 1.0) and fatty acid synthesis from glucose (R.Q. of approximately 8.0). It is obvious from the high R.Q. of lipogenesis, that a small amount of lipogenesis (presumably in the liver in man) can obscure some fat oxidation elsewhere in the body and result in an overall R.Q. of 1.0.

Hence, the importance of measuring the R.Q. across the splanchnic bed, as well as the whole body R.Q., when administering a carbohydrate load such as is an integral part of hyperalimentation.

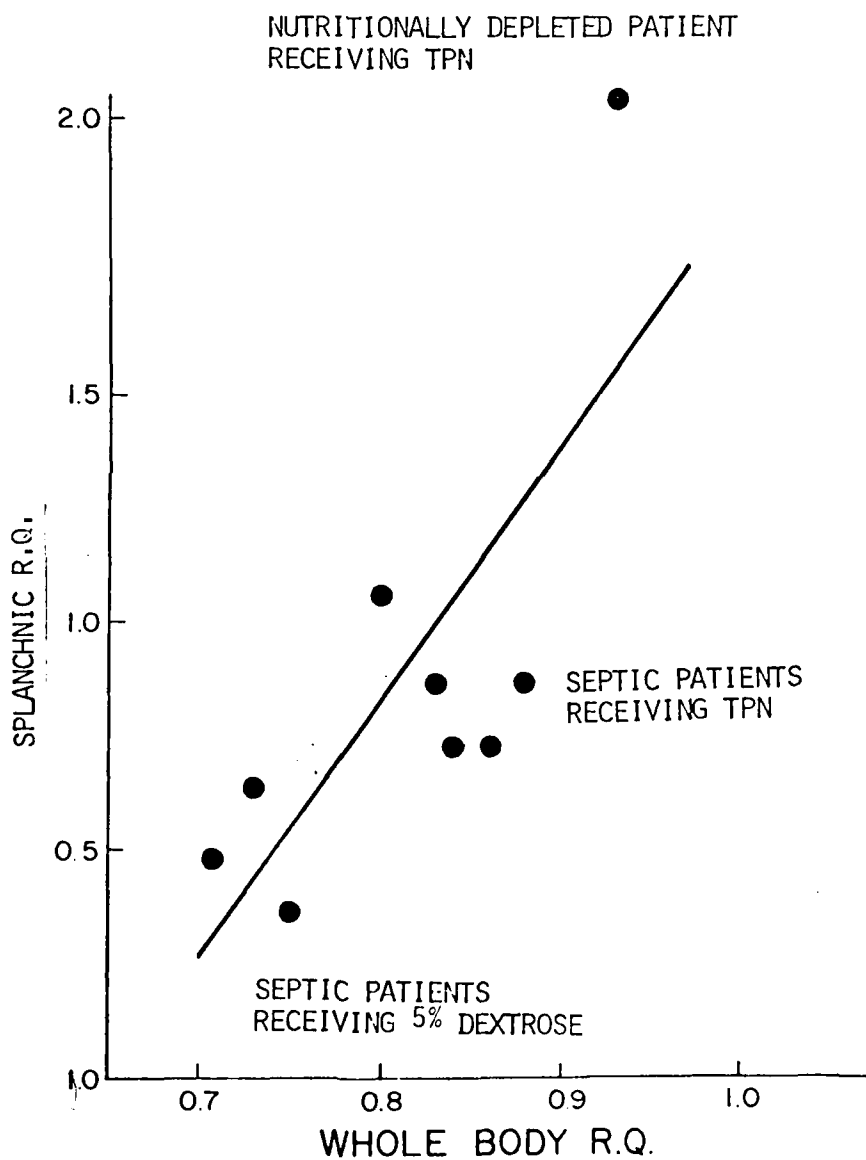


Fig. 1

Figure 1 shows the relationship between the splanchnic and total body R.Q. in 6 surgical patients where data is available to date. Five of these patients were studied during an acute septic episode prior to, and during, the carbohydrate load associated with administering fat-free total parenteral nutrition. The splanchnic R.Q. differs from the whole body R.Q., being lower with the ketogenesis of a low carbohydrate intake and higher when lipogenesis should be present from excess carbohydrate. The single study which we have on a depleted patient receiving comparable high carbohydrate load to that of the septic patients, reveals a much higher splanchnic R.Q. consistent with whole body findings reported to the Army and published during the past year. These previous findings were initially interpreted as indicating that acute injury or sepsis inhibits the conversion of glucose to fatty acids, while at the same time triggering a calorogenic response in some unknown way.

Approximately 10 further cases will be studied during the coming year to see if a large enough study can be completed to establish with statistical significance, the concept presented above. If this can be done, then metabolic correlations will be sought with the following substrates and hormones which will be measured in simultaneous samples of arterial and hepatic vein blood:

- a. plasma and whole blood amino acids.
- b. free fatty acids.

- c. blood urea nitrogen, glucose and glycerol.
- d. acetoacetate and beta-hydroxybutyrate.
- e. glucagon, insulin and catecholamine levels in plasma and urine.
- f. thyroid hormones: T_4 , T_3 and rT_3 .

We are seeking other lines of evidence regarding the difference in the handling of carbohydrate loads between depleted and acutely injured patients. The fact that the latter fails to demonstrate net lipogenesis in the face of a carbohydrate load could be the result of either a) an actual inhibition of lipogenesis or b) an enhanced tendency to burn fat in some tissue. McGarry and Foster* have recently developed evidence from the study of rat liver which may help to explain our finding as being the combined result of both inhibited lipogenesis and accelerated fat oxidation. They report, "High concentrations of malonyl CoA drive lipogenesis and suppress fatty acid oxidation. Glucagon abolishes malonyl CoA synthesis and lipogenesis while stimulating fatty acid oxidation and ketogenesis. The transformation of the liver, from the nonketogenic to the ketogenic mode, is initiated by elevating the glucagon to insulin ratio - independent of the plasma FFA level. This causes glycogen-depletion, reduction of tissue malonyl CoA content, and activation of the fatty acid oxidation machinery."

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PROGRESS REPORT

STUDIES OF LIPID METABOLISM IN INJURY AND INFECTION

I. Clearance of Fat Emulsion in Trauma and Sepsis: A Three-Staged Lipid Clearance Test

Introduction

This study examines the influence of trauma and sepsis on the capacity to remove an intravenously administered fat emulsion from the bloodstream. The advisability of using fat as a substantial portion of non-protein calories in any nutritional regimen depends in part on the patient's capacity to clear the emulsion from the bloodstream. This study also addresses the question of impaired lipid disposal mechanisms as an etiology for the hypertriglyceridemia, which often accompanies sepsis. The measurement of the fractional removal rate (K_2) and maximal clearing capacity (K_1) with the staged lipid clearance test also provides a unique opportunity for the kinetic analysis of lipid clearing mechanisms.

Methods

Thirteen normal volunteers and 16 surgical patients were studied. The surgical patients fall into three subgroups: Major trauma - 6; trauma plus multiple transfusions - 4; and, sepsis - 6. The normal subjects were studied in the postabsorptive state, while surgical patients received 5% dextrose intravenously. Trauma patients were studied 36-72 hours following injury, while septic patients were studied during the course of their infection.

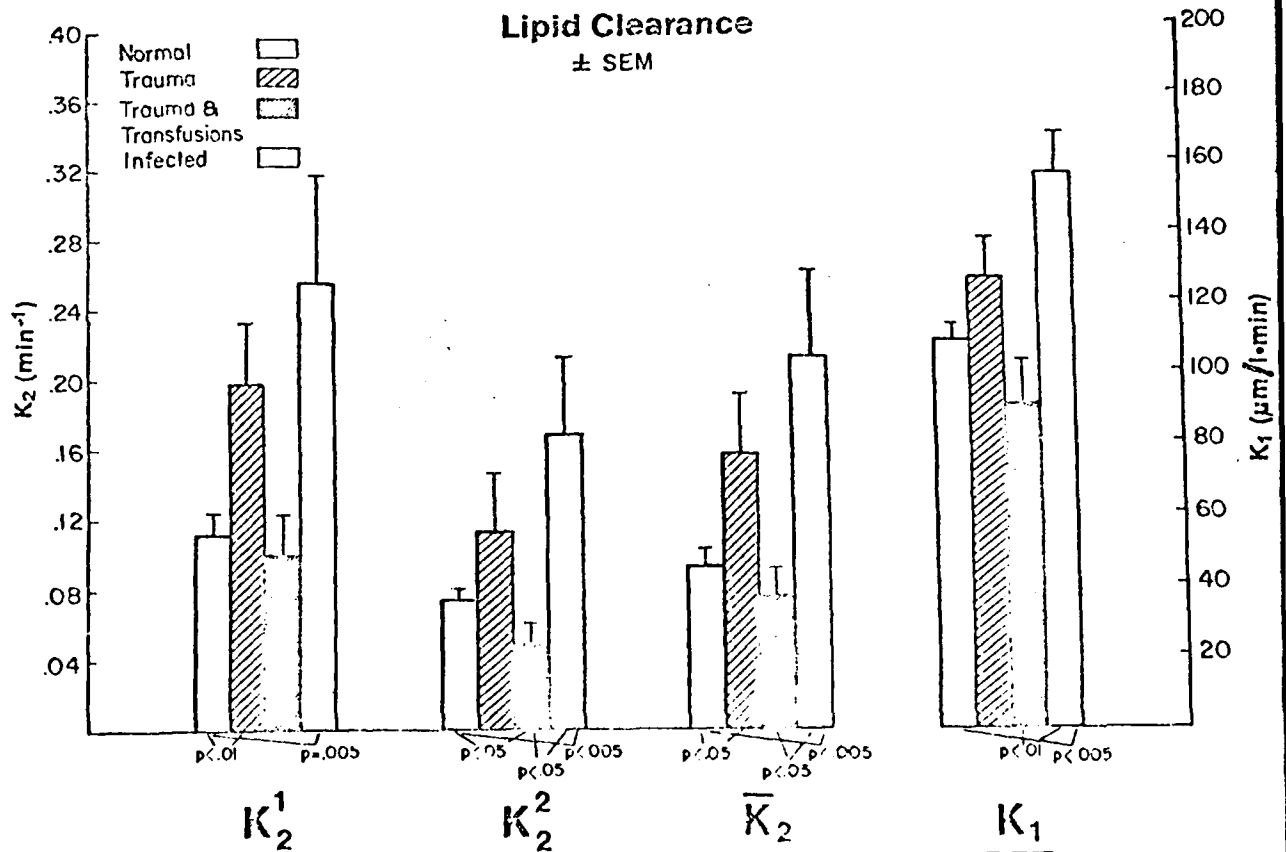
A three-staged infusion of Intralipid^R 10% was used, delivering triglyceride at rates of 60, 120, and 400 $\mu\text{mol}/\text{min}$ for one hour each in that sequence. Blood samples for nephelometric determination of exogenous

triglyceride concentration were obtained prior to the infusions, at 10 minute intervals during the last 30 minutes of the first two infusions, and at 10 minute intervals during the entire third infusion. Steady state plasma concentrations are observed during the slower infusions, indicating first order kinetics for removal, and a linear rise in plasma concentrations is observed during the final infusion, indicating zero order kinetics for removal. The calculations are as follows:

$$K_1 \frac{\mu\text{mol}}{(\text{l min})} = \frac{\text{Infusion rate } (\mu\text{mol/min})}{\text{Plasma volume (l)}} \cdot \frac{\Delta(\text{TG}) (\mu\text{mol/l})}{\Delta t (\text{min})}$$

$$K_2 (\text{min}^{-1}) = \frac{\text{Infusion rate } (\mu\text{mol/min})}{(\text{TG}) (\mu\text{mol/l}) \cdot \text{Plasma Volume (l)}}$$

Results



The results are graphically displayed in the figure on the previous page, where:

K_2^1 = K_2 , calculated from slowest infusion

K_2^2 = K_2 , calculated from intermediate infusion

K_2 = Average from both infusions

In all but one case, higher fractionated removal rates were observed during the slowest infusion than were observed during the intermediate infusion. This observation was confirmed when 4 infusions were performed with the sequence of the first two rates was reversed.

Discussion and Future Directions

We have confirmed an increased capacity for lipid clearance following trauma, as noted by other investigators, on the basis of the single dose intravenous fat tolerance test (IVFTT), (1,2). Greater quantitative changes are seen in fractional, than in maximal, removal rates, indicating that hemodynamic or plasma volume changes may contribute more to the enhanced lipid clearance than actual changes in enzyme activity. Decreased lipid clearance following massive transfusion may reflect a washout phenomenon of either enzyme (lipoprotein lipase), or serum activation (apoprotein CII). The cause of hypertriglyceridemia during sepsis remains unresolved. The septic patients studied herein showed an enhanced, rather than diminished, capacity for removal of exogenous triglyceride.

The dependency of K_2 upon the infusion rate prompted an analysis of our data, based upon enzyme saturation kinetics. With calculations based on the Michaelis-Menten equation, treating emulsion TG as the substrate, and endogenous TG as a competitive inhibition, we were able to accurately predict the observed

ratios of K_2 during the slow:intermediate infusion. In addition, data obtained from high dose intravenous fat tolerance tests (.3 gms TG/KG body wt.) fit well to a family of curves constructed from the integrated Michaelis-Menten equation:

$$S = V \max \cdot t - \ln S/S_0 \cdot K_m + S_0$$

The enhanced lipid clearance observed during sepsis is perplexing in the light of reported decreased postheparin lipolytic activity in the plasma of septic patients and laboratory animals (3,4). We are investigating this further with measurements of tissue lipoprotein lipase and we plan to investigate triglyceride production rates during sepsis, using an isotopic infusion technique.

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II. Tissue Lipoprotein Lipase Activity in Surgical Patients: Influence of Trauma, Sepsis, and Dietary Manipulation

The major pathway by which circulating triglyceride is cleared from the bloodstream and fatty acid is made available to peripheral tissues is by the hydrolytic activity of the enzyme lipoprotein lipase (LPL). The enzyme is located on capillary endothelial luminal surface, requires the presence of an activator (apoprotein CII) on the triglyceride surface (1), and its activity is inhibited by apoproteins C-I and C-III-3 (2). The influence of trauma and sepsis on lipid clearance capacity has been previously described. In this study, we sought to determine whether these changes can be explained by alterations in LPL activity in skeletal muscle and adipose tissue.

The hypertriglyceridemia associated with sepsis has been attributed to defective lipid clearance mechanisms, largely on the basis of studies of postheparin lipolytic activity in plasma. However, lipases other than LPL are released by heparin, and therefore studies of tissue LPL may help to clarify the issue. This study also examines the influence of dietary manipulation on skeletal muscle and adipose tissue LPL activity.

Methods

Subcutaneous fat biopsies from the anterior thigh, and needle biopsies of the vastus lateralis muscle were performed simultaneously in a variety of subjects. Venous blood, obtained at the time of biopsy, was analyzed for

glucose, glycagon, insulin, FFA, and TG concentrations. Trauma patients were studied 3-5 days following injury. All patients were NPO and received either *D5 (500 kcal/day), or TPN (1.5 - 2.0 x measured REE kcal/day) for 3-5 days prior to each study. Depleted patients were studied while on D5 and after 3-5 days of TPN. Normal subjects were studied in the postabsorptive state and after 4 days of 5% dextrose.

For assays of enzyme activity, homogenates (10-20 w/v in sucrose - EDTA buffer) of adipose tissue and heparin-released LPL from muscle specimens were incubated with a TG substrate in the presence of pooled plasma activator. Enzyme activity is expressed as μmol FFA released into the medium per gram of tissue per hour incubation.

Results

		<u>LPLA-Fat</u>	<u>LPLA-Muscle</u>	<u>Insulin $\mu\text{U/ml}$</u>
<u>Normal</u>	PA	0.43 \pm .03 (7)	.023 \pm .003 (3)	8.8 \pm 1.5 (7)
	D5W	0.18 \pm .03 (2)		4.4 \pm 1.6 (2)
<u>Depleted</u>	D5W	0.24 \pm .02 (5)	.058 \pm .011 (2)	5.0 \pm 0.9 (5)
	TPN	2.14 \pm .18 (7)	.036 \pm .005 (2)	41 \pm 13 (7)
<u>Trauma</u>	D5W	0.34 \pm .05 (13)	.039 \pm .004 (8)	10.8 \pm 1.7 (13)
	TPN	0.66 \pm .31 (2)		10.7 (1)
<u>Sepsis</u>	D5W	0.17 \pm .02 (5)	.019 (1)	7.9 \pm 1.5 (5)

mean \pm S.E.M. (number of patients)

Discussion

Four days of semi-starvation in normal subjects resulted in a 60% decrease ($p < .025$) in adipose tissue LPL activity (LPLA). In depleted patients

*D5 = D5W

adipose LPLA was lower than in normal postabsorptive subjects ($p < .01$), probably reflecting their prior state of malnutrition, but increased tenfold during TPN ($p < .001$). Trauma patients had higher activity in adipose tissue than diet-matched normal subjects, associated with higher insulin levels, and they showed a less marked increase with TPN and no increase in insulin. The small number of patients studied in the trauma/TPN group precludes any definitive conclusion at this time. In general, adipose tissue LPLA was well correlated with plasma insulin levels ($r = .70$, $p < .005$). In individual patients, there is a tendency for a reciprocal relationship between muscle and adipose tissue LPLA, except for septic patients, where the activity was low in both tissues. Plasma TG concentrations among the septic patients studied (2.2 ± 0.7 mmol/l) was significantly elevated as compared to normal, postabsorptive subjects (1.1 ± 0.1 mmol/l).

These data suggest that low tissue LPLA, resulting from impaired lipid clearance, contributes to the hypotriglyceridemia associated with sepsis. The enhanced lipid clearance associated with trauma is probably related primarily to hemodynamic or plasma volume alterations, as no major increases in LPLA are noted. Muscle and adipose tissue LPLA appear to be reciprocally related such that triglycerides are largely channelled to adipose tissue for storage in the fed state and to muscle for oxidation in the starved state. Insulin is a major regulator of adipose tissue LPLA.

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III. Effect of Total Parenteral Nutrition on Free Fatty Acid Metabolism in Trauma and Sepsis

Introduction

Elevated plasma levels of free fatty acids (FFA) are often observed following mechanical (1), or thermal (2), trauma. This substrate represents an important energy source in these states, as well as during starvation in normal man. Low tissue carnitine levels, resulting in impaired fatty acid oxidation and necessitating continued breakdown of muscle for energy substrates have been implicated in the prolonged catabolic state, seen in clinical sepsis (3). This study examines the FFA kinetics in various groups of surgical patients and the changes occurring during administration of TPN.

Methods

Nutritionally depleted, injured and infected patients were studied while receiving D5 (500 kcal/day), or TPN (1.5 x REE kcal/day) with non-protein calories supplied as either hypertonic dextrose (glucose system), or as dextrose and Intralipid^R 10%, each providing one-half of non-protein calories (lipid system). Nitrogen intake was fixed. Free fatty acid turnover and oxidation were determined by measuring plasma FFA specific activity and the appearance of ¹⁴C₂ in expired air during a 70 minute period of constant

infusion of ^{14}C -palmitate. These techniques have been described in detail in the previous application.

Results

FFA Kinetics

		<u>Concentration</u> $\mu\text{mol/l}$	<u>Turnover</u> $\mu\text{mol/min}$	<u>Oxidation</u> (% of given dose expired within 390 minutes)
<u>Depleted</u>				
D ₅ W	n = 4	922 \pm 117	996 \pm 70	22.0 \pm 2.0
TPN (lipid)	n = 12	388 \pm 25	588 \pm 110	12.4 \pm 0.9
TPN (glucose)	n = 11	400 \pm 65	666 \pm 100	7.5 \pm 1.2
<u>Trauma or Sepsis</u>				
D ₅ W	n = 15	664 \pm 54	1090 \pm 186	23.3 \pm 1.0
TPN (lipid)	n = 9	411 \pm 76	683 \pm 70	16.9 \pm 2.8
TPN (glucose)	n = 14	742 \pm 96	742 \pm 96	8.9 \pm 1.8

mean \pm S.E.M.

Discussion

All patients on D₅ had high FFA concentrations and met their energy demands largely by fat oxidation. Depleted patients showed a relationship between FFA concentration and turnover, similar to that reported in normals (4). In injured and infected patients, turnover was increased out of proportion to concentration, indicating increased plasma clearance of FFA in these patients. The increased clearance was further accentuated during TPN, and showed up as well in depleted patients during TPN with either system. The decrease in FFA oxidation correlated well with the glucose load, a subject to be taken up in the next project summarized. The septic patients studied herein behaved

in a similar way to the trauma patients with respect to FFA kinetics. Therefore, trauma and sepsis patients have been included here as one group. These data do not confirm the concept of a limitation in fat oxidation in septic patients.

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IV. Inhibition of Fat Oxidation by Carbohydrate

Introduction

Our previous studies indicate that depleted patients respond to carbohydrate loading above energy equilibrium with a shift towards glucose as the major substrate fuel utilized. Net fat oxidation is markedly suppressed and lipogenesis becomes prominent as the RQ approaches, or exceeds, 1.0. In contrast, patients who are acutely ill secondary to major injury, or infection, demonstrate continued net fat oxidation and their RQs remain well below 1.0.

This investigation was undertaken to determine whether the latter response is a reflexion of persistent oxidation of endogenous fat, or a suppression of unidirectional lipogenesis, either of which would result in a greater degree of net fat oxidation.

Methods

Fourteen nutritionally depleted, and 22 acutely ill, patients were studied. The nutritionally depleted patients suffered from chronic gastrointestinal disorders that precluded oral alimentation, but these had no evidence of acute illness or infection. Trauma patients had either suffered severe accidental injury, generally involving two or more organ systems, or had undergone a major operative procedure associated with significant hypermetabolism. Septic patients were entered into the protocol on clinical grounds and infection was later confirmed by positive blood culture, or subsequent drainage of feacely purulent material. Trauma patients were studied during the later flow phase of injury.

Fifty-nine isotopic palmitate infusions were performed. Prior to each infusion, the patients had been stabilized on intravenous diets with the carbohydrate intake varying from 6-35 kcal/kg/day. A primed constant infusion of albumin-bound ^{14}C -palmitate was used: .7 uCi/min for 70 minutes in 47 infusions; and, .2 uCi/min for 240 minutes in 12 infusions. The technique and calculations have been previously described. Free fatty acid oxidation was calculated as follows:

$$\text{FFA ox. (mmol/min)} = \frac{{}^{14}\text{CO}_2 \text{ s.a. } t_{\infty} \times \text{CO}_2 \text{ prod. (mmol/min)}}{\text{FFA s.a.}}$$

$^{14}\text{CO}_2$ s.a. t_∞ was measured during the long infusions, after priming the secondary CO_2 pool with 3-5 μCi of $\text{NaH}^{14}\text{CO}_2$, and was calculated during the short infusions as follows, by the rate at which isotopic equilibrium was reached:

$$^{14}\text{CO}_2 \text{ s.a. } t_\infty = \frac{^{14}\text{CO}_2 \text{ s.a. } t_n - ^{14}\text{CO}_2 \text{ s.a. } t_0}{1 - e^{-k(t_n - t_0)}} + ^{14}\text{CO}_2 \text{ s.a. } t_0$$

Results

Gas exchange data sufficient for analysis was available for 14 depleted patients and 11 acutely ill patients. Nutritionally depleted patients demonstrated a 28.9% use in CO_2 production and 2.3% use in O_2 consumption, when TPN with amino acids and dextrose was administered (total calories = 1.5 - 2.0 x measured REE) after previously receiving a 5% dextrose infusion (500 kcal/day). Acutely ill patients showed a 44.5% rise in CO_2 production, and a 15.3% rise in O_2 consumption. The RQ rose from .77 to .97 in the former group and from .72 to .90 in the latter group. Therefore, the patterns described in the introduction were reproduced among the patients included in this study.

During the long infusions, $^{14}\text{CO}_2$ s.a. t_∞ could be calculated during the first 70 minutes, as with the short infusions, and then actually measured later in the infusion after the $\text{NaH}^{14}\text{CO}_2$ priming dose. The difference between the calculated and measured values in 12 cases was only $5.4 \pm 1.7\%$ of the measured values, speaking for the validity of the method of calculation.

The rate of oxidation of circulating FFA is best correlated to carbohydrate intake: Depleted $r = .74$, $p < .005$; trauma $r = .55$, $p < .01$

In both groups, there is suppression of FFA oxidation with increasing carbohydrate intake. However, the slopes (depleted $-.11$, trauma $-.06$) do differ significantly ($p < .025$) indicating that suppression of FFA oxidation by carbohydrate occurs less readily in the injured and infected group.

Discussion and Future Directions

This study demonstrates that the continuing net fat oxidation in acutely ill patients who have been provided with high carbohydrate intake is associated with continuing unidirectional FFA oxidation. Data from this study (not presented here) also indicates that unidirectional lipogenesis may be inhibited, but these results are inconclusive thus far.

Examination of the gas exchange data reveals that carbohydrate loading in the acutely ill patient is associated with not only continued fat oxidation, but also a significant calorogenic response, which is not seen in the depleted patients. The concept of a calorogenic effect occurring as the result of an increase in plasma FFA concentration is not new (1) and, in fact, the calorogenic action of catecholamines has been attributed to their effect in mobilizing FFA (2). It has recently been shown that a rise in plasma FFA concentration is associated with an increase in O_2 consumption only in the presence of catecholamine stimulation. These authors suggest that the activation of cAMP may facilitate a waste oxidation, or a futile cycling of free fatty acids (3), and have termed this concept the "free fatty acid hypothesis". In this regard, it is interesting to note that acutely ill patients respond to carbohydrate loading with a further rise in an already elevated free norepinephrine excretion (4), whereas depleted patients show

no significant change. Also, mobilization of free fatty acid from adipose tissue stores is not readily suppressed during the course of severe injury or infection. Acutely ill patients have both a higher rate of FFA production and a greater degree of sympathetic nervous system activity (as evidenced by urinary free norepinephrine excretion) during TPN, when compared to depleted patients.

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