Influence of Total Parenteral Nutrition on Fuel Utilization in Injury and Sepsis

J. ASKANAZI, M.D., Y. A. CARPENTIER, M.D., D. H. ELWYN, PH.D., J. NORDENSTRÖM, M.D., M. JEEVANANDAM, PH.D., S. H. ROSENBAUM, M.D., F. E. GUMP, M.D., FACS, J. M. KINNEY, M.D., FACS

Total parenteral nutrition with hypertonic glucose/AA solutions given to eighteen nutritionally depleted patients resulted in a rise in the respiratory quotient (RQ) from 0.83 to 1.05 ($p < .001$), while oxygen consumption ($\dot{V}O_2$) increased only 3%. Excess glucose in depleted patients was converted to fat as evidenced by an RQ greater than 1.0. Administration of a similar glucose load to fourteen hypermetabolic patients (injury/infection) resulted in a rise in RQ from 0.76 to 0.90 while $\dot{V}O_2$ increased 29% ($p < .001$). In hypermetabolic patients, even with administration of glucose in quantities above energy expenditure, there was still ongoing utilization of fat for energy, resulting in a RQ significantly less than 1.0. Excess glucose under these circumstances is apparently converted to glycogen while fat stores are utilized to partially meet energy needs. Septic and injured man seems to preferentially utilize endogenous fat as an energy source. Administration of a large glucose load to hypermetabolic patients does not totally suppress the net fat oxidation as it does in depleted patients. Rather there is an increase in $\dot{V}O_2$, continuing oxidation of fat and apparently an increase in the conversion of glucose to glycogen.

THE NORMAL RESPONSE to a carbohydrate load in excess of energy expenditure is a rise in the nonprotein RQ to 1.0 or greater. This indicates that the main substrate being oxidized for energy is glucose. A nonprotein RQ above 1.0 indicates conversion of glucose to fat. Nutritionally depleted patients receiving total parenteral nutrition (TPN) given as a hypertonic glucose/amino acid mixture respond to excess glucose similarly to normal subjects.[9] We have recently reported a case[2] in which a carbohydrate intake of twice the resting energy expenditure, given to an infected, hypermetabolic patient, resulted in a nonprotein RQ which remained below 1.0. This indicates that there was continued utilization of endogenous fat for energy, even though the carbohydrate intake was over twice the energy requirement. The excess carbohydrate intake appeared to be associated with massive glycogen deposition, increased O_2 consumption and increased excretion of urinary norepinephrine. Thus, high intakes of glucose in a hypermetabolic patient may constitute a physiological stress as well as nutritional support.

The present study examines the influence of parenteral nutrition given as hypertonic glucose/amino acid mixture on fuel utilization and gas exchange in patients who were hypermetabolic secondary to injury or infection.

From the Departments of Anesthesiology and Surgery, College of Physicians and Surgeons, Columbia University, New York, New York

Methods

Patient Selection

Group I: Depleted patients. Eighteen protein-calorie depleted patients who had undergone prior weight loss and who required total parenteral nutrition (TPN) on medical grounds were included in the analysis. Age, Body Surface Area (BSA), diagnosis, and per cent weight loss for each patient are shown in Table 1.

Group II: Septic or injured patients. Fourteen patients with infection or acute injury were studied. The septic patients were febrile and had positive blood cultures and/or evidence of localized intra-abdominal infection. Many septic patients were nutritionally depleted prior to the development of sepsis. The injured patients studied were those cases where the return to normal oral intake was felt to be unlikely for 7 or more days. Total parenteral nutrition was started on the second or third day following injury. Age, sex, BSA and diagnosis are listed in Table 2.

The details of the experiments, including risks, were explained to each patient, usually in the presence of members of his or her family, and written consent was obtained. The protocol of this study has been approved by the Columbia University Institutional Review Board.

Reprint requests: J. Askanazi, M.D., Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York. 10032.

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TABLE 1. *Depleted Patients*

Pt. Number	Age	Sex	BSA	Per Cent Wt Loss	Diagnosis
1	49	F	1.47	12	Crohn's disease
2	59	M	1.70	33	Enterocutaneous fistula
3	32	F	1.33	33	Malabsorption
4	48	M	1.76	25	Pancreatitis
5	58	F	1.40	18	Esophageal achalasia
6	62	M	1.76	18	Esophagogastrectomy and enterocutaneous fistula
7	68	M	1.54	11	Small bowel obstruction
8	41	M	1.39	16	Small bowel obstruction
9	61	F	1.39	23	Small bowel obstruction
10	58	F	1.84	8	Achalasia
11	66	F	1.63	11	Small bowel obstruction
12	71	M	1.76	10	Small bowel obstruction
13	77	F	1.64	22	Jejunal-cutaneous fistula secondary to gunshot of abdomen
14	25	M	1.72	29	Small bowel obstruction
15	76	M	1.54	34	Crohn's disease
16	66	F	1.48	8	Small bowel obstruction Post colon resection
17	85	F	1.48	29	Crohn's disease
18	67	F	1.35	26	Radiation enteritis

Protocol

For the first day, patients were maintained on intravenous 5% dextrose. Resting energy expenditure (REE) was measured,[11,17] and used as a basis for calculating subsequent dietary intake. During TPN, energy intake for both groups ranged from 1.35 to 2.25 times the energy expenditure measured on day 1. Nitrogen balance was measured daily throughout the study in 11 patients in Group I and 11 patients in Group II. Essential fatty acids were supplied with a daily massage of one tablespoon of corn oil.[9] Zinc, copper and iodine were given orally. Apart from trace elements and water *ad libitum*, there was no oral intake. Amino acids were given as 10% Aminosyn (Abbott Laboratories, N. Chicago, Ill.). Gas exchange was measured while receiving 5% dextrose and was repeated after three to five days of administration of total parenteral nutrition.

Balance Measurements

All intake, whether oral or infused, was measured by difference in weights of full and emptied containers. The amounts of each constituent (H_2O), N, etc.) were calculated from the composition obtained from the manufacturer's specifications or by direct analysis in this laboratory, according to established procedures.[4] Energy contents of diets were calculated from published values.[12] Urine, feces and drainages were collected and analyzed for total nitrogen. In addition, urea was determined in urine and drainage, creatinine was determined in urine, and glucose was determined in those urine samples in which qualitative tests (Ketodiastix®, Ames Co., Elkhart, Ind.) were positive. A manual, micro-Kjeldahl procedure was used for digesting samples for total nitrogen determination. Subsequent stages in total nitrogen determination and

TABLE 2. *Septic/Injured Patients*

Pt. Number	Age	Sex	BSA	Diagnosis
1	21	M	1.92	Abdominal abscess following blunt trauma to abdomen
2	57	F	1.64	Abdominal abscess post resection splenic arteriovenous shunt
3	66	M	1.83	Pancreatic abscess
4	59	M	1.52	Abscess following resection of colon carcinoma
5	56	M	1.96	Multiple fractures of pelvis, femur, tibia, fibula secondary to auto accident
6	30	M	2.03	Stab wound chest with development bronchopleural fistula
7	28	M	2.00	Gunshot wound of abdomen, nephrectomy, small bowel resection
8	59	M	1.70	Abdominal abscess, jejunal-cutaneous fistula following colon resection
9	59	M	1.43	Abdominal abscess following perforated carcinoma of the colon
10	67	F	1.96	Abdominal abscess following colon resection
11	48	M	1.42	Radiation enteritis, staph sepsis
12	22	M	1.72	Intra-abdominal sepsis, small bowel obstruction, jejunal cutaneous fistula
13	52	F	1.85	Abdominal abscess following small bowel resection
14	61	F	1.69	Pancreatic abscess

TABLE 3. *Resting Energy Expenditure*

	Actual Mean (Range)	Predicted Mean (Range)	Per Cent Difference $\left(\frac{\text{Actual} - \text{Pred}}{\text{Pred}} \times 100\right)$
Depleted (N = 18)	1173 (954–1742)	1484 (1212–1792)	−21.0
Septic/Injured (N = 14)	1863 (1377–2820)	1632 (1292–2116)	+14.2

analyses of urea and creatinine were carried out with single channel automated analyzers according to the manufacturer's procedures (Auto Analyzer, Technicon Company, Tarrytown, N.Y.) Blood urea nitrogen (BUN) was measured by an automated enzymatic procedure (BUN Analyzer, Beckman Instruments, Inc., Fullerton, Ca.).

Gas Exchange

Oxygen consumption and CO_2 production were measured, with the patients lying at rest, using a rigid lucite head canopy developed in this laboratory.[11,17] This permits frequent measurements of relatively long duration—three to five periods per day of 40–60 minutes each—evenly spaced throughout the 24-hour period, with minimal discomfort to the patient. Resting energy expenditure, total RQ and nonprotein RQ were calculated.[7]

Urinary Norepinephrine

Daily urine collections were analyzed for free norepinephrine (NE). Norepinephrine was adsorbed at pH = 6.5 on a weakly acidic, cation exchange resin (Amberlite CG 50, 200–400 mesh) and then eluted with 4% boric acid. An automatic fluorometric trihydroxyindole method, as described by Viktora et al.[20] was used with slight modifications. An Aminco-Bowman spectrofluorophotometer, Model J4-8202H, was used with a blank substract, solid-state photomultiplier microphotometer, J10-280PM. All samples were analyzed in duplicate. During each run, internal recovery of the standard added to a normal urine sample was also measured. Mean internal recovery averaged 90%.

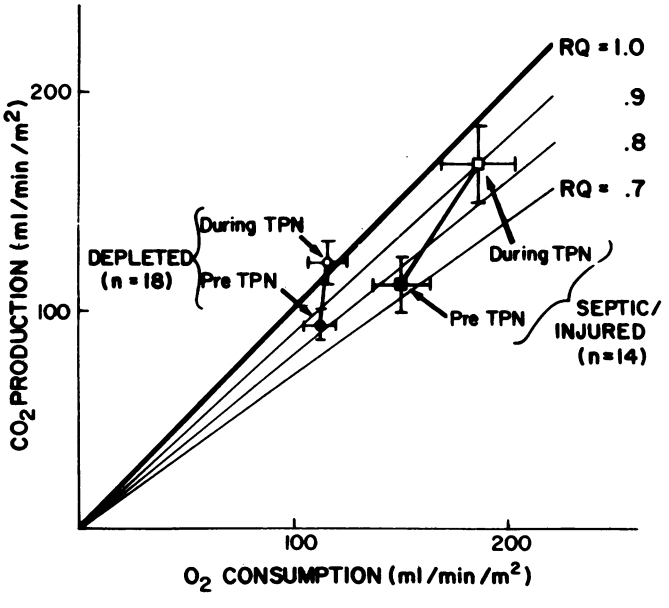

FIG. 1. Alterations in gas exchange secondary to TPN are shown. Clearly 2 different responses are seen. Depleted patients show an RQ > 1.0 with a small increase in $\dot{V}O_2$ while hypermetabolic patients have an RQ < 1.0 with a marked increase $\dot{V}O_2$. Both Groups show a large increase in CO_2 production.

Results

The depleted patients (Group I) had an average energy expenditure 21% below predicted (Table 3). The hypermetabolic patients (Group II) had an energy expenditure of 14.2% above predicted. This is lower than expected and probably reflects the fact that a number of patients developed sepsis after a period of prior nutritional depletion. The carbohydrate intake of the nutritionally depleted patients varied from 1067 to 4150 kcal/day (average 1625). Protein intake varied from 174 to 438 kcal/day (average 308). Carbohydrate intake of the hypermetabolic patients ranged from 1285 to 4259 kcal/day (average 1953) while protein intake ranged from 174 to 418 kcal/day (average 304). Administration of total parenteral nutrition to depleted patients resulted in a 32% rise ($p < .001$) in CO_2 production and a 3% rise in O_2 consumption (Fig. 1). The total RQ rose from 0.83 to 1.05. In the septic injured group, the O_2 consumption rose 29% while the CO_2 production rose 56%. The RQ in this group receiving TPN averaged 0.90 and was never above 1.0.

Substrate intakes and oxidation for the 11 patients in Group I and II in whom N balance was performed are shown in Table 4. In the nutritionally depleted patients, the nonprotein RQ was 1.09 during administration of hypertonic glucose, and there was no net fat oxidation. In the septic/injured group, daily fat oxidation equalled 474 kcal, and there was no fat synthesis although carbohydrate intake markedly exceeded carbohydrate oxidation. Urinary norepinephrine excretion (Table 5) was unchanged during administration of TPN to the depleted subjects but increased

TABLE 4. *Substrate Utilization during Administration of Hypertonic Glucose*

	Intake (kcal/day)			Oxidation (kcal/day)					
	Prot	CHO	Nonprot RQ	Prot	CHO	Fat	Fat Syn	Energy Expenditure of Fat Syn (kcal/day)	REE
Depleted (N = 11)	297	1754	1.09	204	1052	0	427	48	1304
Septic, Injured (N = 11)	322	1997	0.91	257	1160	474	0	0	1891

All measurements made during the third to fifth day of TPN.

markedly, almost threefold, in the septic/injured patients.

Daily changes in substrate oxidation of one patient who was previously reported[2] are shown in Table 6. Initially this patient was septic secondary to an intra-abdominal abscess. As the carbohydrate intake was increased, there was an initial decrease in fat oxidation on day 2, followed by a progressive increase. The rise in fat oxidation was accompanied by a parallel increase in urinary norepinephrine excretion and resting energy expenditure. On day 5 there was 505 kcal of net fat oxidation, even though carbohydrate intake was 4259 kcal/day. On day 17, the sepsis had resolved, there was no fat oxidation, but rather 1194 kcal of fat synthesis. Urinary norepinephrine excretion and REE had decreased.

In four patients who either resolved their sepsis or developed sepsis during administration of TPN, a shift from glucose to fat oxidation with sepsis (Table 7) was noted along with a rise in urinary norepinephrine. In the septic state, 419 kcal/day of fat was oxidized even though carbohydrate intake was in excess of energy needs.

Discussion

Response of Hypermetabolic Patients to Increased Glucose Intake

Resistance to lipogenesis, continued net fat oxidation. The energy intake of total parenteral nutrition in the United States is generally given as glucose and is designed to meet resting energy needs and provide for synthesis of new lean body tissue. Administration of excess calories would be expected to result in lipogenesis. Lipogenesis requires a certain energy expenditure and results in a small increase in O_2 consumption together with a nonprotein RQ which rises above 1.0. The total RQ is somewhat lower than the nonprotein RQ and dependent on protein oxidation. In the nutritionally depleted patients studied here, both the total and nonprotein RQ was greater than 1.0. There was a relatively small (3%) rise in $\dot{V}O_2$ in the depleted patients in response to TPN, presumably reflecting the energy requirement of lipogenesis as well as the specific dynamic action of the amino acids infused.[1] In contrast there was a marked rise (32%) in CO_2 production.

Administration of a large carbohydrate intake in the hypermetabolic patients resulted in an RQ (total and nonprotein) which remained substantially below 1.0 while O_2 consumption rose 29%. Thus even with a glucose intake above energy expenditure there was continued net utilization of fat for energy.

Increased resting energy expenditure and norepinephrine excretion. Administration of hypercaloric glucose amino acid infusions in hypermetabolic patients results in a marked rise in energy expenditure and a rise in urinary norepinephrine excretion. Amino acid infusions alone are associated with a 13% rise in energy expenditure in the postoperative state[1] and cannot explain entirely the marked rise in O_2 consumption observed here. Analysis of the relationship in injured patients between glucose intake and energy expenditure when glucose is infused alone[8] shows a positive (but weak, $0.1 > p > 0.05$) correlation between glucose intake and energy expenditure (slope 0.36 kcal REE/kcal CHO. Additionally there was a positive correlation between glucose intake and norepinephrine excretion.[8] Other studies from this laboratory have suggested an effect of glucose (when infused with AA) is to increase $\dot{V}O_2$ and urinary norepinephrine excretion in hypermetabolic patients.[2,6] Analysis of the relationship of glucose to energy expenditure when infused with amino acids shows a strong positive correlation between glucose intake and energy expenditure ($p < 0.025$, slope = .45 kcal REE/kcal CHO). It should be stressed that the effect of glucose considered here is due to large amounts of glucose given as TPN. Smaller amounts of glucose (90 g/day) when given in addition to amino acids infused peripherally seem to decrease urinary norepinephrine excretion[1] possibly by preventing ketosis.

TABLE 5. *Urinary Norepinephrine Excretion (μg/24 hrs) – Mean ± SD*

	D_5W	TPN	p
Depleted (N = 5)	48 ± 34	62 ± 47	NS
Septic/injured (N = 8)	117 ± 62	338 ± 181	<.05

TABLE 6. *Energy Balance and Urinary Norepinephrine Excretion during Administration of TPN in a Septic Patient*

Day	Intake (kcal/day)		Oxidation (kcal/day)			Energy Expend. of Fat Syn.	REE	Urinary NE	NPRQ	Net Fat Synthesis
	CHO	PROT	PROT	FAT	CHO	kcal/day	kcal/day	(μg/day)		(kcal/day)
1	1512	96	249	550	852	0	1651	164	0.88	0
2	3933	335	297	288	1206	0	1791	163	0.94	0
3	4112	346	233	335	1400	0	1968	264	0.94	0
4	4251	357	209	369	1541	0	2119	253	0.94	0
5	4259	360	186	505	1730	0	2421	281	0.93	0
6–15						Resolution of Sepsis				
16	3996	335	196	0	1839	134	2169	161	1.20	1167
17	4139	347	212	0	1902	131	2245	157	1.19	1142

The analysis included here has partitioned patients into two discrete groups. Previously we have analyzed gas exchange data by dividing patients into 3 groups: 1) depleted (hypometabolic), 2) normometabolic, 3) hypermetabolic.[3] Clearly there is neither two nor three discrete groups of patients but rather a gradation of responses which seem to be based on the degree to which any individual patient is "hypermetabolic." At one extreme end are patients with severe injuries (multiple fractures) and sepsis while nutritional depletion constitutes the other end. The middle ground consists of minor injuries, elective surgery, etc.

Possible mechanisms of action. The balance between insulin and the counterregulatory hormones will determine the response to the hypertonic glucose infusion. Patients who are hypermetabolic with high urinary norepinephrine excretion seem to respond to a glucose load by a further increase in norepinephrine which apparently offsets the rise in insulin which would be expected to occur in response to the glucose. In the patient presented (Table 6) it seemed as though the initial effect of the increased glucose was to decrease fat oxidation presumably by increased insulin secretion. By day 4, however, urinary norepinephrine had increased and apparently offset the insulin effect and restored fat oxidation to its original level. It is unclear as to whether the urinary NE rise was primarily directed at restoring fat oxidation[10,15,18,19] to the pre-TPN level or whether the increase in NE was mediated by another mechanism, and a secondary effect was to promote a relatively high level of fat oxidation, even with a high caloric glucose level.

The effect of glucose on net fat oxidation in the two groups of patients is consistent with studies of peripheral lipolytic rates from this laboratory. Hypermetabolic patients have a high resting value of lipolysis which is minimally suppressed by administrations of TPN. Depleted patients showed a marked decrease in lipolysis when TPN was given at 1.5 × REE.[5,6]

The balance between glucose and fat oxidation is determined by both the hormonal milieu and relative substrate levels.[13,15] Free fatty acid levels are elevated in hypermetabolic states. Although it has been suggested that there is decreased utilization of fat in infection, the opposite seems to be the case.[6] The hyperglycemic hormones stimulate triglyceride lipolysis in adipose tissue and cause plasma FFA to increase while insulin has the reverse effect.[15] Free fatty acids seem to inhibit muscle glucose utilization and oxidation. The suggestion has been made that excessive FFA metabolism might be a key factor underlying the decreased glucose tolerance in diabetes[13,14] and perhaps is also a factor in the "insulin resistance" observed in sepsis. Free fatty acids seem to inhibit glucose transport, glycolysis and pyruvate oxidation while enhancing the conversion of glucose to glycogen.[15] In our previous analysis of the patient presented in Table 6, it was determined that 30 g/kg body weight of glycogen had been stored during the high glucose intake period of days 2–5. Since all of the patients in

TABLE 7. *Shift in Substrate Utilization during Changing Clinical Status in Four Patients Receiving TPN*

	Intake (kcal/day)		Oxidation (kcal/day)			REE (kcal/day)	Non Prot RQ	Urinary NE (ug/day)
	N	CHO	PROT	CHO	FAT			
Septic	311	2066	194	940	419	1553	0.90	297
Nonseptic	321	2082	239	1165	0†	1404*	1.09*	177‡

* $p < .05$.
† $p < .01$.
‡ N = 3.

Group II presented here were on bedrest or extremely limited activity (bed to chair), it is presumed that glucose intakes which were above glucose oxidation resulted in glycogen deposition with only a small amount going to activity energy expenditure. Since glucose oxidation was less than intake, apparently in the septic patient there was conversion of glucose to glycogen, during which time there was also continuing fat oxidation.

The effects of FFA on glucose utilization are linked not only to FFA levels but also to fatty acid oxidation. Free fatty acid oxidation is determined largely by both the intracellular FFA levels, which are in turn proportional to FFA concentrations in plasma as well as intracellular lipolysis, which is regulated by hormone-sensitive lipase.[15] A high level of FFA oxidation will contribute to decreased glucose oxidation leading to increased levels of acetyl coenzyme A (CoA) which inhibits pyruvate dehydrogenase, and citrate which may inhibit phosphofructokinase.[14] Randle[14] has proposed a "glucose/fatty acid" cycle which suggests that increased FFA levels and increased FFA oxidation inhibit glucose oxidation in muscle *in vivo* and impairs the responsiveness of muscle to insulin. Endogenous fat may be a preferential substrate in injury and infection in muscle, while available glucose is utilized for the CNS, red blood cells, white blood cells and renal medulla. The insulin resistance in this state may be secondary to increased fat oxidation, mediated via increased levels of catecholamines. Infusions of hypertonic glucose in this condition may stimulate insulin, suppress fat oxidation and thereby cause a compensatory rise in catecholamines, which tends to restore fat oxidation.

One can advance at least two speculative hypotheses to explain these relationships:

1) One is that in some way a high rate of fat oxidation is somehow required by the hypermetabolic patient. Suppression of this in response to increased glucose administration triggers increased sympathetic drive, as measured by norepinephrine excretion, returning fat oxidation to its original level.[10,15,18,19] In this explanation, the increase in REE is seen as secondary to the need for a high rate of fat oxidation.

2) A second hypothesis supposes that there are quantitative differences in the response of hypermetabolic and normal subjects to glucose loading. There is a reduction in fat oxidation in the hypermetabolic patient which is in the same direction, but not as great, as would occur in the normal. This is because there is already a higher than normal ratio of counterregulatory hormones to insulin. The excess glucose, which cannot now be converted to fat, must be deposited as glycogen. This excessive glycogen deposition triggers increased sympathetic drive resulting in increased oxidation of both glucose and fat. In this explanation, both increased fat oxidation and REE are seen as secondary to the stress of glucose overloading.

Further studies are needed to decide between these and other possible explanations of the metabolic changes in hypermetabolic patients.

Clinical Implication

Increased CO_2 production. In either the case of the depleted patient or the hypermetabolic patient receiving hypertonic glucose/amino acid mixtures, there is an increased CO_2 production (Fig. 1). In the depleted group the increase is essentially a function of the increased RQ, while in the hypermetabolic patients the increased CO_2 production is secondary to both an increased O_2 consumption and an increase in RQ. In either case the increased CO_2 produced will have to be excreted by the lungs. In a patient with compromised pulmonary function, respiratory distress may be precipitated.[2]

The rise in CO_2 production in the depleted patient is most marked when the RQ rises above 1.0 and net lipogenesis occurs. In depleted patients with compromised pulmonary function where energy intakes are given mainly as glucose the total energy intake can be kept at close to resting energy expenditure to avoid the high CO_2 production associated with lipogenesis. Alternately, fat emulsions can replace glucose calories as a source of energy and thereby limit CO_2 production.

In the hypermetabolic patient, the RQ is a poor guide to the increase in CO_2 production. Rather an increase in O_2 consumption occurs with high levels of glucose, with a rather small increase in RQ. The net effect is a large rise in CO_2 production, as high as 75% in some patients. The increase in O_2 consumption may be a cardiovascular stress, while the increase in CO_2 production may be a respiratory stress. Small amounts of glucose (50–100 g) do not seem to cause this phenomenon. Carbohydrate intakes at $1-1.5 \times$ REE which are frequently given as nutritional support to the hypermetabolic patient do seem to be associated with the increased $\dot{V}O_2$ and $\dot{V}CO_2$.

The increase in CO_2 production may be a critical factor in weaning a patient with mechanical ventilatory support. Frequently patients requiring long-term mechanical ventilation will also require nutritional support. The increase in CO_2 production reported here could presumably be a factor in failure to wean. Fat emulsions which are oxidized with an RQ of 0.7 could prove useful under these circumstances.

Summary

Nutritionally depleted patients respond to glucose intake in excess of energy needs by a rise in nonprotein RQ above 1.0, indicating no net fat oxidation but rather net fat synthesis. Administration of similar energy intakes of glucose to hypermetabolic patients is associated with a nonprotein RQ which remains less than 1.0, increased urinary catecholamine excretion and increased energy expenditure, the net result of which is continued fat oxidation. Under these circumstances, large carbohydrate intake may serve as a physiological stress rather than nutritional support. In either the depleted or injured/infected patients, there is a rise in CO_2 production which may compromise the patient with borderline pulmonary reserve.

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