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Effect of Protein Intake on Ventilatory Drive

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Previous studies have demonstrated that if isotonic amino acid infusions were administered at a rate that approximated normal daily protein requirements, a leftward shift of the minute ventilation · Pa_{CO_2} relationship occurred. This study examined the effect of the administration of parenteral nutrition, at a fixed caloric intake and two levels of nitrogen (N) intake, on the ventilatory response to CO_2 in nutritionally depleted patients. The intent was to determine whether increasing protein intake from normal to twice normal requirements would result in a further enhancement of the ventilatory response to CO_2.

Eight patients with nutritional depletion (greater than 10% weight loss) were studied. The resting energy expenditure (REE) was measured during administration of 5% dextrose, using principles of indirect calorimetry. Each patient received parenteral nutrition for a 2-week period. Two diets were examined for a 1-week period each: 1) a high N intake—15 mg nitrogen per kcal REE (approximately 21 g/day), or b) a low N intake—7.5 mg nitrogen per kcal REE (approximately 11 g/day). The initial diet was assigned randomly. Total energy intake was set at 1.35 × REE as measured during administration of 5% dextrose solution. Nonprotein calories were administered as 50% glucose and 50% fat. Breathing patterns at rest and during inhalations of 2 and 4% CO_2 were analyzed using a canopy–computer–spirometer system.

With an increased nitrogen intake there was a significant reduction in resting arterial Pa_{CO_2} from 39.9 to 37.6 mmHg ($P < 0.05$) with no significant change in *p*H. The relationship between $\dot{V}_E$ and Pa_{CO_2} observed during inhalation of CO_2 showed a marked leftward shift ($P < 0.01$), indicating an increased ventilatory sensitivity to CO_2.

These data indicate that increasing the protein component of a fixed caloric intake will enhance the ventilatory response to carbon dioxide. (Key Words: Metabolism: nitrogen; parenteral nutrition. Ventilation: carbon dioxide response.)

IN A PREVIOUS STUDY we observed that parenteral nutrition given as glucose and amino acids resulted in increased ventilation.[1] We suggested that this was due to an increased carbon dioxide production induced by the high carbohydrate loads administered. On occasion, however, we observed a reduction in the resting arterial carbon dioxide tension following the administration of parenteral nutrition given as glucose and amino acids.[2] This suggested that the increase in ventilation that commonly was observed following administration of TPN was at least partly due to an enhanced ventilatory chemosensitivity. Studies performed in our laboratory on normal subjects who had received a 7-day infusion of 5% dextrose solution[3] demonstrated that the infusion of an isotonic amino acid solution enhanced ventilatory drive during room air breathing and resulted in a leftward shift of the minute ventilation · Pa_{CO_2} relationship. It appeared that if amino acids were infused at a daily rate that approximated N requirements, ventilatory sensitivity was enhanced. This study examined the effect of a change in N intake from normal to twice normal levels (or *vice versa*) during isocaloric administration of parenteral nutrition; we also examined the extent to which this effect could be observed in the malnourished patient.

Methods

PATIENT SELECTION

Eight patients with nutritional depletion (defined as greater than 10% weight loss), who required TPN on medical grounds, were studied. Physical characteristics, weight loss, and diagnosis are listed in table 1. None of the patients in this group had evidence of sepsis, diabetes, renal or hepatic dysfunction, or had undergone surgery within the previous 3 weeks; it was considered unlikely that any of them would be able to return to oral intake in less than 2 weeks.

PROTOCOL

The patients were admitted to the Surgical Metabolism Unit and maintained on a 5% dextrose solution for 24 to 48 h. Daily measurements were made of O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), and N excretion during this period. Resting energy expenditure (REE) was calculated using principles of indirect calorimetry.

The study was designed for a 2-week period, during which time the patient received parenteral nutrition according to first one and then the second of two dietary regimens. Each regimen was administered for 7 days. One included a high N intake = 15 mg N/kcal REE (a);

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TABLE 1. Characteristics of Patients

Patient	Age	Sex	Height (cm)	Actual Weight (kg)	% Weight Loss	Diagnosis
1	33	M	180	61.6	20%	Status postcolectomy for ulcerative colitis
2	69	M	168	73.3	18%	Status postcystectomy for bladder cancer
3	63	M	197	74.5	10%	Status postesophagogastrectomy for cancer
4	57	M	166	54.1	21%	Status post-Billroth II; gastric outlet obstruction
5	50	M	182	66.5	11%	Stomach carcinoma
6	59	M	175	63.7	30%	Bowel infarct, jejunocutaneous fistula
7	75	F	140	51.6	16%	Status postcolon resection; small bowel obstruction
8	68	F	155	36.1	28%	Celiac disease
M ± SD	59.3 ± 13.2		168 ± 15	60.2 ± 13	19.3 ± 7	

the other, a low N intake = 7.5 mg N/kcal REE (b). The initial diet was assigned randomly. After 5 to 7 days on one diet, measurements were taken; then the process was repeated with the alternate diet. In three patients, the study protocol was administered for a second 2-week period. Total energy intake was set at 1.35 × REE as measured during the administration of 5% dextrose. The nonprotein calories were administered as 50% glucose and 50% fat. The patients received approximately 11.2 and 21.1 g of N on the low and high N diets, respectively. The nitrogen intake was administered as either Aminosyn (Abbott Laboratories, North Chicago, Illinois) or Neopham (Cutter Laboratories, Berkeley, California). In all cases the composition was kept constant throughout the study. Total calorie intake was 1,891 kcal/day on the low N diet and 1,967 kcal/day on the high. The dextrose and amino acids were administered on a continuous basis, while the fat emulsion was given over an 8 h period (8:00 A.M. to 4:00 P.M.) each day.

The details of the experiments, including risks, were explained to each patient, usually in the presence of his or her family. Written informed consent was obtained. This study was approved by the Institutional Review Board, Health Sciences Center, Columbia University, New York, N. Y.

MEASUREMENTS

Breathing patterns were measured in the supine position using a canopy–spirometer–computer system. This system has been described in detail[4] and consists of a 40 l head canopy connected to a spirometer and a Prime 350 computer. The canopy is a rigid transparent head chamber with a neck seal, ventilated by a continuous 40 l/min air stream that passes through CO_2 and O_2 analyzers for measurement of gas exchange. The spirometer connected to the canopy provides a breath-by-breath record of lung volume changes. Spirometry and gas exchange data are acquired and processed by the digital computer. Air flow to the canopy is controlled to provide a stable spirometer baseline position. Algorithms for quantifying each breath and determining tidal volume (V_T), frequency (f), minute ventilation ($\dot{V}_E$), inspiratory and expiratory time (T_I, T_E), and mean inspiratory flow (V_T/T_I), at evenly spaced points in time, are executed by the computer. An accuracy of ±10 ml in tidal volume measurement is achieved for breathing frequencies in the range of five to 40 breaths/min. The program excludes all tidal volumes below 50 ml, since they are considered too small to represent a breath.

Measurements were taken only when a patient's level of O_2 consumption and CO_2 production achieved a stable value. CO_2 was introduced into the canopy at concentrations of 2 and 4%, using carefully calibrated Matheson valves. A mass-spectrometer confirmed that the concentration in the canopy was correct at 2 or 4%. Measurements made during room air breathing were taken over 15 to 20 min, while those made during the administration of carbon dioxide were performed over steady state periods of 5 to 10 min. Arterial blood gases were drawn from an indwelling radial artery catheter at each condition. Measurements of ventilation during room air

TABLE 2. Changes in Resting Ventilation and Arterial Blood-Gas Composition

	*p*H	P_{O_2} (mmHg)	P_{CO_2} (mmHg)	$\dot{V}_E$ (l/min)	V_T (ml)	f (breaths/min)	T_I (sec)
Low N							
Mean ± SD	7.428 ± 0.027	100.0 ± 24.3	39.9 ± 1.8	4.82 ± 2.16	248 ± 74	20.9 ± 2.1	1.19 ± 0.21
High N							
Mean ± SD	7.428 ± 0.028	109.5 ± 39.8	37.6* ± 3.3	5.53 ± 1.75	293 ± 106	19.3 ± 3.3	1.24 ± 0.24

* $P < 0.05$.

breathing and inhalation of CO_2 were made after 5 to 7 days of each of the parenterally administered diets.

Results

We observed no difference in response as a function of initial N intake. The effects of N intake on ventilation, breathing patterns, and arterial blood gases are shown in Table 2. Comparing the two levels of N intake, the results of the high N diet showed the following changes from those of the low N intake. There was no change in arterial *p*H, Pa_{O_2} increased (NS) and Pa_{CO_2} decreased ($P < 0.05$), $\dot{V}_E$ and V_T increased, and respiratory frequency decreased. There were no significant effects between the high and low levels of N intake on these variables or on T_I and T_E, inspiratory duty cycle (T_I/T_{TOT}), or mean inspiratory flow.

The relationship between $\dot{V}_E$ and Pa_{CO_2} during room air breathing and CO_2 inhalation is shown in figure 1. With increasing N intake there was a marked leftward shift in the position of the curve ($P < 0.01$). Thus, at a

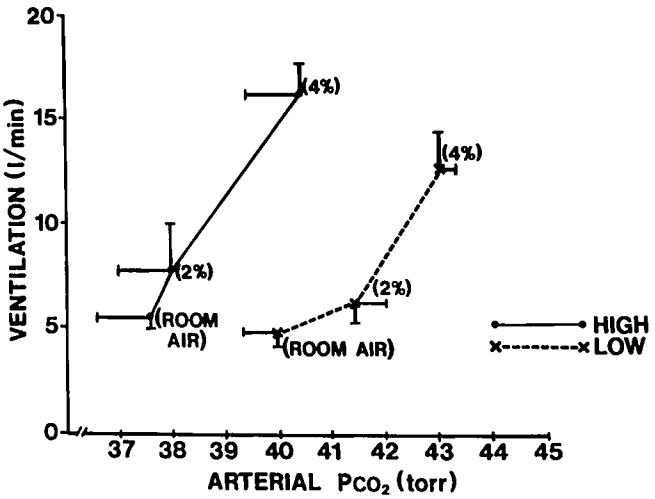

FIG. 1. The $\dot{V}_E \cdot Pa_{CO_2}$ relationship is shown (mean ± SEM). With increasing N intake, there was a leftward shift of the $\dot{V}_E \cdot Pa_{CO_2}$ regression. The concentration of administered CO_2 is noted in parentheses.

Pa_{CO_2} of 40 mmHg, $\dot{V}_E$ with the low N intake was 5.7 l/min in contrast to 15 l/min with the high N intake.

Analysis of the tidal volume *versus* frequency and mean inspiratory flow *versus* inspiratory duty cycle is shown in figure 2. The increase in $\dot{V}_E$ under both conditions was due primarily to an increase in V_T rather than f (fig. 2, *left*). Analysis of the flow timing relationship (fig. 2, *right*), demonstrated that inspiratory flow accounted for the main increase in $\dot{V}_E$ in both groups. The V_T *versus* T_I and T_E relationship is shown in figure 3, which demonstrates that there was little change in V_T *versus* T_I regression with diet, while the V_T-T_E was altered by the high N intake.

Discussion

We have shown previously that, in normal subjects who received 5% dextrose solution as the sole nutrient for 7 days, the parenteral administration of a normal daily N intake resulted in a leftward shift of the $\dot{V}_E$ *versus* Pa_{CO_2} relationship.[3] In the present study, we showed that this phenomenon takes place in depleted patients as well and that it was enhanced by increasing the daily N intake to twice normal. This effect did not appear to be mediated by changes in serum bicarbonate or Pa_{O_2}. The increase in $\dot{V}_E$ at any given P_{CO_2} reflected a markedly increased mean inspiratory flow and tidal volume, while respiratory timing was less affected.

There a number of possible explanations for the data obtained in this study. As we demonstrated in an earlier study, administration of the dietary regimen reported here resulted in an increase in energy expenditure of 9% when the subject changed from 5% dextrose to the low N intake, and a further increase in energy expenditure of 8% when the subject changed from the low to the high energy intake.[5] It seems, therefore, that the specific dynamic action of protein was a dose–response effect, at least with amounts of up to 24 g per day of protein intake. It commonly has been observed that an increase in metabolic rate results in an increase in ventilatory chemosensitivity[6]; this may be one factor in the observed changes. Another possible explanation is that the nutrients administered were effecting neurotransmission.[3] Sero-

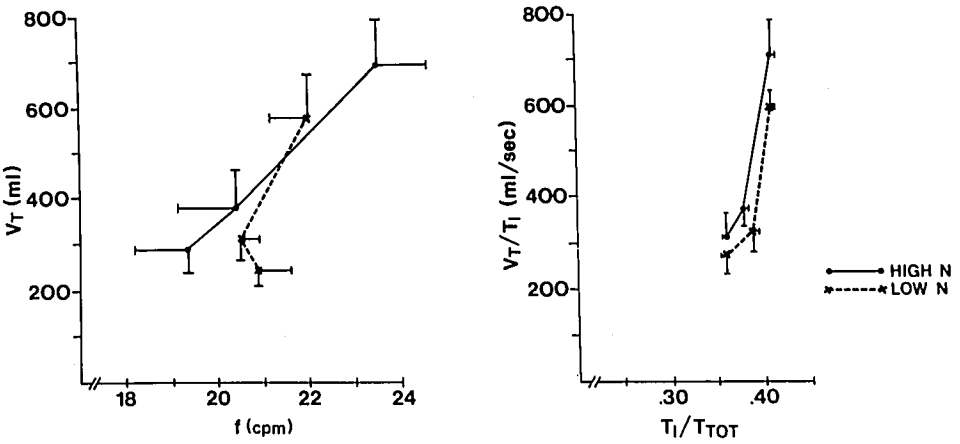

FIG. 2. The tidal volume/frequency and inspiratory flow/inspiratory duty cycle relationship is shown. The changes in $\dot{V}_E$ were due to an increase in tidal volume and inspiratory flow while f and T_I/T_{TOT} were relatively fixed.

tonin is an important neurotransmitter in the control of respiration and has been shown to be directly influenced by amino acid intake.[7] Ketones also have been demonstrated to have important effects on ventilation[8]; however, we observed a marked reduction of plasma ketone levels during the administration of parenteral nutrition and therefore cannot invoke ketosis as a possible explanation for the data obtained. Since the order in which the diets were administered did not affect the results, alterations in respiratory muscle function were not likely to have caused the observed changes.

Clinical Implications

The present study clearly showed that ventilatory drive was enhanced by progressively increasing levels of N intake. Increasing N intake will lead to enhanced protein synthesis and a more rapid restoration of lean body tissue. It is important to emphasize, however, that the increased ventilatory drive observed in this study may or may not be therapeutic; its effects depend on the clinical condition of the patient. In the administration of nitrogen, therefore, it is necessary to consider the cost/benefit ratio between the salutary effects of N on whole body protein synthesis *versus* the effect on the ventilatory drive, as well as other possibly detrimental side effects of high-protein diets.

We have observed occasionally that patients who are receiving high-protein intakes are dyspneic during the administration of CO_2, with increased levels of ventilation, and that they have normal or low Pa_{CO_2} values. Patients with dyspnea have been shown to have increased neuromuscular drive,[9] although the ability of the lung–thorax system to increase $\dot{V}_E$ is limited. Consequently, it is important to be aware of the patient's dietary intake when interpreting CO_2 response curves and Pa_{CO_2} levels.

Recent studies indicate that certain patients have subnormal inborn responses to carbon dioxide.[10,11] If chronic obstructive lung disease develops in such patients, CO_2 retention is likely to occur; if this is the case, administration of a high-protein intake that increases the ventilatory response to CO_2 might be therapeutic.

In patients with respiratory failure who are unable to tolerate high N intakes, parental nutrition should be instituted early. Such patients cannot tolerate crash refeeding programs, since glucose is associated with increased levels of CO_2 production and nitrogen is associated with an enhanced chemosensitivity to carbon dioxide. Therefore both of these nutrients should be administered only in limited quantities to this category of patients. Early institution of parenteral nutrition in modest quantities would seem to be indicated in caring for patients with respiratory failure, particularly those with CO_2 retention secondary to mechanical dysfunction of the lung–thorax system.

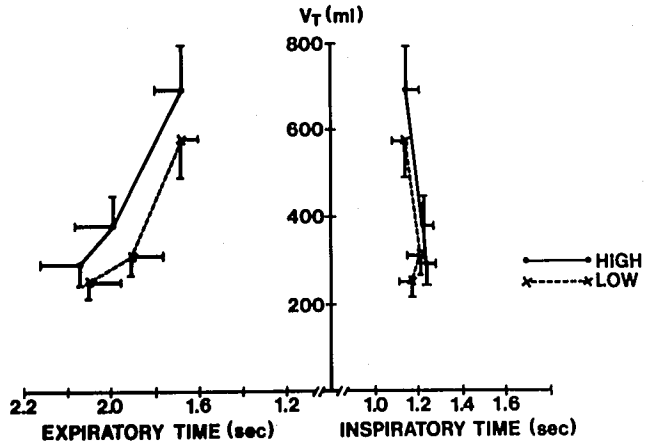

FIG. 3. The V_T/T_I and V_T/T_E relationship is shown. The V_T/T_I relationship was shifted leftward with the high N intake, while the V_T/T_E regression was relatively unaffected.

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