Effects of Protein Intake on Pulmonary Gas Exchange and Ventilatory Drive in Postoperative Patients

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The effects of different protein regimens on pulmonary gas exchange and ventilatory drive were examined in eight postoperative patients receiving inspiratory pressure support ventilation. They were studied during 60 consecutive hours, which included two 12-h periods of high protein intake (33% of total caloric intake provided as protein), each of them being preceded and followed by a 12-h period of standard protein intake (14% of total caloric intake provided as protein). Throughout the study, total caloric intake was 1.5 times the predicted resting energy expenditure. Nitrogen was provided as a 24% branched chain amino acid (BCAA) solution during the period of standard protein intake. During the periods of high protein intake, it was provided as a 24% and a 41% BCAA solution. Pulmonary gas exchange was continuously measured during the second half of each period, with the use of a mass spectrometer system. Measurements of the ventilatory response to CO_2 (FI_{CO_2} 0, 1.5, and 3%) were achieved at the end of each dietary regimen. O_2 consumption, CO_2 production, respiratory quotient, minute ventilation, and Pa_{CO_2} were the same for the three protein regimens. Changing protein intake failed to affect the ventilatory response to CO_2. The authors conclude that, in postoperative patients having inspiratory pressure support ventilation, the administration of a high protein intake does not affect the ventilatory drive and the pulmonary gas exchange. (Key words: Recovery: ventilation. Ventilation: protein intake.)

A HIGH NITROGEN INTAKE with a total caloric intake close to energy expenditure has been proposed to improve nitrogen balance,[1] while avoiding the complications of hypercaloric total parenteral nutrition.[2–4] In addition, Cerra et al.[5] suggested a further improvement in nitrogen balance by the administration of solutions enriched by branched chain amino acids (BCAA).[5]

However, protein intake can modify the ventilatory function in nutritionally depleted patients as well as in healthy subjects.[6,7] Increasing protein intake increases minute ventilation ($\dot{V}E$) and reduces the resting arterial carbon dioxide partial pressure (Pa_{CO_2}), which has been attributed to an enhanced ventilatory drive.[6,7] This effect was observed from the fourth hour after an increase in protein intake[7] and was magnified when a BCAA-enriched solution was used in place of a conventional amino acid

solution.[8] These findings could be clinically relevant in patients with compromised respiratory muscle functions who are unable to properly increase $\dot{V}E$[7] or in patients in the postoperative period of thoracoabdominal surgery, which leads to a decreased efficiency of the respiratory muscles.[9]

Therefore, we examined the effect of different protein regimens on pulmonary gas exchange and ventilatory drive in postoperative patients receiving inspiratory pressure support ventilation.

Materials and Methods

The study was conducted with eight male patients who required 3 days of respiratory and nutritional support after a major surgical procedure. Clinical data are given in table 1. All the patients had normal preoperative pulmonary function tests. None of them had evidence of diabetes, sepsis, hepatic, or renal dysfunction. They were normovolemic and had normal cardiovascular function. This protocol was approved by the ethics committee of our institution, and informed consent was obtained from the patients' nearest relatives.

The patients were tracheally intubated and were undergoing spontaneous ventilation, with a +15 cmH_2O inspiratory pressure support (Siemens Servo C®).

The general outline of the study is shown in figure 1. Each patient was studied during 60 consecutive hours, which included two 12-h high-protein-intake periods (from 0700 to 1900), each of them being preceded and followed by a 12-h standard protein intake period (from 1900 to 0700). Throughout the study, the total caloric intake was set at 1.5 times the predicted resting energy expenditure, calculated according to the reevaluated Harris Benedict formula[10] applied to each patient's ideal weight.[11] During the high-protein periods, protein represented 33% of total caloric intake with a 1-g nitrogen: 50 nonprotein kilocalories ratio. During the standard protein period, protein represented 14% of total caloric intake with a 1-g nitrogen:150 nonprotein kilocalories ratio. Nitrogen was provided as a 24% BCAA standard solution (Totamine®; Cernep Synthelabo) during the standard protein intake periods. During the high-protein-intake periods, nitrogen was provided for each patient in a random order as the 24% or as a 41% BCAA solution (Valinor®; Cernep Synthelabo). The nonprotein calories were given as 50% glucose–50% fat (Intralipid® 20%; Kabi Vitrum). The nutrients were continuously infused with

TABLE 1. Characteristics of Patients

Patient No.	Age (yr)	Height (cm)	Weight (kg)	PREE (kcal/day)	Diagnosis and Surgical Procedure
1	59	169	62	1,395	Esophagus carcinoma; cervicotomy; thoracotomy; laparotomy
2	58	176	92	1,541	Stomach (cardia) carcinoma; thoracotomy; laparotomy
3	49	168	89	1,467	Esophagus carcinoma; thoracotomy; laparotomy
4	57	164	51	1,235	Esophagus carcinoma; thoracotomy; laparotomy
5	53	170	59	1,394	Esophagus carcinoma; cervicotomy; laparotomy
6	55	167	60	1,381	Esophagus carcinoma; cervicotomy; laparotomy
7	67	175	76	1,566	Esophagus carcinoma; thoracophrenolaparotomy
8	64	164	51	1,205	Esophagus carcinoma; cervicotomy; laparotomy
Mean ± SE	58 ± 2	169 ± 2	67 ± 6	1,398 ± 46	

PREE = predicted resting energy expenditure.

an electric pump (IVAC Corporation) through a central venous catheter.

During the second half of each period, oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), respiratory quotient (RQ), $\dot{V}E$, and respiratory rate were continuously measured and recorded with a system using a mass spectrometer (mass spectrometer Perkin Elmer® MGA 1100–microcomputer Kontron® PSI 80). A thorough description and validation of the system has been given in a previous report.[12] The system can be briefly described as follows. Gas samples were drawn from the Y-piece of the patient's breathing circuit to the mass spectrometer and analyzed for inspired O_2 concentration and CO_2 wave form recognition. The latter analysis allowed rejection of artifacted cycles, e.g., coughing. Then, expired gas was sampled from the outlet of a mixing chamber for the measurements of the mixed expired O_2 and CO_2 concentrations. Expired flow was measured by a pneumotachometer. The duration of the entire analysis sequence was about 3 min. The mean values of these parameters were calculated over 6 h. Pa_{CO_2} was measured at the end of each period.

Measurements of the ventilatory response to CO_2 were achieved at the end of each dietary regimen (fig. 1). Carbon dioxide at levels of 1.5% and 3% was introduced in the gas mixture delivered to the ventilator. $\dot{V}E$ and end-tidal P_{CO_2} (PET_{CO_2}) were measured as soon as steady state conditions were achieved at each level of FI_{CO_2}. It took approximately 10 min to achieve a new steady state level.

Results are presented as the mean ± SE and further statistics calculated with the use of analysis of variance with Duncan's multiple-range follow-up tests.[13] Correlations were calculated with the use of regression analysis.

Results

The values of the physiologic variables measured during the three standard protein periods were not statistically different (table 2), and thus were pooled for the comparison with the values measured during high-protein 24% and high-protein 41% BCAA periods.

By comparison with the standard protein period, there were no significant changes in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during both
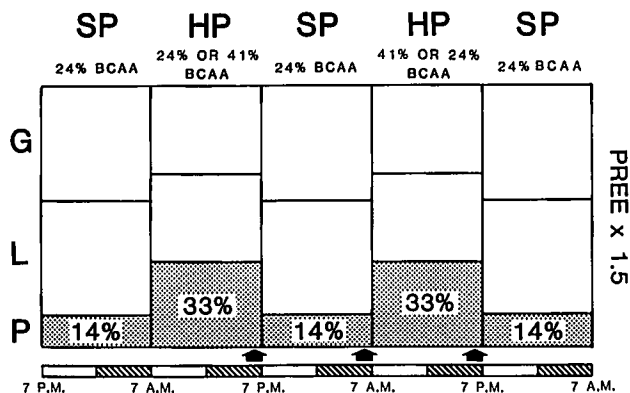

FIG. 1. General outline of the study. The total caloric intake is set at 1.5 times the predicted resting energy expenditure and provided as glucose (G), lipids (L), and proteins (P) as a 24% or 41% branched chain amino acid (BCAA) solution. During the second half of each standard protein period (SP) or high-protein period (HP), $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$, and RQ are continuously recorded with a system with the use of a mass spectrometer. The arrows indicate the time course of the CO_2 tests.

TABLE 2. Metabolic and Respiratory Measurements during the Three Standard Protein (SP) Periods

	$\dot{V}_{CO_2}$ (ml·min⁻¹·m⁻²)	$\dot{V}_{O_2}$ (ml·min⁻¹·m⁻²)	RQ	$\dot{V}E$ (l·min⁻¹)
SP day 1	124 ± 6	141 ± 7	0.88 ± 0.01	10.1 ± 0.7
SP day 2	127 ± 6	146 ± 7	0.87 ± 0.01	10.6 ± 0.6
SP day 3	125 ± 6	143 ± 7	0.87 ± 0.01	9.9 ± 0.5

$\dot{V}_{CO_2}$ = carbon dioxide production; $\dot{V}_{O_2}$ = oxygen consumption; RQ = respiratory quotient; $\dot{V}E$ = minute ventilation.

TABLE 3. Metabolic and Respiratory Measurements during the Three Study Periods

	$\dot{V}_{CO_2}$ (ml·min^{-1}·m^{-2})	$\dot{V}_{O_2}$ (ml·min^{-1}·m^{-2})	RQ	$\dot{V}_E$ (l·min^{-1})	Pa_{CO_2} (mmHg)
SP	125 ± 6	144 ± 7	0.87 ± 0.01	10.2 ± 0.6	32 ± 2
HP 24% BCAA	129 ± 6	151 ± 7	0.86 ± 0.01	10.8 ± 0.6	32 ± 2
HP 41% BCAA	128 ± 6	150 ± 7	0.86 ± 0.02	10.7 ± 0.6	35 ± 2

$\dot{V}_{CO_2}$ = carbon dioxide production; $\dot{V}_{O_2}$ = oxygen consumption; RQ = respiratory quotient; $\dot{V}_E$ = minute ventilation; Pa_{CO_2} = arterial carbon dioxide partial pressure; SP = standard protein period; HP 24%

BCAA = high protein period with a 24% branched chain amino acid solution; HP 41% BCAA = high protein period with a 41% branched chain amino acid solution.

high-protein periods. RQ, $\dot{V}_E$, and Pa_{CO_2} values were the same for the three protein regimens (table 3). Changing protein intake failed to affect the increase in $\dot{V}_E$ induced by the administration of the two levels of FI_{CO_2}, 1.5% and 3% (fig. 2).

Discussion

The results of this study show that increasing total protein intake and/or the amount of BCAA supplied fails to affect the ventilatory response to CO_2 in postoperative patients. These findings are in opposition to some previously published works, which requires further explanation.

First, in some of these studies, changes in protein intake were associated with changes in total caloric intake, and, thus, with changes in the metabolic rate resulting from the thermogenic effect of nutrients.[14] Increasing the metabolic rate, *per se*, enhances the ventilatory response to CO_2.[15] Second, in other studies,[7] proteins were administered without concurrent administration of carbohydrate, which may lead to ketosis, another factor that could

$\dot{V}_E$
l.min^{-1}

FIG. 2. Relationship between minute expired volume ($\dot{V}_E$) and end-tidal partial pressure of CO_2 (PET_{CO_2}) during three levels of CO_2 inhalation (FI_{CO_2}: 0, 1.5, and 3%). Circles: standard protein period (the mean slope ± SE for the eight patients was 1.49 ± 0.25). Squares: 24% BCAA high-protein period (mean slope ± SE: 1.18 ± 0.26). Triangles: 41% BCAA high-protein period (mean slope ± SE: 1.84 ± 0.40). There were no statistically significant differences among the three slopes.

increase ventilatory drive.[16] Third, in the study conducted by Askanazi *et al.*[6] in depleted patients, in which the total caloric intake was kept constant at 1.35 times the measured resting energy expenditure, a leftward shift of the $\dot{V}_E/Pa_{CO_2}$ relationship was observed when the protein intake was increased. Nevertheless, no change in the mean inspiratory flow, a commonly used index of central inspiratory drive, occurred.[17]

In our study, particular attention was paid to minimize changes of the metabolic rate and the CO_2 load induced by the modifications of the protein intake. Thus, the total caloric intake was kept constant at 1.5 times the predicted resting energy expenditure, and $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ values were the same for the three protein regimens. For the same reasons, patients received inspiratory pressure support throughout the study. In postoperative patients, this mode of ventilation takes over the major part of the work of breathing.[18]

In our study, some factors may have interfered with eventual changes in the ventilatory sensitivity to CO_2. First, inspiratory pressure support induces a reduction in the ventilatory drive,[19] which could explain the low values of the slopes of the $\dot{V}_E/PET_{CO_2}$ relationship found in our patients. However, the same mode of ventilation and thus of respiratory mechanical unloading was used during the administration of the three protein regimens and could not have cancelled an increase in the ventilatory drive. Second, a depressive effect of the anesthetic drugs used during the surgical procedure on the CO_2 response could be ruled out because the ventilatory variables (respiratory rate, minute volume) were the same during the three standard protein periods. Third, a recent investigation[20] suggested that the slope of the CO_2 response curve was not linear and was reduced at low levels of Pa_{CO_2}. This factor might have contributed to lower the slope of the $\dot{V}_E/PET_{CO_2}$ relationship in our patients but could not have suppressed a difference in the ventilatory response to CO_2 associated with changes in the protein intake because the initial Pa_{CO_2} was the same from one regimen to the other.

In conclusion, the present study demonstrated that in postoperative patients undergoing inspiratory pressure support ventilation, changing the quality or the amount
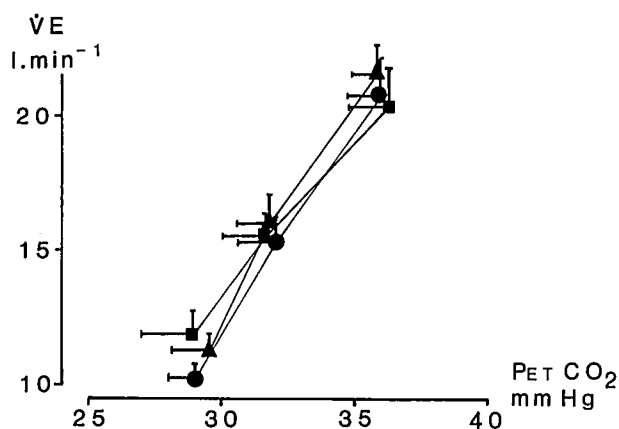
of protein component of a fixed caloric intake failed to affect the pulmonary gas exchange and the ventilatory response to CO_2. From a practical point of view, we conclude that in these patients the potential nutritional advantages of a high protein intake are not cancelled by a deleterious effect on the ventilatory function.

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