Ventilatory and Metabolic Effects of Glucose Infusions

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It has been demonstrated that total parenteral nutrition (TPN) results in increased O₂ consumption (VO₂), CO₂ production (VCO₂) and minute ventilation (VE). TPN consists of a mixture of glucose and amino acids. The individual role of each of these nutrients in mediating these changes has not been well established. To examine the effects of the individual nutrients, continuous infusions of glucose in hypo- and hypercaloric amounts were given to four normal volunteer subjects and four acutely ill patients for a six-day period, with three days on each dietary intake. After each three-day period, gas exchange, VO₂, VCO₂, and ventilatory variables (VE), tidal volume (VT), frequency (f), mean inspiratory flow (VT/TI), inspiratory time (TI) and expiratory time (TE) were measured. With the high carbohydrate diet, CO₂ production increased 18 percent (p>.05) and 7 percent (p>.05) in the normal subjects and the patients, respectively. VO₂ did not change, while the RQ rose. VE rose in parallel with VCO₂, with no significant change in ventilatory sensitivity to CO₂. In light of previous observations, these results suggest that during administration of TPN, the protein component plays a major role in the observed ventilatory changes: a) by bringing about a rise in VO₂, which acts to magnify the effect of an increased RQ on VCO₂, and b) by increasing ventilatory sensitivity to CO₂.

It has been demonstrated that the administration of total parenteral nutrition (TPN), consisting of hypertonic glucose and amino acids, increases minute ventilation (VE) in hospitalized patients previously maintained on 5 percent dextrose solution. This effect is particularly pronounced in the acutely ill patient, who may be least able to tolerate the increased respiratory work load. The increase in VE is largely due to the increase in CO₂ production (VCO₂) associated with high glucose intakes. However, the increases in VE may exceed the changes in VCO₂, especially where acutely ill patients are concerned. The increase in VCO₂ results from a shift in net whole body fuel utilization from fat (respiratory quotient = 0.7) to carbohydrate (respiratory quotient = 1.0), as well as from a thermogenic effect of the nutrients.

The thermogenic effect of TPN (i.e., increased VCO₂) is most pronounced in the acutely ill patient, as are the changes in VE. It is likely that the ability of TPN to increase metabolic rate is at least partially responsible for the stimulus in ventilation associated with this therapy. It has been demonstrated that infusions of amino acids alone will shift the VE:PaCO₂ relationship leftward without any concurrent change in serum bicarbonate level. Thus, the increased ventilatory demand which follows the administration of TPN is likely to result from both an increase in VCO₂ and an increased ventilatory sensitivity to CO₂ (possibly related to the rise in VO₂ that occurs). It is unclear whether and to what extent the increases in VE and VO₂ result from either the amino acid or glucose components of TPN. Furthermore, it has not yet been established whether administering glucose in these amounts to normal subjects will cause changes similar to those observed in acutely ill patients (whose patterns of fuel utilization are altered) with respect to ventilatory sensitivity to CO₂, CO₂ production and possible thermogenic effects. To examine these questions, metabolic and ventilatory measurements were made in both acutely ill patients and normal subjects maintained on intravenous diets with glucose, in hyper- or hypocaloric amounts, as the sole energy component. During the period of hypercaloric glucose infusion, carbohydrate intake was approximately equal to that utilized during administration of TPN, while the hypocaloric infusion was designed to simulate an infusion of 5 percent dextrose solution.

MATERIALS AND METHODS

Four normal subjects and four patients (within 24 hours of major injury) were admitted to the Surgical Metabolism Unit. An infusion of 5 percent dextrose solution at a rate of 100 ml/hr was instituted in the patients upon admission, and in the normal subjects at 7:00 PM of the day of admission. Normal daily requirements of minerals were added to the dextrose solution. During the studies, normal subjects were confined to bed, but the patients were allowed to get out of bed to a chair for brief periods in the afternoon, if their clinical condition permitted.

The only oral intake allowed, in either group, was water, in amounts that did not exceed 30 ml/hr. The body surface area,

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Table 1—Mean ± SEM Patient Characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Wt (lbs)</th>
<th>Ht(cm)</th>
<th>REE</th>
<th>Glucose Intake (kcal)</th>
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<td>Low</td>
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Patients

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<th>Age</th>
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<th>Wt (lbs)</th>
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<th>REE</th>
<th>Glucose Intake (kcal)</th>
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calculated for each patient and subject while he was receiving 5 percent dextrose solution (Table 1), was used as a basis for calculating dietary intake. Intakes on the low and high glucose diet were 79 and 304 gm/m²/day, respectively. This corresponded to an infusion of 2 L per day with approximately 5 percent dextrose (low intake) and 20 percent dextrose (high intake—glucose intake exceeds energy expenditure) solutions. Measurements were performed after three days on the assigned nutritional regimen, following which the alternative regimen was instituted. The initial diet was randomly assigned.

The details of the experiments, including risks, were explained to each subject. The protocol for this study has been approved by the Columbia University Institutional Review Board. Written informed consent was obtained.

Selection of Study Subjects

The normal volunteer subjects selected for the study were all between 22 and 40 years of age, and all within 15 percent of ideal body weight. Patients consisted of a group of men within a similar age range and also within 15 percent of ideal body weight. All patients were hemodynamically and metabolically stable. None had a significant metabolic acidosis or a hematocrit level below 35 percent. In all cases, oral intake was not expected to return for at least seven days, so intravenous therapy was considered medically justified. None of the patients had injuries to the chest wall or pulmonary parenchyma. There was no clinical evidence of pleural effusion, empyema or any fluid collections that could restrict pulmonary movement in the patient group.

Measurements

Measurements were made with the canopy-computer-spirometry system for $V_{O2}$, $V_{CO2}$, and breathing patterns. Measurements were begun when the patient's level of oxygen consumption and carbon dioxide production had achieved a stable value, and were continued for 30 min. Carbon dioxide at levels of 2 percent and 4 percent was introduced into the canopy and measurements were repeated as soon as steady state conditions had been achieved at each level of $CO_2$. It took approximately 10 min to achieve a new steady state level. Approximately 3 ml of arterial blood were sampled through an indwelling radial artery catheter and analyzed for blood gas tensions and pH. Measurements of the ventilatory response to $CO_2$ were taken at the end of each three-day dietary regimen. Gas exchange measurements were performed three to five times daily throughout the 24-hour period. From these data, resting energy expenditure was calculated using principles of indirect calorimetry.

Canopy-Spirometry-Computer System

Gas exchange and ventilatory data were obtained through the use of a computerized gas analyzer/spirometry system. A detailed description and validation of this system has already been published. The subject's head was enclosed in a rigid plexiglass canopy with a neck seal, continuously ventilated with a constant (40 L) inlet flow of room air and maintained at atmospheric pressure by means of an electromechanical flow control system that passes to $CO_2$ and oxygen analyzers for measurement of $V_{O2}$ and $V_{CO2}$. A spirometer of high compliance and low resistance was attached to the rear of the canopy and provided a breath-by-breath record of lung volume changes. Spirometry and gas exchange data were acquired and processed by the digital computer. Airflow to the canopies was controlled to provide a stable spirometer baseline position. Algorithms, for quantifying each breath and determining tidal volume ($V_t$) frequency (f), minute ventilation ($V_e$), inspiratory and expiratory time ($T_i$, $T_e$) and mean inspiratory flow ($V_{FI}$) at evenly spaced points in time, were executed by the computer. The program excluded all $V_t$ below 50 ml, since these were considered too small to represent a breath. The spirometer response to cyclic volume changes of 750 ml, produced by a mechanical pump, has been determined to be within 10 ml of the actual volume for frequencies from 5 to 40 cycles per min.

A real time data acquisition computer system sampled the spirometer position and the $CO_2$ and $O_2$ concentrations of the mixed expiratory gases leaving the canopy. All signals were sampled at 30 Hz. When the breath recognition algorithm located the end of a breath (the end of an inspiratory or expiratory cycle), the values of the sampled variable occurring at the time were stored along with a
time stamp.

Since the flow of room air entering the canopy was maintained at a constant rate, it was possible to calculate the CO₂ output and O₂ uptake of the patient under the steady state conditions of these measurements. These were assumed to be identical to O₂ consumption and CO₂ production. The ventilatory variables were calculated using the spirometer volume displacement and timing data of two successive half breaths.

Statistics

Data within each group was compared using Student's paired t-test; data between the two groups was analyzed using Student's unpaired t-test.

RESULTS

The characteristics of the normal subjects and the patients are shown in Table 1. The two groups were comparable with respect to age, height and weight. All subjects in both groups were men. Carbohydrate intake was 564 j 11 (SE) and 503 j 16 kcal/day on the glucose diet and 2,154 j 109 and 2,016 j 59 kcal/day on the high glucose diet in the normal subjects and patients respectively. This is equivalent to the carbohydrate intake utilized as part of total parenteral nutrition. Resting energy expenditure was 1,443 j 55 and 1,710 j 67 kcal/day, respectively, in the normal subjects and patients.

With the high glucose intake, carbon dioxide production increased in both the normal subjects and patients, by 18 percent (p> .05) and 7 percent (p>.05) respectively. This was due, in both cases, to an increase in the respiratory quotient, while O₂ consumption actually decreased with no changes in resting energy expenditure (Table 2). Arterial oxygenation did not change with dietary intake in either the patients or normal subjects (Table 2). Oxygen consumption and CO₂ production were higher in the patient group during administration of both diets, while respiratory quotient was lower (Table 2). Minute ventilation rose in both groups with the institution of the high glucose intake, in parallel with the rise in CO₂ production (Fig 1). There was little, if any, alteration in ventilatory sensitivity to CO₂ (Fig 2) in the normal subjects, while a small, statistically insignificant leftward shift in position was observed in the patients; there was no change in slope.

At any given dietary intake, the patients had a lower tidal volume and faster respiratory rate (p>.05) than did the normal subjects. The increase in ventilation during CO₂ loading in patients was primarily due to an increase in respiratory frequency (p>.05). In the normal subjects, an increase in VT (p>.05) accounted

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**Table 2—Mean ± SEM Gas Exchange and Breathing Patterns during Room Air Breathing**

<table>
<thead>
<tr>
<th>Gas Exchange</th>
<th>Ventilation</th>
<th>Arterial Blood Gases</th>
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<tbody>
<tr>
<td>VT</td>
<td>V̇CO₂</td>
<td>RQ</td>
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</tbody>
</table>

Normal subjects (N = 4)

| Low | 213 | 176 | .84 | 6.01 | 503 | 15 | 7.41 | 38.4 | 90 | 24. |
| High glucose | ±6 | ±3 | ±.04 | ±.52 | ±76 | ±1.4 | ±.01 | ±.11 | ±2 | ±.9 |
| High glucose | 205 | 207* | 1.01 | 7.35 | 625 | 15 | 7.43 | 37.4 | 94 | 24. |

Patients (N = 4)

| Low | 241 | 201 | .83 | 6.80 | 361 | 19.3 | 7.37 | 43.1 | 77 | 26. |
| High glucose | ±9 | ±8 | ±.02 | ±.92 | ±51 | ±3 | ±.06 | ±.21 | ±5 | ±.3 |
| High glucose | 229 | 214* | .97 | 7.25 | 420 | 18.2 | 7.42 | 41.5 | 77 | 30. |

* p<.05

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**EFFECT OF GLUCOSE INTAKE ON THE VE–V̇CO₂ RELATIONSHIP**

(Mean ± SEM)

Figure 1. Relationship of minute ventilation to endogenous CO₂ production. With increasing glucose intake, the rise in CO₂ production is accompanied by a parallel increase in VT.
Nutritional support is an important therapeutic modality in the care of patients with respiratory failure. Although such support is essential, excessive nutrient intake can be detrimental since it may result in increased metabolic and ventilatory demands. To provide the optimal regimen, it is necessary to delineate the effects of individual nutrients on ventilation and metabolism.

This study demonstrates that increasing glucose intake from a 5 percent dextrose infusion to amounts which exceed energy expenditure and equal the carbohydrate intakes utilized during administration of TPN results in an increased CO₂ production, no change in O₂ consumption, and an increase in minute ventilation with little change in the \( V_E - PaCO_2 \) relationship. There is no significant stimulation of energy metabolism (thermic effect). These changes are far less pronounced than those which occur with the administration of TPN, which includes amino acids as well as glucose in amounts utilized in the present study. The thermic effect contributed by the protein component of TPN magnifies the changes in VCO₂ which result from the glucose-induced rise in the respiratory quotient. The increases in ventilatory sensitivity that occur with the administration of total parenteral nutrition are also likely to be due primarily to the protein component of the solution. It remains to be demonstrated whether glucose will enhance ventilatory drive and have a

**Discussion**

Thus, at any given inspiratory duty cycle, mean inspiratory flow was higher with the high glucose intake.
Effect of Hypertonic Glucose on the Inspiratory Flow-Duty Cycle Relationship

The mechanism for the increase in CO₂ production was due to a shift from fat to glucose oxidation, resulting in an increase in the respiratory quotient. Increasing glucose intake without concurrent amino acid administration did not result in any increases in O₂ consumption or energy expenditure in either normal subjects or patients. In contrast, during the administration of total parenteral nutrition including amino acids, an increase in glucose intake was associated with an increase in energy expenditure. Zwillich et al. demonstrated that a large oral carbohydrate load administered as a single bolus resulted in a rise in O₂ consumption, as well as a rise in the hypoxic ventilatory response. Patients with stable chronic obstructive pulmonary disease, as well as normal subjects, have shown a rise in O₂ consumption and CO₂ production in response to carbohydrate, while arterial CO₂ tension remains normal. In the present study, there was no rise in O₂ consumption, although almost 2,000 kcal/day of glucose were administered. The current study differs from previous studies in that the glucose was given via continuous infusion, thereby allowing glycogen stores to fill gradually. Under these conditions, no thermic effect of glucose was observed.

In stable patients, the increase in CO₂ production is easily managed. However, Covelli demonstrated that, in patients with a fixed minute ventilation, carbohydrate loading may result in respiratory acidosis. In the present study, no increase in arterial PaCO₂ occurred in either patients or normal subjects. Waterman has shown that ventilation increases immediately when bulk CO₂ delivery to the lung is enhanced. Under these conditions, V̇E may increase while PaCO₂ remains constant, as occurred in the present study.

In the study by Zwillich et al., a 1,000 kcal oral bolus of carbohydrate exerted a thermic effect and resulted in an enhanced ventilatory sensitivity to hypoxia. In the present study a continuous infusion of carbohydrate in both normal subjects and patients did not result in a thermic effect or an enhanced ventilatory response by hypercarbia. Thus, the lack of any enhancement of the CO₂ response by the glucose infusion could be related to the absence of any thermic effects. The shape of the CO₂ response curves reported in the normal subjects on the low carbohydrate intake differs somewhat from both the "hockey stick shape" observed during stimulation with low amounts of CO₂ by Lambertson and data obtained in postabsorptive normal subjects in our laboratory. This may be due to genetic and personality factors in the normal subjects studied, or to a phenomenon primarily related to changes in ventilatory control which occur during semistarvation.
The patient group demonstrates a steep CO₂ response curve. Although these patients had no overt pulmonary injury, it is quite likely that there was an element of mild accumulation of lung water and, due to the systemic response to the tissue injury, possibly some atelectasis and clinically unrecognized bronchoconstriction. In patients with bronchial asthma, an enhanced ventilatory response to carbon dioxide has been demonstrated. This phenomenon may be related to that observed in the present study and is possibly related to increased sensitivity of the autonomic nervous system, a phenomenon known to occur in the injured patient. Our studies have demonstrated an enhanced ventilatory response to CO₂ during epinephrine infusions. The increased sensitivity to CO₂ may also be related to the increase in metabolic rate observed in injury and during infusions of catecholamines.

The ventilatory response to low levels of CO₂ inhalation in the normal subjects occurs primarily due to increases in tidal volume during administration of either dietary regimen. This is similar to findings reported in our previous studies of supine postabsorptive normal subjects using the canopy system, and to observations by Gilbert et al using magnetometry. In the patient group, frequency clearly contributes a greater component to the rise in \( V_{\text{E}} \) than it does in the normal subject. As a result, these patients not only have a rapid shallow breathing pattern, but also respond to increased CO₂ with an enhanced frequency response. This may be due to either alterations in central chemical drive arising from central and peripheral chemoreceptors, or non-chemical drives originating from mechanoreceptors in the chest wall and pulmonary parenchyma. Infusions of epinephrine tend to enhance the response of frequency to CO₂ challenge. This would implicate neural changes in the control of breathing, at least in part, for the changes observed. The mean inspiratory flow-duty cycle relationship in both patients and normal subjects is shifted leftward with the hypertonic glucose infusion. It may be that this change results from increases in CO₂ production in the absence of increases in metabolic rate.

It should be emphasized that administration of glucose in patients with greater levels of stress than those studied here (burns, severe sepsis, hyperthyroidism) may lead to a different response than the one we observed. These conditions must be examined individually before extensive conclusions on the effect of glucose during stress states can be drawn.

When hypertonic, continuous, 24-hour glucose infusions were administered in amounts that exceed energy expenditure by 10 to 50 percent, there was no significant thermic effect. An enhanced ventilatory response to CO₂, seen with administration of TPN containing similar amounts of carbohydrates, did not occur either. Rather, we observed an increase in \( V_{\text{E}} \) during room air breathing that paralleled the increase in CO₂ production in both patients and normal subjects. These data would imply that the protein component of TPN plays a major role in mediating the previously reported changes.

References

1. Askanaiz J, Rosenbaum SH, Hyman AI, Silverberg PA, Milic-Emili J, Kinney JM. Respiratory changes induced by the large glucose loads of TPN. JAMA 1980; 243:1444-47
Symposium on Electrophysiologic Basis for Diagnosis and Management of Cardiac Arrhythmias

This third international symposium will be held at the Wyndham Hotel, Orlando, Florida, December 27-30. Sponsors are the University of Wisconsin, Continuing Medical Education; Mount Sinai Medical Center, Milwaukee; American Heart Association (Central Florida and Wisconsin Affiliates); Florida Heart Institute (Orlando); and Continuing Education and Research Foundation, Elm Grove, WI. For information, contact Ms. Sarah Z. Aslakson, Continuing Medical Education, 465B WARF Building, 610 Walnut Street, Madison, Wisconsin 53705 (608): 263-2856.

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The City of Hope National Medical Center will present this one-day course on December 13 at the Marriott Hotel, Newport Beach, California. For information, contact the Department of Continuing Medical Education, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, California 91010 (818): 359-5111, ext 2694.