Glucose and pyruvate metabolism in severe chronic obstructive pulmonary disease

Christina C. Kao,1,2 Jean W.-C. Hsu,2 Venkata Bandi,1 Nicola A. Hanania,1 Farrah Kheradmand,1 and Farook Jahoor2

1Department of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, 2Department of Pediatrics, US Department of Agriculture/Agricultural Research Service, Children’s Nutrition Research Center, Baylor College of Medicine, Houston, Texas

Submitted 24 May 2011; accepted in final form 17 October 2011

Kao CC, Hsu JW, Bandi V, Hanania NA, Kheradmand F, Jahoor F. Glucose and pyruvate metabolism in severe chronic obstructive pulmonary disease. J Appl Physiol 112: 42–47, 2012. First published October 20, 2011; doi:10.1152/japplphysiol.00599.2011.—The mechanisms leading to weight loss in patients with chronic obstructive pulmonary disease (COPD) are poorly understood but may involve alterations in macronutrient metabolism. Changes in muscle oxidative capacity and lactate production during exercise suggest glucose metabolism may be altered in COPD subjects. The objective of this study was to determine differences in the rates of glucose production and clearance, the rate of glycolysis (pyruvate production), and oxidative and nonoxidative pyruvate disposal in subjects with severe COPD compared with healthy controls. The in vivo rates of glucose production and clearance were measured in 14 stable outpatients with severe COPD (seven with low and seven with preserved body mass indexes) and 7 healthy controls using an intravenous infusion of [13C]bicarbonate and [13C]pyruvate. Endogenous glucose flux and glucose clearance were significantly faster in the combined COPD subjects (P = 0.002 and P < 0.001, respectively). This difference remained significant when COPD subjects were separated by body mass index. Pyruvate flux and oxidation were significantly higher in the combined COPD subjects than controls (P = 0.02 for both), but there was no difference in nonoxidative pyruvate disposal or plasma lactate concentrations between the two groups. In subjects with severe COPD, there are alterations in glucose metabolism leading to increased glucose production and faster glucose metabolism by glycolysis and oxidation compared with controls. However, no difference in glucose conversion to lactate via pyruvate reduction is observed.

cachexia; nutrition; glycolysis

There is both in vivo and in vitro evidence suggesting that chronic obstructive pulmonary disease (COPD) is associated with alterations in energy expenditure and macronutrient metabolism (3, 5, 8, 27). Specifically, in vivo studies of protein and lipid metabolism have shown increased whole-body protein turnover (5) and impaired β-adrenergic-mediated and exercise-induced lipolysis (8, 26) in COPD patients compared with healthy controls. Impaired lipolysis in COPD can lead to an increased dependence on glucose for energy production because of decreased availability of nonesterified fatty acids. If true, glucose production, utilization, and oxidation should be increased in patients with COPD. However, evidence that lactic acidosis occurs in some subjects with COPD early in exercise and at low work rates (6) suggests that oxidation of pyruvate, hence glucose, may be impaired.

Using enzymatic assays to assess glycolytic activity and oxidative capacity in the muscle tissues of COPD patients, some studies reported a normal potential for glycolysis but impaired citric acid cycle activity (17, 18). These results suggest that impaired oxidative capacity may be a primary contributing factor to the lactic acidosis in COPD, leading to increased nonoxidative disposal of glucose as lactate and possibly alanine. Despite the evidence suggesting possible alterations in glucose metabolism in COPD, it remains poorly understood because of a paucity of metabolic data. One in vivo study using 6,6-2H2-glucose to measure glucose rate of appearance did find increased whole-body glucose production at rest in underweight COPD patients (7). In this study, we used stable isotope tracer techniques to estimate the in vivo rate of glucose production and clearance, rate of production of pyruvate (i.e., rate of glycolysis), and the oxidative and nonoxidative disposal of pyruvate to determine differences in the metabolic fate of glucose in subjects with severe COPD compared with controls. We hypothesized that subjects with COPD have increased rates of glucose production, glycolysis, and glucose oxidation compared with healthy controls.

METHODS

Subjects. Fourteen clinically stable adult outpatients with severe COPD [post-bronchodilator forced expiratory volume in 1 s (FEV1) of <50% of predicted] were enrolled in the study. Seven subjects had body mass index (BMI) of <21 kg/m2 (low BMI group), and seven subjects had BMI of ≥21 kg/m2 (preserved BMI group). Fat-free mass (FFM) was not determined before enrollment in the study. None of the subjects suffered from upper respiratory tract infection or exacerbation of disease for at least 8 wk before the study. Exclusion criteria included malignancy, cardiac failure, and severe endocrine, hepatic, or renal disorders. In addition, subjects receiving systemic corticosteroids within 3 mo before the study were excluded. Maintenance therapy of the COPD subjects consisted of inhaled medications, including β2-agonists, anticholinergics, and/or corticosteroids as per the current guidelines (9).

Seven healthy adult volunteers who were current or former smokers participated in the study as control subjects. All controls had at least a 10 pack/yr smoking history. They were all in good health as established by medical history, physical examination, and blood chemistry measurements. They were selected to be similar in age as the COPD patients. All patients and controls were enrolled after written, informed consent was obtained. The study was reviewed and approved by the Institutional Review Board at Baylor College of Medicine in Houston, TX. This study was part of a larger study of metabolic alterations in patients with COPD.
Isotope tracer infusions. Although the leucine kinetic data are reported in another paper (16), we are including the leucine tracer infusion here to give an accurate description of the actual infusion protocol that was conducted. All isotope tracers were obtained from Cambridge Isotopic Laboratories (Woburn, MA). Tracer infusions were performed in all subjects in the adult General Clinical Research Center (GCRC) of Baylor College of Medicine. After an overnight fast of at least 8 h, subjects were admitted to the GCRC, and an intravenous catheter was placed in an antecubital vein for isotope infusions and a hand vein of the contralateral arm for blood sampling. The hand was heated to arterialize the blood samples. The subjects received infusions of stable isotope solutions for a total of 8 h. After baseline blood and breath samples were obtained, a primed, constant infusion of $^{13}$C bicarbonate (prime dose 7 mmol/kg in COPD subjects and 5 mmol/kg in controls; infusion = 6 mmol·kg$^{-1}$·h$^{-1}$) was administrated for 2 h. COPD subjects required a higher priming dose due to a larger bicarbonate pool size. After 1 h, an intravenous bolus of deuterium oxide (D$_2$O) (0.1 ml/kg) was given slowly over 5 min. After 2 h, the $^{13}$C bicarbonate infusion was stopped, and a primed-continuous infusion (prime = 6 mmol/kg; infusion = 6 mmol·kg$^{-1}$·h$^{-1}$) of $^{13}$C-leucine was started and maintained for 3 h. At the end of the 1-$^{13}$C-leucine infusion, simultaneous primed, constant infusions of 1-$^{13}$C-pyruvate (prime = 12 mmol/kg; infusion = 48 mmol·kg$^{-1}$·h$^{-1}$) and 6,6-$^{2}$H$_2$ glucose (prime = 25 mmol/kg; infusion = 20 mmol·kg$^{-1}$·h$^{-1}$) were started and maintained for 3 h. The bicarbonate pool was also reprimed with $^{13}$C bicarbonate (18 mmol/kg). Additional breath samples were obtained every 20 min between hours 1 and 2, 4 and 5, and 7 and 8 of the infusions. Additional blood samples were obtained every 15 min during the last 45 min of the leucine infusion and during the last 45 min of the glucose and pyruvate infusions.

Additional tests. All subjects with COPD underwent spirometry with determination of FEV$_1$ and forced vital capacity (FVC) according to the guidelines set by the American Thoracic Society (20).

Sample analyses. The blood samples were drawn into tubes containing EDTA or sodium fluoride and potassium oxalate. The tubes were centrifuged immediately at 4°C, and the plasma was removed and stored immediately at −70°C for later analysis. Plasma glucose and lactate concentrations were measured using a biochemical analyzer (YSI, Yellow Springs, OH). Plasma insulin concentrations were measured using a commercially available human insulin ELISA kit (Millipore, Billerica, MA).

Breath samples were analyzed for $^{13}$C abundance in CO$_2$ by gas isotope ratio-mass spectrometry, with monitoring of ions at m/z 44 and 45. The plasma isotopic enrichment of lactate, a surrogate for intracellular pyruvate (31), was measured by negative chemical ionization gas chromatography-mass spectrometry (GC-MS) of its pentfluorobenzyl derivative, monitoring ions at m/z 131 and 132. The plasma glucose isotopic enrichment was measured by electron impact ionization GC-MS of its penta-acetate derivative, monitoring ions m/z 242 to 244.

The $^{2}$H$_2$ content of plasma water was measured in the baseline, 195-min, and 240-min blood samples by reducing water extracted from 10 μl of plasma with zinc in quartz vessels and measuring the $^{2}$H$_2$ abundance of the resulting hydrogen gas by gas isotope ratio mass spectrometry (Delta-E; Finnigan MAT, San Jose, CA).

Calculations. Rate of appearance (total flux) of CO$_2$, pyruvate, and glucose were calculated from the steady-state equation:

$$Ra = \frac{(IE_{fast} - IE_{plateau})i}{IE_{fast}}$$

where IE$_{fast}$ is the isotopic enrichment (mole % excess) of bicarbonate, pyruvate, or glucose in the infusate, IE$_{plateau}$ is the isotopic enrichment of CO$_2$ in the expired air or plasma lactate (a surrogate for pyruvate) or glucose in plasma at isotopic steady state, and i is the infusion rate of the tracer in mmol·kg$^{-1}$·h$^{-1}$ for bicarbonate and mmol·kg$^{-1}$·min$^{-1}$ for glucose and pyruvate. Plasma lactate isotopic enrichment was used to calculate Ra pyruvate, because plasma lactate is in isotopic equilibrium with intracellular pyruvate (28, 31). Endogenous flux was calculated by subtracting the infusion rate, i, from the Ra.

Under steady-state conditions, the rate of appearance of glucose (RaGlu) equals rate of disappearance (RdGlu). Therefore,

$$Glucose clearance (ml·kg^{-1}·min^{-1}) = \frac{Ra_{13}CO_2}{IE_{plateau}}$$

Pyruvate oxidation (Py$_{000}$) was calculated as

$$Py_{000} (\mu mol·kg^{-1}·min^{-1}) = Ra_{13}CO_2/IE_{plateau}$$

where Ra$_{13}$CO$_2$ is the rate of production of labeled CO$_2$ obtained from the product of RaCO$_2$ and the plateau enrichment of expired CO$_2$ during the $^{13}$C pyruvate infusions and IE$_{plateau}$ is the plasma isotopic enrichment of lactate at isotopic steady state. The enrichment of expired CO$_2$ during the $^{13}$C pyruvate infusion did not reach a plateau in all subjects. In those subjects, a plateau value was obtained by nonlinear regression curve fit using GraphPad Prism version 4 (GraphPad software, San Diego, CA, USA).

Non-oxidative pyruvate disposal to lactate and alanine was determined by subtracting pyruvate oxidation from pyruvate flux.

Insulin resistance was calculated using the homeostatic predictive model (19) as follows:

$$Insulin resistance (mU · mmol^{-1}·l^{-1}) = \left(\text{fasting plasma insulin} \times \text{fasting plasma glucose}\right)/22.5$$

Total body water (TBW) was calculated as follows:

$$\text{TBW(mL)} = ED_{D_{2}O} \times (dose/E_{D_{2}O} \times 1.04)$$

where ED$_{D_{2}O}$ is the enrichment of the deuterium oxide dose, E$_{D_{2}O}$ is the plasma water enrichment, and 1.04 is the factor that converts deuterium dilution space to total water (29). FFM and fat mass (FM) were calculated assuming 0.73 as the water content or hydration of FFM in adult humans (30).

Statistics. Data are expressed as means ± SE unless otherwise noted. Differences in subject characteristics and metabolic parameters between the three groups of subjects were assessed by one-way ANOVA using Tukey’s test for post hoc comparisons. When data from the 14 COPD subjects were combined, differences between the two groups were made by non-paired t-test. Correlations were performed using Pearson’s correlation. Tests were considered statistically significant when P < 0.05. Data analysis was performed with STATA software (version 9, College Station, TX).

RESULTS

The general characteristics and anthropometric parameters of all subjects are shown in Table 1. Control subjects were younger than COPD subjects with low BMI (P = 0.01, ANOVA; P < 0.05, post hoc Tukey’s test). Low BMI subjects had lower FFM than controls (P < 0.01, ANOVA; P < 0.05, post hoc Tukey’s test). Both groups of COPD subjects had lower FFM index (FFMI) compared with controls (P < 0.001, ANOVA; P < 0.05, post hoc Tukey’s test), and all subjects with COPD but one had low FFMI indexes [defined as <15 kg/m$^2$ for women and <16 kg/m$^2$ for men (15)]. COPD subjects with low BMI had lower FM compared with those with preserved BMI (P = 0.02, ANOVA; P < 0.05, post hoc Tukey’s test). The clinical characteristics and spirometric values of subjects with COPD are given in Table 2. Treatment with inhaled corticosteroids and oxygen therapy were similar between the two groups.

All kinetic data are expressed per kilogram of FFM since FFM is the major contributor to glucose metabolism in the fasted state. These data are shown in Fig. 1. Endogenous
Table 1. Characteristics and anthropometric parameters of all subjects

<table>
<thead>
<tr>
<th></th>
<th>COPD With Low BMI (n = 7)</th>
<th>COPD With Preserved BMI (n = 7)</th>
<th>Controls (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67 ± 5</td>
<td>61 ± 9</td>
<td>55 ± 6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Height, in.</td>
<td>67.4 ± 3.1</td>
<td>67.9 ± 5.7</td>
<td>68.9 ± 3.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>55.0 ± 7.5*</td>
<td>75.4 ± 13.1</td>
<td>81.3 ± 16.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.7 ± 1.1†</td>
<td>25.4 ± 3.5</td>
<td>26.4 ± 3.9</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>36.9 ± 6.1*</td>
<td>45.2 ± 10.2</td>
<td>55.2 ± 11.0</td>
</tr>
<tr>
<td>Percent fat-free mass}</td>
<td>0.67 ± 0.07</td>
<td>0.60 ± 0.09</td>
<td>0.68 ± 0.08</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>18.1 ± 4.2†</td>
<td>31.5 ± 9.8</td>
<td>26.3 ± 8.9</td>
</tr>
<tr>
<td>Percent fat mass, %</td>
<td>0.33 ± 0.07</td>
<td>0.40 ± 0.09</td>
<td>0.32 ± 0.08</td>
</tr>
<tr>
<td>Fat-free mass index, kg/m²</td>
<td>12.6 ± 1.6**</td>
<td>15.2 ± 1.2*</td>
<td>18.5 ± 3.3</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Former</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>88 ± 14</td>
<td>81 ± 13</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Resting O₂ saturation, %</td>
<td>95 ± 5</td>
<td>96 ± 3</td>
<td>99 ± 1</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. BMI, body mass index. *Significant difference compared with control group by ANOVA and post hoc Tukey’s test (P < 0.05). †Significant difference compared with preserved BMI group by ANOVA and post hoc Tukey’s test (P < 0.05).

Table 2. Spirometric values and clinical characteristics of subjects with COPD

<table>
<thead>
<tr>
<th></th>
<th>COPD With Low BMI (n = 7)</th>
<th>COPD With Preserved BMI (n = 7)</th>
<th>Controls (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, liter</td>
<td>0.84 ± 0.20</td>
<td>0.91 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>26 ± 11</td>
<td>30 ± 10</td>
<td></td>
</tr>
<tr>
<td>FVC, liter</td>
<td>1.79 ± 0.27</td>
<td>2.26 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>46 ± 4</td>
<td>57 ± 6</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>45 ± 5</td>
<td>42 ± 4</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta agonist</td>
<td>7/7</td>
<td>7/7</td>
<td></td>
</tr>
<tr>
<td>Inhaled steroid</td>
<td>5/7</td>
<td>5/7</td>
<td></td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>4/7</td>
<td>6/7</td>
<td></td>
</tr>
<tr>
<td>Home oxygen use</td>
<td>3/7</td>
<td>3/7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity. All P values are nonsignificant by t-test for parametric variables and χ² or Fisher’s exact test for nonparametric variables.

DISCUSSION

The purpose of this study was to determine whether whole-body glucose production and its metabolism through pyruvate in the postabsorptive state differed in subjects with severe glucose flux and glucose clearance were significantly faster in the combined COPD subjects compared with controls (P = 0.002 and P < 0.001, respectively). When separated by BMI, COPD subjects with both low BMI and preserved BMI also had higher endogenous glucose flux and clearance compared with control subjects (P = 0.008 and P < 0.001, respectively, by ANOVA; P < 0.05 by post hoc Tukey’s test). Pyruvate flux and oxidation were significantly higher in COPD subjects and controls. As depicted in Table 3, plasma glucose concentration was lower in COPD subjects than in controls (P = 0.008), but plasma concentrations of insulin and lactate as well as insulin resistance, as measured by HOMA, were not different in COPD subjects compared with control subjects.

Fig. 1. Endogenous glucose flux (A) and glucose clearance (B) in chronic obstructive pulmonary disease (COPD) and control subjects. *Significant difference compared with control subjects (P < 0.05).

Fig. 2. Mean enrichment of 13CO₂ in exhaled breath during [13C]bicarbonate, [13C]leucine, and [13C]pyruvate infusions in COPD and control subjects.

J Appl Physiol • doi:10.1152/japplphysiol.00599.2011 • www.jap.org
COPD and healthy controls. Our results show that COPD subjects produced glucose at a faster rate than healthy control subjects. This increased glucose production is associated with a significantly higher glucose clearance, indicating increased uptake and utilization of glucose. Pyruvate production and its oxidation are also increased in COPD subjects compared with controls, but there is no difference in nonoxidative pyruvate disposal between the two groups. These results suggest that subjects with COPD are producing more glucose, which enters the glycolytic pathway, leading to greater pyruvate formation. The majority of this pyruvate is then oxidized via the citric acid cycle rather than being disposed via nonoxidative pathways to lactate and alanine. These alterations in glucose metabolism were not associated with a change in plasma insulin concentration or insulin resistance.

Multiple studies have examined the glycolytic and oxidative capacity of subjects with COPD using in vitro assays of enzymatic activity. However, these studies have had inconsistent results, demonstrating the need for in vivo studies of glucose metabolism. For example, studies of phosphofructokinase (PFK), the rate-limiting enzyme in glycolysis, have shown both higher activity (14) and no difference in activity (10, 18) in the muscles of COPD subjects compared with control subjects. The rate of glycolysis in COPD is important because glycolysis produces pyruvate, and the availability of pyruvate, in turn, is a key factor in determining the rate of production of lactate. We found that subjects with COPD have faster rates of whole-body production of both glucose and pyruvate compared with control subjects, indicating that more glucose is entering the glycolytic pathway to form pyruvate. The finding of increased glycolysis in COPD is supported by the results of Green et al. (11), who found elevated concentrations of glycolytic metabolites in the vastus lateralis of COPD subjects compared with control subjects.

An imbalance between pyruvate produced from glycolysis and pyruvate oxidation via the citric acid cycle leads to increased lactate production. An increased rate of glycolysis could lead to increased lactate production in the absence of a proportionate increase in the rate of pyruvate oxidation. Engelen et al. reported that venous lactate was higher at rest in COPD subjects than in physically inactive healthy volunteers (6), and there was an early lactate response to exercise in COPD subjects compared with control subjects. On the other hand, other studies have found normal resting muscle lactate in COPD (11, 23). For example, Green et al. (11) did not find increased muscle lactate despite increased concentrations of glycolytic metabolites in COPD subjects, because of increased activation of pyruvate dehydrogenase in COPD, leading to increased conversion of pyruvate to acetyl CoA. These findings suggest that the extra pyruvate formed from a faster rate of glycolysis was being channeled preferentially into the TCA cycle for oxidation. Our results similarly show that increased whole-body pyruvate oxidation in COPD subjects allowed them to maintain normal lactate concentrations despite a faster rate of glycolysis and increased pyruvate availability. Together, these in vitro and in vivo findings suggest that COPD subjects at rest compensate for the greater pyruvate production from glycolysis by increasing pyruvate oxidation and not by converting pyruvate to lactate and alanine. However, these measurements were made at rest, and the greater exercise-induced increase in blood lactate in COPD subjects compared with healthy control subjects (2, 6) suggests that metabolism of glucose and pyruvate changes appreciably during exercise, resulting in increased nonoxidative disposal of pyruvate in COPD.

Our present finding that postabsorptive COPD patients produce glucose at a faster rate than healthy control subjects corroborates the findings of Franssen et al. (9). Despite faster production of glucose in COPD, plasma glucose concentration

### Table 3. Plasma glucose, lactate, and insulin concentrations and HOMA in COPD and control subjects

<table>
<thead>
<tr>
<th></th>
<th>COPD With Low BMI (n = 7)</th>
<th>COPD With Preserved BMI (n = 7)</th>
<th>All COPD (n = 14)</th>
<th>Control Subjects (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose, mM</td>
<td>4.66 ± 0.08</td>
<td>4.72 ± 0.12</td>
<td>4.69 ± 0.07*</td>
<td>5.12 ± 0.16</td>
</tr>
<tr>
<td>Plasma lactate, mM</td>
<td>0.76 ± 0.05</td>
<td>0.83 ± 0.05</td>
<td>0.79 ± 0.04</td>
<td>0.80 ± 0.06</td>
</tr>
<tr>
<td>Plasma insulin, μU/ml</td>
<td>4.44 ± 1.39</td>
<td>4.01 ± 0.93</td>
<td>4.22 ± 0.80</td>
<td>5.39 ± 0.72</td>
</tr>
<tr>
<td>HOMA, mmol·mU⁻¹·l⁻²</td>
<td>0.92 ± 0.29</td>
<td>0.82 ± 0.18</td>
<td>0.87 ± 0.17</td>
<td>1.21 ± 0.14</td>
</tr>
</tbody>
</table>

Values are means ± SE. To convert glucose concentration from mM to mg/dl, multiply by 18. *Significant difference compared with controls (P < 0.05).
was normal as a result of faster whole-body glucose clearance, indicating increased glucose uptake and utilization. This increase in glucose clearance was not associated with a higher plasma insulin concentration or HOMA, an estimate of insulin resistance. This is in contrast to the findings of prior studies reporting insulin resistance in COPD subjects with normal BMI (1, 4). The differences in our results compared with those of others (1, 4) may be secondary to small sample size in this study or the different body compositions of the COPD subjects in the different studies.

We previously found faster whole-body protein breakdown, as measured by endogenous leucine flux, as well as nonoxidative leucine disposal in COPD subjects compared with control subjects. However, there was unexpectedly no difference in leucine oxidation between the two groups (16). Increased protein breakdown in COPD subjects has also been demonstrated using other isotopic tracers (5, 25). Changes in protein metabolism may, in turn, affect glucose metabolism, including the oxidative and nonoxidative disposal of pyruvate as alanine. Leucine is metabolized via branched chain amino acid transaminase to α-ketoisocaproic acid and glutamate, and the latter, in turn, can transaminate with pyruvate to form alanine. α-Ketoisocaproic acid is converted via acetoacetate to acetyl CoA, which can enter the Krebs cycle, thereby potentially decreasing the entry of pyruvate to the Krebs cycle and increasing nonoxidative disposal of pyruvate. However, the finding that leucine oxidation was not increased in COPD subjects suggests that the faster leucine flux in COPD did not affect nonoxidative pyruvate disposal. In addition, because in the fasted state the majority of glucose production is derived from gluconeogenesis, faster release of amino acids from protein may be fueling a faster gluconeogenesis in COPD. In support of this, Fransen et al. found that resting glucose flux was increased in underweight COPD patients compared with control subjects and was inversely related to FFM (7). However, further studies are needed to directly measure gluconeogenesis in COPD.

Alterations in other macronutrient metabolism may also lead to an increased need for glucose. Those COPD subjects with preserved BMI had selective loss of FFM with preservation of BMI (1, 4). The differences in our results compared with those of others (1, 4) may be secondary to small sample size in this study or the different body compositions of the COPD subjects in the different studies.

In conclusion, whole-body glucose production, clearance, and oxidation, and rate of glycolysis are increased in COPD subjects compared with control subjects. However, there is no change in the rate of nonoxidative disposal of pyruvate as lactate and alanine in COPD subjects at rest. Furthermore, we speculate that the increased protein breakdown and catabolism of COPD may be a consequence of the faster rate of glucose production and oxidation for energy. Therefore, interventions to counteract the preferential use of glucose for energy in patients with COPD may have significant effects on energy expenditure and attenuate the loss of FFM.

ACKNOWLEDGMENTS

We are grateful to the nursing staff of the General Clinical Research Center at Baylor College of Medicine for care of the subjects, Sarah Perusich for assistance in recruiting subjects, and Melanie Del Rosario, Margaret Frazer, and Vy Pham for assistance in laboratory analyses.

GRANTS

This work was supported in part by The Chest Foundation and ALTANA Pharma, US, and National Heart, Lung, and Blood Institute (HL-082487). Work at the General Clinical Research Center is supported by the National Institutes of Health (M01-RR-00188). This research was also supported with federal funds from the US Department of Agriculture, Agricultural Research Service under Cooperative Agreement Number 58-6250-6001.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS

C. C. Kao, V. Bandi, N. A. Hanania, F. Kheradmand, and F. Jahoor provided conception and design of research; C. C. Kao, V. Bandi, and F. Jahoor performed experiments; C. C. Kao, J. W.-C. Hsu, and F. Jahoor analyzed data; C. C. Kao, J. W.-C. Hsu, V. Bandi, N. A. Hanania, F. Kheradmand, and F. Jahoor interpreted results of experiments; C. C. Kao prepared figures; C. C. Kao and F. Jahoor drafted the manuscript; C. C. Kao, J. W.-C. Hsu, V. Bandi, N. A. Hanania, F. Kheradmand, and F. Jahoor edited and revised the manuscript; C. C. Kao, J. W.-C. Hsu, V. Bandi, N. A. Hanania, F. Kheradmand, and F. Jahoor approved final version of the manuscript.

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