Clinical Nutrition 28 (2009) 203–208

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://intl.elsevierhealth.com/journals/clnu

Original Article

Plasma branched-chain amino acid levels and muscle energy metabolism in patients with chronic obstructive pulmonary disease

Tomoko Kutsuzawa [a,*], Sumie Shioya [b], Daisaku Kurita [b], Munetaka Haida [b]

[a] School of Health Sciences, Tokai University, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
[b] School of Medicine, Tokai University, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan

ARTICLE INFO

Article history:
Received 2 May 2008
Accepted 29 January 2009

Keywords:
Exercise
Lactate
pH
^{31}P-magnetic resonance spectroscopy

SUMMARY

Background & aims: Although several studies have shown that plasma concentrations of branched-chain amino acids (BCAAs) are reduced in patients with chronic obstructive pulmonary disease (COPD), little is understood about how low concentrations of BCAAs limit exercise in such patients. The present study investigated whether plasma BCAAs are related to energy metabolism in exercising muscle using ^{31}P-magnetic resonance spectroscopy (MRS).

Methods: We analyzed the plasma amino acid profiles of 23 male patients with COPD (aged 69.2 ± 5.1 years) and of 7 healthy males (aged 64.1 ± 6.0 years). We normalized the exercise intensity of repetitive lifting by adjusting the weight to 7% of the maximal grip power. The intracellular pH and the phosphocreatine (PCr) index (PCr/(PCr + Pi); Pi, inorganic phosphate) were calculated from MR spectra. We evaluated the relationship between intracellular pH and PCr index at the completion of exercise and the plasma BCAA concentration.

Results: Glutamine concentrations were elevated in patients with COPD compared with healthy individuals. Plasma concentrations of BCAAs correlated with intracellular pH and PCr index at the completion of exercise.

Conclusions: The findings are consistent with the notion that BCAAs affect muscle energy metabolism during exercise in patients with COPD.

1. Introduction

Recent studies have demonstrated that reduced oxidative capacity in skeletal muscles correlates with an accelerated lactate response to exercise in patients with chronic obstructive pulmonary disease (COPD).[1,2] We previously found, using 31-phosphorus nuclear magnetic resonance spectroscopy (^{31}P-MRS), that the skeletal muscle metabolism of patients with chronic respiratory impairment undergoes specific changes.[3,4] Skeletal muscle intracellular pH (pHi) and high-energy phosphate compounds can be dynamically measured using noninvasive ^{31}P-MRS.[5] A decrease in pHi during exercise suggests lactic acid accumulation in exercising muscle.[5,6] Patients with chronic respiratory impairment have significant decreases in phosphocreatine (PCr) and in pHi during even mild exercise, suggesting that adenosine triphosphate (ATP) production is reduced and that lactate rapidly accumulates in their muscles. Several factors such as inactivity, malnutrition or hypoxemia might contribute to altered muscle metabolism.[3,7–9]

Muscle wasting contributes to muscle weakness and exercise limitations in patients with COPD[10] in whom weight loss and muscle wasting are common features.[11] Skeletal muscle is the major protein store that supplies amino acids to other tissues under specific conditions. Plasma-free amino acid concentrations express the balance between exogenous uptake and intercurrent metabolites in protein synthesis and breakdown.[12] Several investigators have reported that the amino acid profile is altered in the plasma and skeletal muscles of patients with COPD.[13–16] Most of these studies have shown that the plasma concentrations of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine are reduced.[13,15,16] Yoneda et al.[15] demonstrated that decreased concentrations of BCAAs in COPD are specifically related to weight loss and decreased muscle mass.

Abbreviations: MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; Pi, inorganic phosphate; pHi, intracellular pH; TCA cycle, tricarboxylic acid cycle; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TSF, skin fold thickness; pHi-ex, intracellular pH at completion of exercise; PCr index-ex, PCr/(PCr + Pi) at completion of exercise; BCKDH, branched-chain α-keto acid dehydrogenase.

* Corresponding author. Tel.: +81 463 93 1121; fax: +81 463 90 2074.
E-mail addresses: tkutsu@is.icc.u-tokai.ac.jp (T. Kutsuzawa), sumie@is.scc.u-tokai.ac.jp (S. Shioya), kurita@is.icc.u-tokai.ac.jp (D. Kurita), haida@is.icc.u-tokai.ac.jp (M. Haida).

0261-5614/$ – see front matter © 2009 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.
doi:10.1016/j.clnu.2009.01.019

Muscle energy metabolism might be affected by BCAAs during exercise as energy sources and as substrates that expand the pool of tricarboxylic acid (TCA) cycle intermediates.[12] However, few studies have investigated whether changes in amino acid profiles in plasma affect exercise metabolism in COPD patients.[17] Muscle energy metabolism is similarly altered in patients with liver cirrhosis who also usually have decreased plasma BCAAs, that is, a significant decrease in PCr and in pHi during forearm exercise.[18] The present study uses ^{31}P-MRS to clarify whether or not plasma amino acid profiles, especially those of BCAAs, are related to the altered energy metabolism of exercising muscle in patients with COPD.

2. Materials and methods

2.1. Patients and controls

We studied 23 ambulatory male outpatients with stable COPD (aged 69.2 ± 5.1 years) diagnosed according to spirometric findings from moderate to very severe airflow limitation (FEV_1/FVC <70% and FEV_1/FEV_1pred <80%; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity).[19] None of the patients had ever received systemic corticosteroid therapy and 3 of them had been treated with oxygen inhalation only while walking. The exclusion criteria were malignancy, cardiac failure, renal failure, liver cirrhosis, diabetes mellitus, and infection.

We also examined a control group of 7 healthy males (aged 64.1 ± 6.0 years) who were recruited from an advertisement at our institute and at an outpatient clinic. Their health status was determined by evaluating their present condition by spirometry and by obtaining their medical history of cardiac, respiratory, hepatic and metabolic disease. None of them regularly participated in exercise. The ethics committee at our institution approved the study protocol, and both the control individuals and the patients provided written informed consent to participate. Tables 1 and 2 show the physical characteristics of the participants.

2.2. Study design

All participants fasted overnight, and then anthropometric parameters and grip strength were measured at our outpatient clinic. The maximal voluntary grip strength of the non-dominant arm was measured using a dynamometer (DM-100N; Yagami, Nagoya, Japan). Fasting venous blood was obtained from an antecubital vein. Arterial blood was taken from brachial artery for blood gas analysis only in patients with COPD while breathing room air.

Thereafter, all participants repetitively gripped a lever attached to a weight via a pulley system, using the non-dominant forearm at a rate of 20 grips per min for 3 min while supine and breathing room air. Gripping the lever lifted the weight by 5 cm. Exercise intensity was normalized by adjusting the weight to 7% of the maximal grip strength, which was suitable for this study because all patients could complete the exercise. Moreover, a previous study has shown that the pHi at this intensity of exercise frequently decreases in patients with COPD, but not in healthy controls.[4] Muscle metabolism was measured using ^{31}P-MRS (see below) during 1.5 min of rest, 3 min of exercise, and 4 min of recovery.

Table 1
Anthropometric and biochemical data of study participants.

Parameter	Units	Healthy individuals $N = 7$	COPD patients $N = 23$	p (t-test)
Age	y	64.1 ± 6.0	69.2 ± 7.0	0.096
Height	cm	165.3 ± 5.0	163.5 ± 5.1	0.419
Weight	kg	61.2 ± 7.1	58.1 ± 9.3	0.433
BMI	kg/m^2	22.4 ± 2.5	21.7 ± 2.8	0.975
Forearm circumference	cm	24.1 ± 1.8	23.3 ± 1.5	0.309
Fat	%	13.2 ± 9.4	13.2 ± 5.2	0.982
Grip Power	kg	34.3 ± 5.2	34.0 ± 5.5	0.904
Albumin	g/dL	4.6 ± 0.3	4.5 ± 0.3	0.469
Prealbumin	mg/dL	30.9 ± 2.0	26.5 ± 6.1	0.079

All values are means ± SD.

Table 2
Comparison of pulmonary function in patients with COPD and healthy individuals.

Parameter	Units	Healthy individuals $N = 7$	COPD patients $N = 23$
VC	L	3.96 ± 1.07	3.00 ± 0.52
VC%	%	105.4 ± 21.4	92.1 ± 14.3
FEV_1	L	3.22 ± 0.76	1.14 ± 0.35*
FEV_1/FVC	%	81.5 ± 10.7	40.6 ± 11.8*
FEV_1/FEV_1pred	%	108.4 ± 22.3	46.4 ± 15.5*
pH		NA	7.411 ± 0.029
$PaCO_2$	Torr	NA	40.4 ± 4.6
PaO_2	Torr	NA	80.8 ± 10.5
SaO_2	%	NA	95.6 ± 1.5

All values are means ± SD. NA, not available. *$p < 0.01$.

2.3. Nutritional assessment

Nutritional status was evaluated using biochemical blood tests for albumin and prealbumin as well as anthropometric measurements such as height, weight, and non-dominant forearm circumference. The circumference of the non-dominant forearm was measured at the proximal one-third of the forearm, where the MRS surface coil was placed.

Fasting blood samples were obtained by venipuncture between 8 and 10 a.m. A portion of each sample was immediately cooled on ice and plasma that was obtained by centrifugation at 4 °C was stored at −80 °C. Thawed plasma samples were deproteinized using 5% sulfosalicylic acid, and then amino acid concentrations were measured by ion-exchange, high-pressure liquid chromatography with fluorometric detection (Model 8500; Hitachi, Tokyo, Japan).[20] Total BCAAs included leucine, isoleucine and valine, total aromatic amino acids included phenylalanine and tyrosine, and total amino acids included all measured amino acids. Serum albumin and prealbumin were measured in another portion of the same sample by routine clinical analysis.

2.4. Magnetic resonance spectroscopy

Unlocalized MR spectra were obtained using a 2.0-Tesla, 31-cm-bore superconducting magnet (BEM 250/80; Otsuka Electronics Co., Osaka, Japan). The spectrometer was operated at 85 MHz for ^{1}H and at 34.5 MHz for ^{31}P. A surface coil (4 cm) was placed on the proximal third of the non-dominant forearm. The ^{31}P-MR spectra were obtained using a single 90° pulse (50 μs) (see Ref. 3) and accumulated every 3 s for 1 min.

The signal area for inorganic phosphates (Pi) and PCr was determined by means of Gaussian curve fitting (see Ref. 3 for details) from each spectrum. Since absolute values of concentrations of PCr and Pi could not be determined because the muscle volume of the signal source is unclear when using a surface coil, relative concentrations of PCr and Pi were evaluated using the normalized units of the PCr index (PCr/(PCr + Pi)).[6] The PCr index reached a plateau in healthy controls at 3 min after the onset of exercise.[3] The pHi value was calculated from a difference in chemical shifts between the Pi and PCr peaks.[6] When the Pi peak was split, the pH was determined from the greater peak. When the