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Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD

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KEYWORDS
COPD;
Nutritional support;
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Pulmonary rehabilitation

Summary
Study objectives: The first aim of this study was to investigate the effects of nutritional supplementation combined with low-intensity exercise on body components, exercise tolerance, and health-related quality of life (HRQOL) in malnourished patients with COPD. The second aim of this study was to examine the degree of systemic inflammation and the actual changes in levels of systemic CRP, TNFα, IL-6 and IL-8 actual changes after a combination of nutritional supplementation and low-intensity exercise in these patients.
Design: A prospective randomized trial.
Patients: Thirty-two moderate to severe, clinically stable malnourished COPD patients.
Methods: Patients were randomly divided into a nutritional supplementation with low-intensity exercise group and a control group. Lung function, maximum inspiratory and expiratory muscle force, the Chronic Respiratory Disease Questionnaire (CRQ), the 6-min walking distance (6MWD), and the Borg scale were measured at baseline and were re-assessed at 3 months after intervention. The degree of systemic inflammation and the changes in levels of systemic CRP, TNFα, IL-6 and IL-8 were assessed before and after a combination nutritional supplementation with low-intensity exercise.
Results: Body weight and FFM increased significantly after 12 weeks of nutritional supplementation therapy in patients with COPD. The dietary intake energy increased and the

Abbreviations: ANOVA, analysis of variance; CRQ, Chronic Respiratory Disease Questionnaire; GOLD, global initiative for chronic obstructive lung disease; HRQOL, health-related quality of life; 6MWD, 6-min walking distance; MRC, Medical Research Council; PR, pulmonary rehabilitation.

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REE:REEpred ratio decreased significantly in the nutrition with low-intensity exercise group. PI_{max}, Quadriceps muscle force and the 6-min walking distance (6MWD) increased significantly from baseline through week 12. Health status, as assessed by CRQ, improved in the domains of dyspnea and total sores significantly in the nutrition with low-intensity exercise group after intervention. In this group, hsCRP, IL-6, IL-8, and TNFα, decreased significantly after intervention compared with the control group.

Conclusions: The combination of nutritional supplementation with low-intensity exercise training was successful in increasing weight and energy intake as well as exercise capacity and health-related QOL in our patients. Moreover, REE and major inflammatory cytokines decreased significantly after nutritional supplementation with low-intensity exercise training. The present study results suggest a potential role for the combination of nutritional supplementation and low-intensity exercise in the management of malnourished patients with COPD.

Introduction

The commonly occurring weight loss and muscle wasting in patients with chronic obstructive pulmonary disease (COPD) adversely affect respiratory and peripheral muscle function, exercise capacity, and health status.[1–3] Weight loss may be the result of an increased energy expenditure unbalance caused by inadequate dietary intake.[4] In addition, evidence for a relation between an enhanced systemic inflammatory response, on the one hand, and relative anorexia, on the other hand, has been found in patients with COPD.[4] Resting energy expenditure (REE) and total daily energy needed for activities have been reported to be elevated in stable COPD.[6,7]

Selective wasting of fat-free mass, is seen in a substantial proportion of patients,[8] suggesting a disturbed protein balance. Decreased protein intake, especially during the first days of an acute exacerbation,[9] decreased protein synthesis,[10] and increased protein balance turnover[11] has been reported. Also, an enhanced systemic inflammatory response has been described as a possible cause of a selectively disturbed protein balance.[12]

Several attempts have been made to reverse weight loss and muscle wasting in patients with COPD by instituting oral nutritional therapy.[13,14] However, a recent meta-analysis concluded that intervention with nutritional supplementation alone has no effect on improving anthropometric measures, lung function, or functional exercise capacity.[15,16] A systematic review by Puhan et al.[17] also suggested that there was insufficient evidence for additional benefits of nutritional support.

It can be deduced from these evidences regarding protein balance disturbances that nutritional therapy in COPD must consist of both sufficient dietary protein and anti-inflammatory ingredients must be combined with an anabolic stimulus such as exercise training to enhance improvements in muscle mass and physiologic function. The first aim of the present study was to investigate the effects of oral nutritional supplementation therapy, which has anti-inflammatory effects, incorporated into a 12-week home-based pulmonary rehabilitation program on body composition, muscle function, exercise capacity, and health status in depleted or weight-losing patients with COPD. There is also no information as to whether combination nutritional supplementation and low-intensity exercise in patients with COPD can affect the systemic inflammation. Therefore, the second aim of this study was to examine the degree of systemic inflammation and actual changes in the levels of systemic CRP, TNFα, IL-6, and IL-8 actual changes after a combination of nutritional supplementation and low-intensity exercise in patients with COPD.

Materials and methods

Subjects

Thirty-two patients with COPD were enrolled in the study between June 2007 and September 2008 according to the following inclusion criteria: (1) clinical diagnosis of moderate to severe COPD, (2) a clinically stable condition without recent exacerbations, and (3) the absence of significant associated medical problems that might interfere with the patient's ability to undergo PR. Patients who could not visit our hospital every 2 weeks were excluded. No patients were receiving oxygen inhalation at the time of this study. The Medical Research Council (MRC) dyspnea score[18] was grade 2 in 9 patients, grade 3 in 19 patients and grade 4 in 4 patients.

The patients were included if they fulfilled the criteria for COPD according to the American Thoracic Society (ATS) guidelines.[19] Force expiratory volume in 1 s (FEV_1) had to be less than 70% of the reference value, and the increase in FEV_1 after inhalation of a β2-agonist had to be less than 10% of the reference value. Patients with concomitant confounding disease such as malignant disorders, gastrointestinal abnormalities, recent surgery, or severe endocrine disorders were excluded. Only patients in clinically stable condition (not suffering from a recent respiratory tract infection) were included in the study. Eligibility for nutritional supplementation was defined as a body mass index (BMI; body weight/height squared) of less than 19 kg/m^2. This study was approved by the medical ethical committee of our hospital and the Akita University School of Health Sciences, and all subjects provided informed consent. All procedures were performed according to the research ethics guidelines of the Declaration of Helsinki.[20]

Assessments

Energy balance

REE was measured in early in the morning by an open-circuit indirect calorimetry system using a fitting mask (Metavine; Vain, Inc, Tokyo, Japan).[21] The system was calibrated daily before the start of the experiment. Patients were in a fasting state for at least 10 h and had a bedrest period of at least 30 min before measurement. Patients received their maintenance medications 2 h before measurements started. REE was measured when subjects were comfortably lying on a bed in the supine position. REE was calculated from oxygen consumption and carbon dioxide production with an abbreviated Weir formula.[22]

Before and during the last week of nutritional therapy, patients were asked to register their food intakes over 3 consecutive days in order to assess dietary intake. The obtained information was coded for computer nutrient analysis. The nutrient data base was derived from the Standard Tables of Food Composition (The Science and Technology Agency of Japan, 1982). Dietary intake was calculated by taking the average intake over 3 d. The use of dietary records provides a good representation of the actual food consumption because food intake is averaged over 3 consecutive days, so day-to-day variations are largely discarded.[21] Total protein, carbohydrate, and fat intake are presented as percentages of total energy intake. The total protein intake is also expressed as grams per kilogram of bodyweight every 24 h.

Collection and analysis of laboratory parameters

High-sensitivity serum CRP levels were assessed by latex turbidimetric immunoassay (Nittobo Medical; Tokyo, Japan). The analytical sensitivity of this CRP assay is 0.1 mg/L. Serum TNFα and IL-6, IL-8, leptin and ghrelin were measured using commercially available enzyme-linked immunosorbent assay kits (SRL, Inc; Tokyo, Japan). At the time of the collection of venous blood samples, an arterial blood sample was obtained by puncture of the radial artery for blood gas analysis.

Exercise performance and health status

To measure exercise performance, patients performed in a corridor walk for 6 min according to the ATS guidelines.[23] The distance walked in 6 min (6MWD) and the dyspnea scale was used in the analysis. Patients were not encouraged during the walk.[23]

The disease specific health status was measured using the Japanese version of the Chronic Respiratory Disease Questionnaire (CRQ).[24] The questionnaire scores four domains — dyspnea, fatigue, emotion and mastery. It contains 123 items, of which 62 deal primarily with physical function and 61 with emotional function. The results are presented as mean scores per question in each dimension. The threshold for clinically significant change for each dimension has been previously identified as 0.5.[25]

Intervention protocol

All patients were randomly classified into two groups: a nutrition with low-intensity exercise group and a control group. In the nutrition with low-intensity exercise group, patients received nutritional support of 400 kilocalories per day for 12 weeks. Two 200 ml packages of nutritional drink consisted of 60% energy from carbohydrates, 25% energy from fat, and 15% energy from protein. This drink contains omega-3 PUFAs 0.6 g and vitamins A 248 μg in total ingredients. Patients were encouraged to continue the consumption of their regular meal portions. In the control group, patients underwent a monthly 45-min education program including lectures on respiratory disease, control of dyspnea, medication and equipment use, nutrition, stress management, and relaxation techniques once every 4 weeks. All patients received anticholinergic or β2-agonist as bronchodilators. Six patients received inhaled corticosteroids and three received theophylline. These maintenance medications remained unchanged during the study.

Low-intensity exercise program

A multidisciplinary home-based low-intensity program[26] was used in the present study. Briefly, breathing retraining consisted of pursed-lip breathing, diaphragmatic breathing, and slow deep breathing, both in the supine and sitting position. Exercise training included upper and lower and lower limb exercises, respiratory muscle stretching calisthenics,[27] level walking at least 15 min, inspiratory and expiratory muscle exercises using Threshold® (HealthScan Products Inc., Cedar Grove, NJ) set at a training intensity of 20—30% of the maximal inspiratory (PI_{max}) and expiratory (PE_{max}) muscle forces. Patients also underwent a monthly 45-min education program including lectures and discussions on respiratory disease, control of dyspnea, medication and equipment use, nutrition, stress management, relaxation techniques, home exercises and the benefits of PR. Patients were strongly instructed to practice this program daily at home and were supervised by a respiratory therapist every 2 weeks in our hospital. A nurse periodically visited each patient at home and provided information regarding the role of the PR program. Relaxation and stair-climbing exercises were also carried out under the supervision of the respiratory therapist when the patients visited the hospital. The overall training intensity was set at 40—50% of the maximum oxygen consumption.[26,28]

Results

Table 1 lists the baseline parameters of the study group. As expected, lung function was severely impaired with the reference values. Mean arterial blood gases were normal. No baseline differences between the nutrition with exercise group and the control group were seen with regards to age, FEV_1, vital capacity, carbon dioxide tension, BMI, arterial oxygen tension and 6MWD (Table 1).

Body weight, %IBW and FFM increased significantly after 12 weeks of nutritional supplementation therapy (Table 2). The dietary Intake Energy increased and the REE:REEpred ratio decreased significantly in the nutrition with low-intensity exercise group compared with the control group (Table 2).

PI_{max}, Quadriceps muscle force, WBI, and 6MWD increased significantly from baseline through week 12 in the

Table 1 Characteristics of patients with COPD.

Valuables	Nutrition + Exercise group ($n = 17$)	Control group ($n = 15$)	P value
Age	77.3 ± 7.0	78.2 ± 6.6	ns
Height, cm	160 ± 7.1	158 ± 7.9	ns
Weight, kg	46.5 ± 5.2	47.1 ± 5.8	ns
BMI	18.0 ± 1.2	18.6 ± 1.3	ns
Smoking, pack-year	72.8 ± 32.2	72.0 ± 30.2	ns
MRC dyspnea scale	2.6 ± 1.0	2.7 ± 1.2	ns
FEV_1, L	1.23 ± 0.63	1.27 ± 0.63	ns
FEV_1%pred, %	53.3 ± 25.9	58.1 ± 26.2	ns
FVC, L	2.81 ± 0.73	2.74 ± 0.83	ns
FEV_1/FVC, %	42.8 ± 15.8	45.0 ± 14.3	ns
TLC, L	6.06 ± 1.00	5.91 ± 0.93	ns
FRC, L	s4.25 ± 0.90	4.04 ± 0.80	ns
RV, L	3.02 ± 0.87	3.02 ± 0.77	ns
DLco, ml/Torr/min	9.31 ± 4.22	9.61 ± 4.26	ns
PaO2, Torr	78.1 ± 5.7	75.5 ± 9.4	ns
PaCO2, Torr	42.3 ± 6.1	44.7 ± 6.9	ns
PI_{max}, cmH_2O	53 ± 26	53 ± 24	ns
PE_{max}, cmH_2O	86 ± 31	79 ± 25	ns
6MWD, m	373 ± 153	383 ± 156	ns

Abbreviation; BMI; Body Mass Index, MRC; Medical Research Council, FEV_1; Forced Volume in 1 s, FVC; Forced Vital Capacity, TLC; Total Lung Capacity, FRC; Functional Residual Capacity, RV; Residual Capacity, PI_{max}; Maximum Inspiratory Pressure, PE_{max}; Maximum Expiratory Pressure, 6MWD; 6-min walking distance.

Table 2 Changes of body composition, muscle force, HRQOL and biomarkers.

	Nutrition + Exercise group ($n = 17$)			Control group ($n = 15$)			Significant difference
	Baseline	12 weeks	Δ ratio, %	Baseline	12 weeks	Δ ratio, %	P value
Weight, kg	46.5 ± 5.2	47.9 ± 5.4	3.1 ± 3.6	47.1 ± 5.8	46.5 ± 5.9	−1.1 ± 2.9	0.0015
%IBW, %	81.8 ± 5.3	84.4 ± 6.5	3.1 ± 3.7	84.8 ± 6.0	84.0 ± 6.4	−0.5 ± 2.3	0.0023
Energy Intake, %pred	81.2 ± 20.6	91.1 ± 19.8	13.8 ± 14.6	92.0 ± 18.9	86.7 ± 13.9	−7.8 ± 12.2	0.0004
REE, kcal	1418 ± 186	1355 ± 171	−2.5 ± 7.8	1385 ± 207	1436 ± 223	3.6 ± 2.4	0.0116
REE/REEpred,	1.44 ± 0.26	1.18 ± 0.50	−4.4 ± 7.4	1.40 ± 0.24	1.47 ± 0.27	4.6 ± 3.1	0.0006
FMI, kg/m^2	4.04 ± 0.85	4.00 ± 1.46	4.5 ± 11.6	4.38 ± 1.22	4.21 ± 1.21	−4.0 ± 8.0	0.0376
FFMI, kg/m^2	14.0 ± 0.8	14.3 ± 1.0	2.4 ± 3.9	14.3 ± 1.16	14.3 ± 1.19	−0.3 ± 2.0	0.0159
PI_{max}, cmH_2O	53.4 ± 26.2	58.7 ± 27.0	12.3 ± 23.0	53.0 ± 24.3	44.5 ± 20.3	−12.6 ± 16.1	0.0025
Quadriceps force, kg	23.9 ± 8.1	28.9 ± 10.8	20.9 ± 20.5	23.4 ± 9.0	22.8 ± 10.6	−3.8 ± 19.1	0.0022
WBI, kg/kg	0.52 ± 0.17	0.60 ± 0.21	17.2 ± 19.3	0.50 ± 0.18	0.49 ± 0.19	−2.8 ± 19.5	0.0091
6MWD, m	373 ± 153	397 ± 153	8.7 ± 12.5	383 ± 155	342 ± 158	−8.8 ± 14.4	0.0014
CRQ (HRQOL)							
Total	105 ± 24	108 ± 22	3.6 ± 7.1	114 ± 24	113 ± 24	−0.9 ± 3.1	0.0284
Dyspnea	23.4 ± 7.5	25.5 ± 6.2	13.7 ± 20.6	26.5 ± 6.6	26.0 ± 7.6	−2.6 ± 15.8	0.0238
Fatigue	20.4 ± 5.6	19.4 ± 5.2	−3.5 ± 12.6	20.9 ± 6.0	20.5 ± 6.4	−2.6 ± 9.8	ns
Emotional function	39.0 ± 8.6	41.2 ± 8.1	6.4 ± 11.1	42.6 ± 7.9	42.6 ± 7.3	0.4 ± 5.1	ns
Mastery	22.4 ± 4.7	22.4 ± 5.0	0.17 ± 10.4	23.7 ± 5.1	23.8 ± 4.6	1.5 ± 8.2	ns
hsCRP, mg/l	1.73 ± 1.61	1.23 ± 1.26	−26.7 ± 27.	1.67 ± 1.54	2.02 ± 1.66	79.4. ±270.8	0.0035
IL-6, pg/ml	2.26 ± 1.16	2.04 ± 1.02	5.6 ± 37.2	2.51 ± 1.03	3.63 ± 2.04	50.6 ± 55.8	0.0173
IL-8, pg/ml	4.04 ± 2.29	2.20 ± 0.48	−31.2 ± 29.0	2.69 ± 1.30	4.26 ± 2.27	71.3 ± 99.6	0.0005
TNFα, pg/ml	2.95 ± 2.52	2.29 ± 1.77	−8.5 ± 26.6	3.39 ± 2.26	4.20 ± 2.67	57.2 ± 137.3	0.0037
Leptin, ng/ml	2.32 ± 1.56	2.42 ± 1.52	6.1 ± 15.0	2.66 ± 1.73	2.37 ± 1.36	−1.2 ± 15.1	ns
Ghrelin, fmol/ml	161 ± 134	146 ± 102	11.9 ± 82.5	163 ± 116	181 ± 141	44.8 ± 88.7	ns
Albumin, g/dl	3.99 ± 0.53	4.09 ± 0.33	3.5 ± 9.6	3.96 ± 0.63	4.01 ± 0.62	4.0 ± 28.9	ns
Transferrin, mg/dl	233 ± 27	232 ± 40	2.6 ± 9.0	238 ± 44	236 ± 28	−3.0 ± 7.9	ns

Abbreviation; IBW; Ideal Body Weight, REE; Resting Energy Expenditure, FMI; Fat Mass Index, FFMI; Free Fat Mass Index, WBI; Weight Bearing Index, 6MWD; 6-min walking distance, CRQ; Chronic Respiratory Disease Questionnaire.

nutrition with low-intensity exercise group compared with the control group (Table 2).

Health status, as assessed by the chronic respiratory questionnaire, improved significantly in the domains of dyspnea and total scores in the nutrition with exercise group after intervention in the nutrition with low-intensity exercise group compared with the control group (Table 2).

In the nutrition with low-intensity exercise group, hsCRP, IL-6, IL-8, and TNFα decreased significantly after intervention compared with the control group. Ghrelin, leptin, albumin and transferrin did not change significantly after intervention in the nutrition with low-intensity exercise group.

Discussion

We report herein the results of a pilot study of a combination of nutritional support and home-based low-intensity exercise in malnourished patients with COPD. The combination of nutritional supplementation with low-intensity exercise training was successful in increasing weight and energy intake as well as and also in exercise capacity and health-related QOL in our patients. Moreover, REE and major inflammatory cytokines decreased significantly after nutritional supplementation with low-intensity exercise training. This study suggests that there is a potential role for the combination of nutritional support and low-intensity exercise in the management of malnourished patients with COPD.

Our data demonstrate that REE/REEpred increased to approximately 140% in both the nutrition with low-intensity exercise group and the control group in malnourished COPD patients. These marked increases in REE in patients with malnourished COPD are in line with previous studies.[29,30] The high metabolic rate seen in malnourished COPD leads to an increase in respiratory muscle work, since the energy cost of increasing ventilation is higher in patients with malnourished patients with COPD than in healthy controls of compatible age and sex.[31] It has recently been reported that underweight COPD patients show signs of an exaggerated systemic inflammatory response attributed to an increase in REE, appetite suppression, and progress cachexia.[5,32] Indeed, COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages, and lymphocytes.[33] These cells release inflammatory mediators such as IL-6, IL-8, and TNFα and interact with structural cells in both the lung and airway.[34] Our data demonstrate significant increases in the levels of IL-6, and IL-8 in patients with malnourished COPD, and these data are in line with previous studies.[33,34] We have shown that the levels of elevated inflammatory cytokines decreased significantly after intervention with the nutrition combined with the low-intensity exercise group in this study. Human skeletal muscle has been shown to be one of the main sources of IL-6, and muscle-derived IL-6 stimulates CRP production in the liver.[35,36] It has recently been shown that exercise-induced muscle-derived IL-6 is reduced after low-intensity endurance training.[37] Taken these together, our data showing that inhibition of IL-6 and CRP, after 3-month rehabilitation with nutritional support and low-intensity exercise training suggest that inhibition might have occurred, at least in part, in the skeletal muscle, not in lung or airway.

Recently the effects of nutritional support with an omega-3 polyunsaturated fatty acid (PUFA) diet have been reported in two studies.[38,39] Matsuyama et al.[38] have reported that the effectiveness of nutritional support with PUFA improves exercised capacity and decreases in inflammatory cytokine levels in both in the sputum and serum in patients with COPD. Whereas Broekhuizen et al.[39] have shown that the positive effects of nutritional support with PUFA on exercise capacity cannot be attributed to decreased systemic levels of inflammatory cytokines. We have hypothesized here that the combination of an omega-3 polyunsaturated fatty acid diet and low-intensity exercise might be more effective in increasing exercise capacity and can also inhibit systemic inflammation in COPD. We therefore adopted a new approach to pulmonary rehabilitation with nutritional supplementation that includes an omega-3 PUFA-rich diet and low-intensity exercise. Indeed, the combination of nutritional supplementation with low-intensity exercise training in the present study was successful in increasing in exercise capacity and health-related QOL accompanied by a reduction in the inflammatory cytokines in this study.

Our results also demonstrate marked differences in the pattern of weight change in the control group, whereas those in the combination group gained weight. Notably, these changes in weight were due to alterations in lean mass rather than fat. Lean mass appeared to increase significantly in the combination group, while in the control group it was unchanged. While loss of lean or fat-free mass may be considered to be more relevant to function in COPD, lean mass depletion may not simply be the result of energy imbalance but may reflect disordered protein metabolism due to other factors such as muscle disuse, hypoxia, or drug treatment.[40] Many of these factors have not been addressed by rehabilitation and supplementation.[5,40] While muscle mass can be increased by strength training, this would also be expected from a training program with nutritional support and low-intensity training program such as ours.

These findings also suggest that our low-intensity exercise training does not result in a negative energy balance in many patients, as this issue is overcome by supplementation. Exercise in physical activity imposes a high energy cost for patients with COPD.[41] The increase in exercise capacity for many patients who attend rehabilitation is substantial, and dietary calorie intake may be sufficient to meet this metabolic demand. Nutritional supplementation might therefore confer a performance advantage by allowing greater adherence to an exercise training program.

Our data is in line with the data by Steiner et al.[42] showing that increases in walking performance are related to increases in carbohydrate ingestion. An improvement in performance from carbohydrate supplementation is biologically plausible. Carbohydrates are an important source of energy for endurance exercise but intramuscular stores are limited.[42] Carbohydrate feeding can prolong endurance in healthy subjects and there is evidence that a high carbohydrate diet can enhance the effects of endurance training.[43] Muscle glycogen stores may be lower in COPD patients[44] and like other deconditioned individuals, they are likely to be highly reliant on carbohydrate as a source of fuel for

muscular contraction.[45] If physical activity increases, carbohydrate availability may become an important factor in sustaining exercise.

In this study, we used nutritional drink supplement for nutritional intervention. Two 200 ml packages of nutritional drink cost about 4.4 dollars (3.2 Euro). Total cost for 12 week nutritional support in this study was about 370 dollars (270 Euro) per a patient. Therefore, it was suggested that cost-effectiveness of this intervention was efficient and that nutritional support in this study was able to be applied to malnourished COPD patients in clinical practice.

Pulmonary rehabilitation has been established as an effective treatment for enhancing performance in COPD. The long-term aim of rehabilitation is the maintenance of physical fitness through a more active lifestyle. The implication of our study is that, for some patients, this lifestyle change can also result in a negative energy balance and progressive weight loss. The sample size and the time period used in our study were insufficient for reaching a definitive conclusion. We believe that a study on a larger scale and for a longer period of time should be conducted to assess the effectiveness of nutritional supplementation with low-intensity exercise during rehabilitation in underweight patients with COPD.

In conclusion, our data suggest a potential role for the combination of nutritional support and low-intensity exercise, and that this combination may improve the outcomes of exercise tolerance and health-related QOL in patients with malnourished COPD. Thus a combination of nutritional support and low-intensity exercise may provide a new therapeutic approach for pulmonary cachexia.

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Conflict of the interest

Authors have no conflict to disclose.

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