Eur Respir J, 1993, 6, 729–734
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European Respiratory Journal
ISSN 0903 - 1936

REVIEW

Weight loss in chronic obstructive pulmonary disease

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ABSTRACT: Weight loss occurs in about a third or more disabled patients with chronic obstructive pulmonary disease (COPD), and appears to be a poor prognostic factor. As such, it correlates only weakly with FEV_1, transfer factor and other measures of respiratory physiology and is probably, to a certain extent, independent of them. Recent studies of basal metabolic rate (BMR) in COPD using steady-state, non-invasive calorimetry, have shown it to be elevated by 10–20% in up to 40% of such patients. It is likely that this represents true hypermetabolism per kilogram of fat free mass. An elevated BMR cannot be predicted from combinations of detailed lung function tests or arterial gases, as patients with similar physiology have differing BMRs. Thus, although an increased work of breathing is the probable explanation for some of the increase, other factors such as cytokines or possibly drug therapy almost certainly contribute.

Muscle loss in weight-losing COPD appears to involve both type I and type II fibres, because of a combination of reduced calorie intake and disuse atrophy. Respiratory muscles share this fibre loss. Review of the controlled studies on nutritional supplementation in COPD suggests that an energy increase of about 30% is needed to achieve substantial weight gain and improve exercise tolerance. Fat-rich supplements have some theoretical advantages. Further work is needed particularly with regard to the determinants of the increased BMR in COPD, and the effect of longer term nutritional supplements on prognosis.

Eur Respir J., 1993, 6, 729–734.

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Keywords: Basal metabolic rate
chronic obstructive pulmonary disease (COPD)
metabolism
nutrition

Received: April 8 1992
Accepted after revision January 23 1993

Severe chronic obstructive pulmonary disease (COPD) is frequently marked by weight loss [1–6]. Although the mechanism is not fully understood, it is of clinical importance, since patients who are losing weight have a poorer prognosis than those who are of stable weight [1, 4], and there is some evidence that it may be a prognostic factor independent of, or at least not closely correlated with, the degree of airflow obstruction [7].

Weight loss in COPD

In COPD, low body weight is strongly correlated with worse disease state, and may be found in more than a third of more disabled patients [2, 5, 7–10]. In the 779 COPD patients studied in the US Intermittent Positive Pressure Breathing (IPPB) Trial, 95 out of 275 (35%) with forced expiratory volume in one second (FEV_1) less than 35% predicted, were less than 90% ideal body weight (IBW), compared with 54 out of 262 (21%) with an FEV_1 between 35–47% predicted, and 38 out of 242 (16%) with an FEV_1 between 47–60% predicted [7]. Similarly, in a study of 153 COPD patients, with a mean FEV_1 of 38% predicted, SCHOLS *et al.* [10] showed that 30 hypoxic patients (mean arterial oxygen tension (Pao_2) 6.5±0.7 kPa) were significantly lighter than 123 patients with mean Pao_2 10.1±1.7 kPa. A similar positive correlation was seen for the transfer factor, and an inverse correlation for total lung capacity (TLC). Although loss of weight is sometimes taken to be a "terminal" event in the progression of COPD [1], there is now evidence that, independently of FEV_1, it is a poor prognostic factor for survival even in patients with an FEV_1 greater than 40% predicted [7].

Mechanism of weight loss

Intake

Weight loss occurs when energy expenditure exceeds energy intake, *i.e.* when an individual is in negative energy balance. Although patients may lose weight acutely in exacerbations of COPD, they usually regain it upon recovery. In the majority of patients, weight loss appears to develop gradually, when they are otherwise in a stable clinical state [8, 9].

Two early studies of dietary histories in COPD patients [1, 2], showed that their calorie intake was equivalent to, or exceeded, their estimated daily requirements. However, intake estimates from dietary studies are not very reliable, and it has more recently been shown that the energy requirements of some COPD patients who are losing weight may be abnormally high [11].

In healthy man, the normal adaptation to an increase in energy requirements, is a *pari passu* increase in calorie intake.

The reasons for a relatively deficient energy intake in COPD are not clearly understood. It has been suggested that patients with severe COPD may eat suboptimally because chewing and swallowing may change breathing pattern and decrease arterial oxygen saturation (Sa_{O_2}) [12, 13]. Furthermore, gastric filling in these patients may reduce the functional residual capacity (FRC) and lead to an increase in dyspnoea [13]. It is possible that the hypothalamic appetite regulator is abnormal in COPD, but no evidence for this hypothesis is available.

Thus, the energy requirements of some of these more breathless patients are likely to be greater than predicted from standard tables, and attempts to increase oral intake may be difficult for mechanical reasons.

Energy expenditure

There have now been many studies of metabolic energy expenditure in COPD, using non-invasive calorimetric methods in the stable state [5, 14–18]. In sedentary patients, the major component of 24 h energy expenditure is the resting energy expenditure (REE), with diet-induced thermogenesis (DIT) contributing approximately 15% to the total. Exercise-induced thermogenesis contributes a variable amount, but is almost certainly smaller in these less active patients. For example, DIT might typically be about 375 cal·day^{-1}, equivalent in energy expenditure terms to walking at 5 kph^{-1} for 1 h carrying a 20 kg load.

These recent metabolic studies have shown that many patients with COPD have basal rates of energy expenditure, some 10–20% higher than predicted from age, height, weight and gender using the Harris-Benedict equation. An elevation of energy expenditure of 10–20% above energy intake, would explain the weight loss. In the case of a patient who is expending about 500 kJ of energy above intake per day, a weight loss in the order of 10% of body weight over 1–2 yrs would be expected. The proportion of patients who are hypermetabolic has not been estimated in a large cohort, but was about 40% in smaller studies, where the mean FEV_1 was about 1 litre [16, 19]. Hypermetabolism appears to be more common in more severe disease, and in patients who are losing weight [5].

However, the Harris-Benedict equation for predicted basal metabolic rate (BMR) in these studies assumes a standard body composition. A better way of expressing metabolic rate under these circumstances is as a function of fat free mass. However, to date, the use of skinfold anthropometry to derive this has not been validated in COPD, and it is possible that it is overestimated. Bioelectrical impedence (BI) measurements may be better, but the same criticisms apply. In 32 COPD patients, SCHOLS *et al.* [20] recently reported a very high (0.93) correlation between BI and total body water measurements made by dueterium dilution. However, this study did not allow the strict validation of BI as a measure of fat free mass (as opposed to total body water) in these subjects. More research in this area is required, but the available evidence supports the conclusion that there is indeed hypermetabolism in COPD when BMR is expressed as a function of fat free mass.

The other difficulty here is that not all COPD patients who lose weight are hypermetabolic [21]. The increase in metabolic rate has been attributed to an increase in respiratory muscle work, since the energy cost of increasing ventilation is higher in patients with advanced COPD than in healthy controls of comparable age and gender [22]. However, REE correlates only weakly [5], or not at all [23], to individual or combinations of detailed lung function tests and blood gases, including measurements of volume and transfer factor. Thus, patients with the worst lung function, and in whom the work of breathing should be the highest, are not necessarily hypermetabolic. In addition, in a recent report, nasal intermittent positive pressure ventilation, which eliminated diaphragmatic and intercostal activity, did not reduce BMR to normal in a group of hypermetabolic patients [24].

Thus, whilst an increased work of breathing may contribute to weight loss, there is no convincing evidence that this is the only explanation, and other factors which could stimulate metabolism have to be considered. Possible candidates include catecholamines, cortisol and thyroid hormones, cytokines and drug treatment.

Circulating cortisol and thyroxine levels are normal in COPD [19]; noradrenaline but not adrenaline levels are raised [23]. It is not known whether the latter causes any change in skeletal muscle β-receptor density or sensitivity, and there have been no experiments directly to test the hypothesis that high catecholamine levels in COPD contribute to hypermetabolism. Likewise, it is not known whether the routine use of inhaled β-agonists increases metabolic rates. Even if it did, their use could only partly explain the raised BMR in COPD; whereas this may be increased by 10–20% above normal, two weeks of oral terbutaline sulphate increased BMR by less than 8% in healthy men [25]. Furthermore, in 23 patients with chronic asthma or tobacco-related COPD, there was no correlation between inhaled β-agonist dose or theophylline dose and BMR [23].

Another possibility is that hypermetabolism is cytokine-mediated. The polypeptide cytokine tumour necrosis factor (TNF) is produced by monocytes and macrophages. It inhibits lipoprotein lipase activity and is pyrogenic [26, 27]. It also triggers the release of other cytokines, including interleukins-1 and 2, which themselves mediate an increase in energy expenditure, as well as mobilization of amino acids and muscle protein catabolism [27, 28]. Cytokines are raised in cardiac cachexia [29], and they could be associated with the weight loss and hypermetabolism seen in COPD. Further work is needed to define their role.

Skeletal muscle metabolism in COPD

Skeletal muscle is a major component of fat free body mass. Postmortem studies have shown a correlation between body weight and diaphragm muscle mass [30];

and that in emphysematous patients diaphragm weights were less than predicted from body weight [31]. Whether, in COPD, loss of respiratory muscle mass leads to physiologically important decreases in function is less clear. Experimental work in animals has shown that diaphragm weight and, therefore, maximal force was decreased in proportion to induced total body weight loss, as compared with normally nourished controls [32, 33]. However, this loss of muscle bulk was predominantly amongst the type II fast-twitch (mainly glycolytic-dependent) fibres, and less marked in the type I, or slow-twitch, oxidative, fibres. If this were to happen in COPD patients, then one might expect that maximum power output of the respiratory muscles would be decreased, whereas muscle function during basal activities would be less affected [34].

In underweight humans without lung disease, respiratory muscle power measured by maximal static inspiratory pressure (PImax) and maximal static expiratory pressure (PEmax) is lower than in well-nourished controls [35, 36]. However, studies in COPD patients have produced conflicting results. Three have shown a reduction in PImax and PEmax in lighter or malnourished patients [22, 37, 38], whilst three others could not demonstrate this [11, 39, 40]. A conclusion is, therefore, difficult, but it seems likely that a clinically important decrease in respiratory muscle strength is probably not present in all underweight patients with COPD, although it is probably the case in the most severely affected.

The factors likely to lead to a loss of muscle bulk in COPD have been considered above, but the interaction between the clinical and metabolic abnormalities in COPD and skeletal muscle function needs to be considered separately.

Skeletal muscle atrophy quickly follows disuse, and is commonly seen in bed-rested patients. Physical inactivity could contribute to muscle wasting in severe COPD. Since disuse-wasting, in contrast to malnourishment, mainly affects type I fibres, one would expect aerobic exercise performance, including respiratory muscular work, to be impaired more than anaerobic capacity, in relation to the degree of wasting. In particular, loss of oxidative capacity would be expected to reduce the aerobic, but not the anaerobic, regeneration of adenosine triphosphate (ATP) during muscular activity.

There are two anaerobic mechanisms for restoring ATP, one involving the breakdown of creatine phosphate to provide inorganic phosphate, and the other involving anaerobic glycolysis. Creatine phosphate stores are limited, being exhausted within 5–8 s of maximal exercise. These stores are subsequently replenished by the aerobic breakdown of ATP. Thus, if the ratio of inorganic phosphate to creatine phosphate is abnormally high, the aerobic capacity of the muscle must be reduced. The concomitant decrease in pH would be expected to interfere with the contractile mechanism, thereby contributing to fatigue. Evidence for such an explanation for impaired exercise performance in COPD comes from two recent studies of muscle metabolism, using nuclear magnetic resonance (NMR) spectroscopy, published in a former issue of this journal [41–43].

In the absence of infection or right ventricular failure, patients with stable COPD were found to have normal resting levels of forearm muscle intracellular substrates and pH. However, with increasing levels of forearm muscular work, these patients displayed an abnormal rise in the ratio of inorganic phosphate to creatinine phosphate, and an abnormal fall in pH. These results are consistent with the presence of impaired muscular oxidative capacity in COPD. Although this impairment is probably because of disuse-wasting of oxidative fibres (mainly type I) it could also be secondary to reduced tissue blood flow.

By contrast with the normal intracellular substrate and pH levels seen in stable COPD, biochemical studies have shown aberrations in skeletal muscle metabolite levels in patients during acute infective episodes [44, 45]. In particular, the quadriceps and intercostal intramuscular pH, and concentrations of ATP, creatine phosphate and glycogen were lower, and those of glucose and lactate were higher, on admission than at discharge [44]. The patients with the longest duration of an exacerbation before hospital admission had the lowest ATP levels. Reduced availability of energy-rich compounds for respiratory muscular work would be expected to reduce the efficiency of respiratory muscle activity. All of these patients received parenteral nutrition during part of their hospital stay, and at discharge the concentrations of intramuscular metabolites were much improved.

These results imply, that skeletal muscle function is abnormal in some COPD patients, and is likely to be worse in exacerbations. Extrapolation from these limb muscle studies to conclusions about respiratory muscle physiology must be made with care, however, because of the differing proportions of fibre types [46].

Nutritional supplementation

To increase body weight in malnourished COPD patients, and thereby improve their muscle function, would seem to be a logical treatment in the light of the foregoing experimental evidence, but it has not yet been shown that this results in a better prognosis. The data available are essentially from short-term studies, with weight gain and some functional indices as end-points.

The first question is whether malnourished COPD patients handle nutrients normally, or whether, like septic patients, they are catabolic, and unable to improve nitrogen balance despite an increased protein intake. GOLDSTEIN *et al.* [14] showed that there appeared to be an increased utilization of carbohydrate in malnourished COPD patients, compared with malnourished patients without lung disease. However, two more recent studies have suggested that the metabolic response to food in COPD patients is in fact similar to healthy age-matched controls, with no consistent evidence for the preferential utilization of glucose, or differences in protein oxidation [16, 19]. Thus, it seems unlikely that fuel oxidation in stable COPD patients is abnormal; and weight gain should be expected as a result of increased mixed nutrient intake.

There have been five controlled studies of nutritional supplementation in COPD [39, 40, 47–49]. Patient numbers ranged 7–25, duration 8–13 weeks, and calorie intake 15–48%, above the control groups. Only the patients with energy increases of more than 30% appeared to increase body weight and to have improvements in respiratory muscle function or exercise performance. There is now an urgent need for more studies in this field, since this conclusion depends largely on the single study by EFTHIMIOU and co-workers [48].

High carbohydrate loads could theoretically be worse for COPD patients, because of their reduced capacity to excrete the resulting CO_2 load. This has been observed in ventilated patients receiving total parenteral nutrition (TPN) [50, 51]. However, in ambulant patients, these effects seem small [52, 53]. Nevertheless, there may be an advantage in prescribing high fat, rather than high carbohydrate supplements. EFTHIMIOU and co-workers [54] have recently studied ventilatory parameters, 6 min walk distance, and perceived breathlessness, in 10 COPD patients receiving double-blind, 920 kcal in a fat rich drink, or an isocalorific amount of a carbohydrate-rich drink, or an equal volume of a control liquid. They found that the carbohydrate-rich drink resulted in significantly greater increases in minute ventilation ($\dot{V}E$), carbon dioxide elimination ($\dot{V}CO_2$), oxygen consumption ($\dot{V}O_2$), respiratory quotient (RQ), arterial carbon dioxide tension ($PaCO_2$) and Borg score, together with a greater fall in the distance walked in 6 min, than the fat-rich drink. This result is similar to an earlier study by BROWN *et al.* [55]. Few data exist comparing different methods of supplementation in clinical practice, although experience suggests that supplements given between meals, and supplemental oxygen during feeding need to be considered [12, 56].

The interesting suggestion has been made in preliminary reports, that growth hormone therapy may improve nitrogen balance in COPD. This is likely to be due to increased insulin concentrations, since insulin promotes protein synthesis, whilst inhibiting protein degradation and urea synthesis [57, 58].

Summary

Figure 1 shows a model of the events which may lead to weight loss in some patients with COPD. This hypothetical cycle starts with lung damage, leading to impaired lung function. This causes an increase in the energy cost of breathing, thereby increasing the body's total energy requirements. In the absence of a compensatory increase in energy intake, both fat and fat-free mass are lost. The loss of skeletal muscle mass impairs exercise performance, and the loss of respiratory muscle mass, in particular, causes further impairment of alveolar ventilation. As the disease progresses, the patient becomes more dyspnoeic on effort which, together with the decline in muscle mass, makes him more sedentary, thus causing further muscle wasting and a reduced capacity for protein synthesis. In addition, humoral factors may stimulate the metabolic rate and push the patient further into negative energy balance. The end result of such a cycle would eventually be dramatic weight loss. Many elements of this cycle require further research, which is important because of the independent adverse prognostic effect of weight loss in COPD.

Acknowledgement: The authors would like to very sincerely thank E. Power for her secretarial assistance.

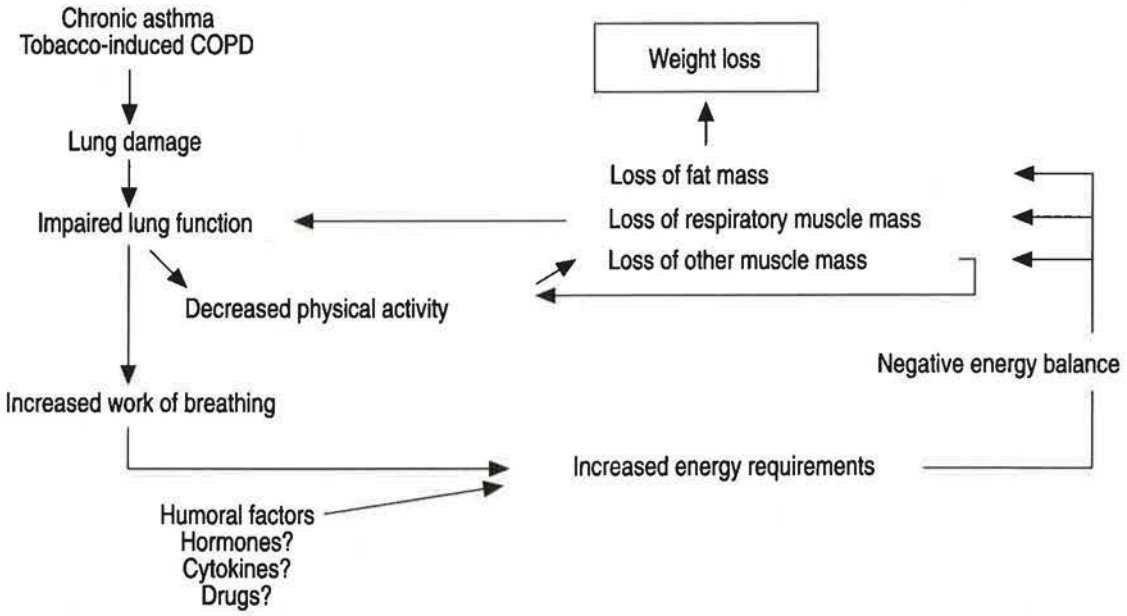

Fig. 1. – Hypothetical cycle of positive feedfack leading to weight loss in chronic obstructive pulmonary disease (COPD).

References

1. Vandenbergh E, Van De Woestijne KP, Gyselen A. – Weight changes in the terminal stages of chronic obstructive pulmonary disease: relation to respiratory function and prognosis. *Am Rev Respir Dis* 1967; 96: 556–565.
2. Hunter AMB, Carey MA, Larsh HW. – The nutritional status of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1981; 124: 376–381.
3. Driver AG, McAlevy MT, Smith JL. – Nutritional assessment of patients with chronic obstructive pulmonary disease. *Chest* 1982; 5: 568–571.
4. Openbrier DR, Irwin MM, Rogers RM, *et al.* – Nutritional status and lung function in patients with emphysema and chronic bronchitis. *Chest* 1983; 83: 17–22.
5. Schols AMWJ, Soeters PB, Mostert R, Saris WHM, Wouters EFM. – Energy balance in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 143: 1248–1252.
6. Wilson DO, Rogers RM, Saunders MH, Pennock BE, Reilly JJ. – Nutritional intervention in malnourished patients with emphysema. *Am Rev Respir Dis* 1986; 134: 672–677.
7. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. – Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989; 139: 1435–1438.
8. Mitchel RS, Filley GF. – Chronic obstructive bronchopulmonary disease. I. Clinical features. *Am Rev Respir Dis* 1964; 89: 360–371.
9. Sukumalchantra Y, Williams MH. – Serial studies of pulmonary function in patients with chronic obstructive pulmonary disease. *Am J Med* 1965; 39: 941–945.
10. Schols A, Mostert R, Soeters P, Greve LH, Wouters EMF. – Inventory of nutritional status in patients with COPD. *Chest* 1989; 96: 247–249.
11. Braun SR, Keim NL, Dixon RM, *et al.* – The prevalence and determinants of nutritional changes in chronic obstructive pulmonary disease. *Chest* 1984; 86: 558–563.
12. Schols A, Mostert R, Cobben N, Soeters P, Wouters EFM. – Transcutaneous oxygen saturation and carbon dioxide tension during meals in patients with chronic obstructive pulmonary disease. *Chest* 1991; 100: 1287–1292.
13. Smith J, Wolkove N, Colacone A, Kreisman H. – Coordination of eating, drinking and breathing in adults. *Chest* 1989; 96: 578–582.
14. Goldstein SA, Thomashow BM, Kvetan V, *et al.* – Nitrogen and energy relationships in malnourished patients with emphysema. *Am Rev Respir Dis* 1988; 138: 636–644.
15. Lanigan C, Moxham J, Ponte J. – Effect of chronic airflow limitation on resting oxygen consumption. *Thorax* 1990; 45: 388–390.
16. Green JH, Muers MF. – The thermic effect of food in underweight patients with emphysematous chronic obstructive pulmonary disease. *Eur Respir J* 1991; 4: 813–819.
17. Fitting JW, Frascarolo Ph, Jequier E, Leuenberger Ph. – Energy expenditure and rib cage-abdominal motion in chronic obstructive pulmonary disease. *Eur Respir J* 1989; 2: 840–845.
18. Donahoe M, Rogers RM, Wilson DO, Pennock BE. – Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: 385–391.
19. Green JH, Muers MF. – Comparisons between basal metabolic rate and diet-induced thermogenesis in different types of chronic obstructive pulmonary disease. *Clin Sci* 1992; 83: 109–116.
20. Schols AMWJ, Wouters EFM, Soeters PB, Westerterp KR. – Body composition by bioelectrical impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1991; 53: 421–424.
21. Congleton J, Green JH, Muers MF. – Basal metabolic rate, weight loss and decline in FEV_1 in COPD. *Thorax* 1993, (in press).
22. Donahoe M, Rogers RM, Wilson DO, Pennock BE. – Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: 385–391.
23. Hofford JM, Milakofsky L, Vogel WH, *et al.* – The nutritional status in advanced emphysema associated with chronic bronchitis: a study of amino acid and catecholamine levels. *Am Rev Respir Dis* 1990; 141: 902–908.
24. Hugli O, Schutz Y, Leuenberger PH, Fitting JW. – Cost of breathing in stable ambulatory COPD patients. *Eur Respir J* 1992; 5 (Suppl. 15): 474S.
25. Scheidegger K, O'Connell M, Robbins DC, Danforth E Jr. – Effects of chronic β-receptor stimulation on sympathetic nervous system activity, energy expenditure and thyroid hormones. J *Clin Endocrinol Metab* 1984; 58: 895–903.
26. Cerami A, Neutler B. – Role of cachectin/TNF in endotoxic shock and cachexia. *Immunol Today* 1987; 9: 28–31.
27. Evans RD, Argiles JM, Williamson DH. – Metabolic effects of tumour necrosis factor-x (cachectin) and interleukin-1. *Clin Sci* 1989; 77: 357–364.
28. Oppenheim JJ, Kovacs EJ, Matsushima K. – There is more than one interleukin-1. *Immunol Today* 1986; 7: 45–46.
29. Lavine B, Kalman J, Mayer L, Fillit H, Packer M. – Elevated circulating levels of tumour necrosis factor in severe chronic heart failure. *N Engl J Med* 1990; 323: 236–241.
30. Arora NS, Rochester DF. – Effect of body weight and muscularity on human diaphragm muscle mass, thickness, and area. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982; 52: 64–70.
31. Thurlbeck MM. – Diaphragm and body weight in emphysema. *Thorax* 1978; 33: 483–487.
32. Kelson SG, Ference M, Kapoor S. – Effects of prolonged undernutrition on structure and function of the diaphragm. *J Appl Physiol* 1985; 58: 1354–1359.
33. Lewis MI, Sieck GC, Fournier M, Belman MJ. – Effect of nutritional deprivation on diaphragm contractility and muscle fiber size. *J Appl Physiol* 1986; 60: 596–603.
34. Gray-McDonald K, Gibbons L, Shapiro SH, Martin JG. – The effect of nutritional state on exercise performance in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 139: 1435–1438.
35. Arora NS, Rochester DF. – Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis* 1982; 126: 5–8.
36. Kelly SM, Rosa A, Field S, *et al.* – Inspiratory muscle strength and body composition in patients receiving total parenteral nutrition therapy. *Am Rev Respir Dis* 1984; 130: 33–37.
37. Rochester DF, Braun NMT. – Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; 132: 42–47.
38. Gray-McDonald K, Carrey Z, Martin JG. – Effect of nutritional status on exercise performance in COPD. *Am Rev Respir Dis* 1988; 137(4), 154 (Abstract).
39. Lewis MI, Belman MJ, Dorr-Uyemura L. – Nutritional supplementation in ambulatory patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1987; 135: 1062–1068.
40. Knowles JB, Fairbar MS, Wiggs BJ, Chan-Yan C, Pardy RL. – Dietary supplementation and respiratory muscle performance in patients with COPD. *Chest* 1988; 93: 977–983.
41. Wuyam B, Payen JF, Levy P, *et al.* – Metabolism and aerobic capacity of skeletal muscle in chronic respiratory failure

related to chronic obstructive pulmonary disease. *Eur Respir J* 1992; 5: 157–162.
42. Tada H, Kato H, Musawa T, *et al.* – ^{31}P-nuclear magnetic resonance evidence of abnormal skeletal muscle metabolism in patients with chronic lung disease and congestive heart failure. *Eur Respir J* 1992; 5: 163–169.
43. Jakovsson P, Jorfeldt L. – Nuclear magnetic resonance spectroscopy: a tool for skeletal muscle metabolic research. *Eur Respir J* 1992; 5: 151–154.
44. Gertz I, Hedenstierna G, Wellers G, Wahren J. – Muscle metabolism in patients with chronic obstructive lung disease and acute respiratory failure. *Clin Sci Mol Med* 1977; 52: 395–403.
45. Del Canale S, Soderlung K, Fiaccadori E, *et al.* – Abnormal energy metabolism in severe chronic obstructive lung disease (COLD). *Eur J Respir Dis* 1986; 69 (Suppl. 146): 239–243.
46. Faulkner JA, Maxwell LC, Ruff GL, Waite TP. – The diaphragm as a muscle. *Am Rev Respir Dis* 1979; 119: 89–92.
47. Otte KE, Ahlburg P, D'Amore F, Stellford M. – Nutritional repletion in malnourished patients with emphysema. *J Parent Ent Nutr* 1989; 13: 152–156.
48. Efthimiou J, Fleming J, Gomes C, Spiro SG. – The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; 137: 1075–1082.
49. Whittaker JS, Ryan CF, Buckley PA, Road JD. – The effect of re-feeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *Am Rev Respir Dis* 1990; 142: 283–288.
50. Covelli HD, Waylon Black J, Olsen MS, Beekman JF. – Respiratory failure precipitated by high carbohydrate loads. *Ann Intern Med* 1981; 95: 579–581.
51. Dark DS, Pingleton SK, Kerby GR. – Hypercapnia during weaning. A complication of nutritional support. *Chest* 1985; 88: 141–143.
52. Angelillo VA, Bedi S, Durfee D, *et al.* – Effects of low and high carbohydrate feeding in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. *Ann Intern Med* 1985; 103: 883–885.
53. Sue DY, Chung MM, Grosvenor M, Wasserman K. – Effect of altering the proportion of dietary fat and carbohydrate on exercise gas exchange in normal subjects. *Am Rev Respir Dis* 1989; 139: 1430–1434.
54. Efthimiou J, Mounsey PJ, Benson DN, *et al.* – Effect of carbohydrate-rich *versus* fat-rich loads on gas exchange and walking performance in patients with chronic obstructive lung disease. *Thorax* 1992; 47: 451–456.
55. Brown SE, Nagenclern EC, McHugh JW, *et al.* – Effects of a large carbohydrate load on walking performance in chronic airflow obstruction. *Am Rev Respir Dis* 1985; 132: 960–962.
56. Fitting JW. – Nutritional support in chronic obstructive lung disease. *Thorax* 1992; 47: 141–143.
57. Suchner U, Rothkopf MM, Stanislaus G, *et al.* – Growth hormone and pulmonary disease: metabolic effects in patients receiving parenteral nutrition. *Arch Intern Med* 1990; 150: 1225–1230.
58. Pape GS, Friedman M, Underwood LE, Clemmons DR. – The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. *Chest* 1991; 99: 1495–1500.