Clinical Nutrition 28 (2009) 455–460

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guidelines on Parenteral Nutrition: On Cardiology and Pneumology

S.D. Anker [a], A. Laviano [b], G. Filippatos [c], M. John [d], A. Paccagnella [e], P. Ponikowski [f], A.M.W.J. Schols [g]

[a] Department of Cardiology, Charité-Universitätsmedizin, Berlin, Germany
[b] Department of Clinical Medicine, University La Sapienza, Rome, Italy
[c] Department of Cardiology, Athens University Hospital Attikon, Athens, Greece
[d] Department of Cardiology Pulmonology & Angiology, Charité-Universitätsmedizin, Berlin, Germany
[e] Department of Medicine, Nutritional Service, Treviso Healthcare Authority, Italy
[f] Cardiac Department, Military Hospital, Wroclaw, Poland
[g] Department of Respiratory Medicine, University Hospital, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Received 19 April 2009
Accepted 29 April 2009

Keywords:
Chronic heart failure
Chronic obstructive pulmonary disease
Cardiac cachexia
Dyspnoea

SUMMARY

Nutritional support is becoming a mainstay of the comprehensive therapeutic approach to patients with chronic diseases. Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are frequently associated with the progressive development of malnutrition, due to reduced energy intake, increased energy expenditure and impaired anabolism. Malnutrition and eventually cachexia have been shown to have a negative influence on the clinical course of CHF and COPD, and to impinge on patients' quality of life. Nutritional support in these patients should be therefore considered, particularly to prevent progressive weight loss, since restoration of lean and fat body mass may not be achievable. In CHF and COPD patients, the gastrointestinal tract is normally accessible and functioning. Although recent reports suggest that heart failure is associated with modifications of intestinal morphology, permeability and absorption, the clinical relevance of these are still not clear. Oral supplementation and enteral nutrition should represent the first choices when cardiopulmonary patients need nutritional support, particularly given the potential complications and economic burden of parenteral nutrition. This appropriately preferential enteral approach partly explains the lack of robust clinical trials of the role of parenteral nutrition in CHF and COPD patients. Based on the available evidence collected via PubMed, Medline, and SCOPUS searches, it is recommended that parenteral nutrition is reserved for those patients in whom malabsorption has been documented and in those in whom enteral nutrition has failed.

Summary of statements: Parenteral Nutrition in Cardiology

Subject	Recommendations	Grade	Number
Background	The prevalence of cardiac cachexia, defined from weight loss of at least 6% in 6 months, has been estimated at about 12–15% in patients in New York Heart Association (NYHA) classes II–IV. The incidence of weight loss >6% in CHF patients with NYHA class III/IV is approximately 10% per year. CHF affects nutritional state, energy and substrate metabolism.	B	1.1
	The mortality in CHF patients with cardiac cachexia is 2–3 times higher than in non-cachectic CHF patients.	B	1.2
	Although there is limited evidence that gut function is impaired in CHF, decreased cardiac function can reduce bowel perfusion and lead to bowel wall oedema, resulting in malabsorption.	B	1.3
Indications	Although there is no evidence available from well-designed studies, PN is recommended to stop or reverse weight loss in patients with evidence of malabsorption, on the basis that it improves outcome in other similar conditions and there is a plausible physiological argument for it.	C	1.4
	Currently there is no indication for PN in the prophylaxis of cardiac cachexia. Further studies are needed to assess the impact of the parenteral administration of specific substrates on cardiac function.	C	1.5

(*continued on next page*)

E-mail address: espenjournals@espen.org.

0261-5614/$ – see front matter
doi:10.1016/j.clnu.2009.04.023

Summary of statements: Parenteral Nutrition in Cardiology			
Subject	**Recommendations**	**Grade**	**Number**
Contra-indications	There are no specific contraindications to PN in CHF patients. However, considering that cardiac function is decreased and water retention is frequently found in CHF patients, it is recommended that PN should be avoided, other than in patients with evidence of malabsorption in whom enteral nutrition has been shown, or is strongly expected, to be ineffective.	B	1.6
Implementation	When feeding CHF patients, either enterally or parenterally, fluid overload must be avoided.	C	1.6
Summary of statements: Parenteral Nutrition in Respiratory Medicine			
Subject	**Recommendations**	**Grade**	**Number**
Background	Between 25% and 40% of patients with advanced COPD are malnourished.	B	2.1
	Being underweight and having low fat-free mass are independently associated with a poor prognosis in patients with chronic respiratory insufficiency, especially in COPD.	B	2.2
Indications	There is no evidence showing that gut function is impaired in COPD patients. Therefore, considering that enteral nutrition is less expensive and associated with fewer and less severe complications than parenteral nutrition, enteral nutrition should represent the first approach to patients with COPD in need of nutritional support.	B	2.3
	There is limited evidence that COPD patients intolerant of EN profit from PN. Small studies do however suggest that, in combination with exercise and anabolic pharmacotherapy, PN has the potential to improve nutritional status and function.	C	2.4
Effect of PN	Loss of body weight is correlated with increased morbidity and mortality. However, due to the lack of studies of its effects, it is not possible to be sure if prognosis is influenced by the provision of PN.	B	2.5
Regimen selection	In patients with stable COPD, glucose-based PN causes an increase in the respiratory CO_2 load. PN composition should accordingly be orientated towards lipids as the energy source. There is not sufficient evidence to recommend specific lipid substrates.	B	2.6

1. Chronic heart failure

1.1. Introduction

The prevalence of CHF among the general population is approximately 1%[1,2], and the average 5-year survival-rate is approximately 50%.[1] Considering the improvement in diagnostic tools and the advances in treatment opportunities which will likely occur during the next few years, it is expected that the survival of patients suffering from chronic heart failure (CHF) will increase [3]. Therefore, the prevalence of this disease among the elderly, particularly in its advanced form, is likely to increase. Since malnutrition and eventually cardiac cachexia (i.e., weight loss associated with increased inflammatory response, and impaired metabolic response to starvation) will be more common in the future, and nutritional support will necessarily find an increasing place in cardiological practice.

1.2. Does CHF have an influence on nutritional status, and on energy and substrate metabolism?

The prevalence of cardiac cachexia, defined from weight loss of at least 6% in 6 months, has been estimated at about 12–15% in patients in New York Heart Association (NYHA) classes II–IV. The incidence of weight loss >6% in CHF patients with NYHA class III/IV is approximately 10% per year (B). CHF affects nutritional state, energy and substrate metabolism (B).

Comments: CHF is accompanied by complex changes in the neurohumoral and immunological status of the patient, inducing a continuing catabolic state.[4] Comparing CHF patients with and without weight loss, no significant differences have been observed in terms of cardiac function. Among patients in NYHA classes II and III with no overall weight loss, muscle atrophy of the lower limbs is observed in up to 50% [5] (IIb). Cardiac cachexia, which affects 12–15% of CHF patients,[6,7] can be diagnosed if, over 6 months or more, there is weight loss of more than 6% (in the absence of oedema) compared to normal premorbid weight[8,9] (III). This definition has been validated in the SOLVD and V-HeFT-II study populations.[6] Generalized muscle atrophy of the limbs and significant loss of fat tissue are common in cardiac cachexia,[10] but osteoporosis is rare [11] (III). This definition of cardiac cachexia has yet to be tested in the context of surgery in heart failure patients.

Patients with cardiac cachexia have increased resting energy expenditure,[12] although, due to decreased overall activity, total energy expenditure is reduced by 10–20% compared to CHF patients without cachexia.[13] Neuroendocrine and immunological disturbances underlie the altered balance between anabolism and catabolism in these patients.[10] with increased plasma levels of catecholamines, cortisol, aldosterone, and renin.[14] (IIb), steroid and growth hormone resistance,[15,16] and activation of cytokines.[17,18] There also appears to be excess muscle fibrosis in cachexia.[19] Protein malabsorption plays no part in the development of cardiac cachexia,[20] although fat malabsorption could be of importance.[21] It has been estimated that loss of appetite (anorexia) plays a significant role in only 10–20% of all cases of cardiac cachexia,[8] although detailed studies of food intake and appetite are lacking. Interestingly, a recent study has shown that non-obese, weight stable, free-living patients with clinically stable CHF and a body mass index (BMI) of less than 25 kg/m^2 have a lower intake of calories and protein and expend less energy in physical activity[22] (IIb). More research into these issues is necessary.

1.3. Does nutritional status have prognostic significance?

The mortality in CHF patients with cardiac cachexia is 2–3 times higher than in non-cachectic CHF patients (B).

Comments: independently of other established markers of CHF prognosis, such as peak oxygen consumption, plasma sodium concentration, left ventricular ejection fraction, and functional NYHA class, the presence of cardiac cachexia predicts a worse prognosis[3,6,7] (IIb). There are no published epidemiological data available to show that weight gain, by whatever means, improves outcome in this group of patients. However, in the COMET study of 3000 CHF patients in NYHA classes II–IV who were treated with one of two beta-blockers for a period of 5 years, weight gain was independently associated with significantly better survival and lower hospitalization rates (Anker SD, personal communication).

1.4. Is gut function impaired by CHF?

Although there is limited evidence that gut function is impaired in CHF (B), decreased cardiac function can reduce bowel perfusion and lead to bowel wall oedema, resulting in malabsorption.

Comments: in recent research, the gut has received very little attention from cardiologists as its role in the pathogenesis of cardiovascular disease is usually minor. However, it is acknowledged that decreased cardiac function may reduce bowel perfusion and therefore impair the function of gut barrier. Evidence exist suggesting that a "leaky" bowel wall may lead to translocation of bacteria and/or endotoxins, which in turn may sustain the inflammatory cytokine activation in CHF and exacerbate its detrimental effects on nutritional status.[23] Decreased cardiac function may lead to bowel wall oedema and thus malabsorption,[24] which may prevent, at least in patients with advanced CHF, digestion and absorption of food and/or enteral diets. Recent data obtained from 22 patients with cardiac failure show that CHF is a multisystem disorder in which intestinal morphology, permeability and absorption are modified[25] (III).

1.5. Is PN indicated in the treatment of cardiac cachexia?

Although there is no evidence available from well-designed studies, PN is recommended to stop or reverse weight loss in patients with evidence of malabsorption, on the basis that it improves outcome in other similar conditions and there is a plausible physiological argument for it (C).

Comments: in the absence of good evidence, there is an urgent need for controlled studies of nutritional treatment in this condition with the aim of improving function through increased supply of nutrients and energy.

A small study investigated the role of pre- and post-operative parenteral nutrition in patients with cardiac cachexia undergoing cardiac surgery[26] (III). Data showed improved clinical indices in patients receiving nutritional support without adversely influencing cardiac function. However, it should be noted that more recent data suggest that angiotensin-converting enzyme inhibitors,[6] and (in burns patients) beta-blockers,[27] may exert more pronounced anti-catabolic effects than PN. There is also a case for anabolic agents[28] and suggestions that amino acid supplements may help to maintain muscle protein metabolism.[29] Standard enteral nutrition should however represent the first approach to patients with cardiac cachexia in need of nutritional support. However, parenteral nutrition should be considered in those patients with advanced CHF with evidence of malabsorption (B).

1.6. Is there an indication for PN in the prophylaxis of cardiac cachexia?

Currently there is no indication for PN in the prophylaxis of cardiac cachexia (Grade C). Further studies are needed to assess the impact of the parenteral administration of specific substrates on cardiac function.

Comments: PN in general does not seem to offer useful prophylaxis. There are however data on L-arginine (Arg), the substrate for the synthesis of nitric oxide (NO), which stimulates angiogenesis, and inhibits leukocyte adhesion, platelet aggregation, and superoxide generation. Arg also has NO-independent effects, including synthesis of creatine, proline and polyamines, and secretion of insulin and growth hormone. Preliminary evidence from seven patients with severe congestive cardiac failure indicates that intravenous Arg (30 g in 30 min) may reduce heart rate and improve haemodynamics.[30] Parenteral administration of Arg also appears able to reverse some of the endothelial dysfunction associated with major cardiovascular risk factors[31] (III). However, intravenous Arg is not currently available for clinical use and confirmatory data are clearly needed in this field.

1.7. Is there any known influence of PN on the disease progression, survival, and morbidity of CHF patients?

It is not yet possible to answer this question, because there are no studies available.

1.8. Are there any contraindications to PN in patients with CHF?

There are no specific contraindications to PN in CHF patients. However, considering that cardiac function is decreased and water retention is frequently found in CHF patients, it is recommended that PN should be avoided, other than in patients with evidence of malabsorption in whom enteral nutrition has been shown, or is strongly expected, to be ineffective (B). When feeding CHF patients, either enterally or parenterally, fluid overload must be avoided (C).

2. Chronic obstructive pulmonary disease (COPD)

2.1. Does COPD have an influence on nutritional state, energy and substrate metabolism?

Between 25% and 40% of patients with advanced COPD are malnourished (B).

Comments: clinically relevant weight loss (5% within three months, or 10% within 6 months) is found in 25–40% of all cases in whom lung function is severely impaired (FEV1 $<$ 50%). Muscle wasting, defined as fat-free mass index (FFMI) $<$16 kg/m^2 in males, and $<$15 kg/m^2 in females, is found in 25% of patients with GOLD stages 2 and 3, and in up to 35% of cases with severe disease (GOLD stage 4)[32,33] (IIb). A French cross-sectional survey of 300 COPD outpatients on long-term oxygen therapy found FFM depletion in 38% of patients, whereas BMI levels were low ($<$20 kg/m^2) in only 17% of patients[34] (IIb). FFM is therefore considered the most sensitive tool for detecting wasting in COPD patients. A high prevalence of osteoporosis is also observed in these patients[35] (IIb).

COPD, usually due to cigarette smoking, is the most common cause of chronic respiratory insufficiency, affecting more than 1% of the world's population.[36,37] Respiratory insufficiency can also be caused by a number of other non-malignant lung diseases, including asthma, lung fibrosis, pneumoconiosis, allergic alveolitis, and sarcoidosis, which lead to progressive impairment of lung function in their advanced stages. There is limited information regarding nutritional status and metabolic abnormalities in these conditions.

The causes of cachexia in COPD are thought to be multifactorial, and include tissue hypoxia, ageing, physical inactivity, increased resting metabolic rate, chronic inflammatory processes,[38] and certain drugs, resulting in net catabolism and muscle wasting.[39,40] Endogenous protective anabolic mechanisms are insufficiently effective, due possibly to hormonal resistance syndromes.[41] A pronounced loss of appetite (anorexia) and decreased food intake are of central importance in the weight and fat loss which accompany COPD[41,42] (IIb). This is particularly marked during acute exacerbations, and may be triggered by difficulties in chewing and swallowing secondary to the altered mechanics of breathing, although hypoxia might also be responsible for appetite loss via the neurohumoral actions of leptin and cytokines[43–45] (IIb). The resting metabolic rate is increased in a substantial proportion of COPD patients, but is unrelated to total and activity-induced energy expenditure. A specific increase in activity-induced energy expenditure has also been shown to trigger weight loss in COPD[46] (IIb).

Linked to absolute or relative loss of fat-free mass, abnormalities in whole body and muscle protein and amino acid metabolism have been described, as well as a decreased whole body lipolytic response after beta-adrenergic stimulation.[47] Muscle wasting

secondary to reduced nutritional intake increases energy consumption, and treatment with steroids[48,49] also affects the respiratory muscles whose consequent weakness further exacerbates respiratory failure, prevents weaning from ventilators, and impairs outcome of treatment during acute exacerbations.

2.2. Does nutritional status have an influence on prognosis?

Being underweight and having low fat-free mass are independently associated with a poor prognosis in patients with chronic respiratory insufficiency, especially in COPD (B).

Comments: independently of other factors, weight loss and a low BMI predict poor survival in COPD patients[50–52] (IIb). Mean survival of COPD patients with both cachexia and an FEV1 $< 50\%$ is 2–4 years, considerably shorter than in those without cachexia.

The prevalence and prognostic importance of weight change in unselected subjects with COPD was examined in the Copenhagen City Heart Study.[53] Individuals attended two examinations 5 years apart and were then followed for 14 years. After adjusting for age, smoking habits, baseline BMI and lung function, weight loss was associated with higher mortality in those with and without COPD (IIb). In those with severe COPD, the baseline BMI and subsequent weight change had significant effects on risk ratios. In the normal-to-underweight (BMI < 25 kg/m^2), the best survival was seen in those who gained weight, whereas for the overweight and obese (BMI > 25 kg/m^2), best survival was seen when weight remained stable. Recent studies indicate that FFMI is an independent predictor of mortality in COPD irrespective of FM[54–57] (IIb). This may be related to adverse effects of low FFM on skeletal muscle function,[58] exercise capacity,[59] and overall health status,[60] that increase the frequency and severity of acute exacerbations.

2.3. Is gut function impaired by COPD?

There is no evidence showing that gut function is impaired in COPD patients. Therefore, considering that enteral nutrition is less expensive and associated with fewer and less severe complications than parenteral nutrition, enteral nutrition should represent the first approach to patients with COPD in need of nutritional support (B).

2.4. Is there any benefit of PN in the treatment of patients with advanced non-malignant lung diseases?

There is limited evidence that COPD patients intolerant of EN profit from PN. Small studies do however suggest that, in combination with exercise and anabolic pharmacotherapy, PN has the potential to improve nutritional status and function (C).

Comments: Dyspnoea is one of the main symptoms of COPD patients. Dyspnoea may significantly reduce food intake. Consequently, COPD patients may not meet their nutritional requirements with food or oral supplements. Also, enteral feeding tubes may reduce ventilation and worsen dyspnoea. Therefore, in COPD patients who are intolerant to enteral feeding, PN may provide an opportunity to provide the correct amounts of macro- and micronutrients. Only few studies have investigated the role of PN in replenishing COPD patients. Suchner et al. demonstrated that the administration of PN combined with growth hormone improved nitrogen balance in severely malnourished COPD patients[61] (IIb). Aguilaniu et al. demonstrated that hypercaloric (55 kcal/kg/d), high-lipid (55%) parenteral nutrition improved nitrogen balance in COPD patients[62] (IIb). However, the small number of patients enrolled (six and eight, respectively) limits the confidence to be drawn from the results. More studies are needed in this field.

Artificial nutrition may have a role as part of an integrated pulmonary (exercise) rehabilitation programme to meet increased energy requirements or to support other therapies (e.g. protein supplementation during treatment with anabolic steroids or growth factors). A recent Cochrane review[63] on caloric supplementation for at least 2 weeks in patients with stable COPD concluded that "nutritional support has no effect on anthropometric measures, lung function or exercise capacity in patients with stable COPD" (Ia). Unfortunately this review did not make a distinction between a failure to intervene and a failure of intervention. In the studies that did achieve an increase in energy intake, functional improvements were also observed. Therefore, additional studies are needed to investigate whether PN, by providing nutritional support while minimally influencing food intake, may lead to improved nutritional status of COPD patients.

2.5. Is there an influence of PN on disease progression, survival, and mortality in patients with COPD?

Loss of body weight is correlated with increased morbidity and mortality (Grade B). However, due to the lack of studies of its effects, it is not possible to be sure if prognosis is influenced by the provision of PN.

Comments: no controlled data are available regarding the effects of long-term nutritional support on disease progression or prognosis in advanced COPD. Although in one study short-term weight gain (>2 kg in 8 weeks) was associated with better survival,[52] the SUPPORT study revealed that parenteral hyperalimentation was associated with decreased survival only in acute respiratory failure[64] (IIb). There is a need to perform long-term studies of PN in cachectic patients with COPD, in a controlled double-blind fashion. The adverse effect of depletion of FFM on mortality, even in weight stable COPD patients indicates that FFM, in particular muscle mass, is an important therapeutic target in these patients. Nutritional support could therefore be used not only to maintain stable body weight, but also to contribute to induction of muscle anabolism either on its own or in combination with exercise and/or pharmacological interventions.

2.6. What type of formula should be used?

In patients with stable COPD, glucose-based PN causes an increase in the respiratory CO_2 load. PN composition should accordingly be orientated towards lipids as the energy source (B). There is not sufficient evidence to recommend specific lipid substrates.

Comments: glucose-based PN increases arterial CO_2 concentrations, especially if the glucose load is in excess of metabolic capacity, and it can thus be harmful to patients with COPD. By preferentially selecting lipids as the energy source, the respiratory quotient can be lowered.[65] The proportion of lipid-derived non-protein calories should probably be at least 35% (but probably not more than 65%).

Only one study has investigated the effects on clinical parameters of the provision of specific lipid substrates. Iovinelli et al. recently reported that ventilated patients with COPD receiving PN containing a mixture of soybean derived long-chain triglycerides (LCT) and medium-chain triglycerides (MCT) had a shorter weaning time from mechanical ventilation than patients receiving purely LCT-based PN[66] (IIa). Due to the limited number of patients enrolled in this study, confirmatory data are needed before specific recommendations could be made.

Conflict of interest

Conflict of interest on file at ESPEN (espenjournals@espen.org).

References

1. Cowie MR, Mosterd AA, Wood DA, et al. The epidemiology of heart failure. *Eur Heart J* 1997;**18**:208–25.
2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;**10**:933–89.
3. Springer J, Filippatos G, Akashi YJ, Anker SD. Prognosis and therapy approaches of cardiac cachexia. *Curr Opin Cardiol* 2006;**21**:229–33.
4. Berry C, Clark AL. Catabolism in chronic heart failure. *Eur Heart J* 2000;**21**:521–32.
5. Mancini DM, Walter G, Reichek N, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation* 1992;**85**:1364–73.
6. Anker SD, Negassa A, Coats AJS, et al. Prognostic importance of weight loss in chronic heart and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;**361**:1077–83.
7. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor of survival in chronic heart failure. *Lancet* 1997;**349**:1050–3.
8. Anker SD, Coats AJS. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. *Chest* 1999;**115**:836–47.
9. Lainscak M, Filippatos GS, Gheorghiade M, Fonarow GC, Anker SD. Cachexia: common, deadly, with an urgent need for precise definition and new therapies. *Am J Cardiol* 2008;**101**(11A):8E–10E.
10. Anker SD, Ponikowski PP, Clark AL, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur Heart J* 1999;**20**:683–93.
11. Anker SD, Clark AL, Teixeira MM, Helleerll PG, Coats AJS. Loss of bone mineral in patients with cachexia due to chronic heart failure. *Am J Cardiol* 1999;**83**:612–5.
12. Poehlmann ET, Scheffers J, Gottlieb SS, Fisher ML, Vaitekevicius P. Increased resting metabolic rate in patients with congestive heart failure. *Ann Intern Med* 1994;**121**:860–2.
13. Toth MJ, Gottlieb SS, Goran MI, Fisher ML, Poehlman ET. Daily energy expenditure in free-living heart failure patients. *Am J Physiol* 1997;**272**:469–75.
14. Anker SD, Chua TP, Swan JW, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure: the importance for cardiac cachexia. *Circulation* 1997;**96**:526–34.
15. Anker SD, Clark AL, Kemp M, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. *J Am Coll Cardiol* 1997;**30**:997–1001.
16. Anker SD, Volterrani M, Pflaum C-D, et al. Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. *J Am Coll Cardiol* 2001;**38**:443–52.
17. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;**323**:236–41.
18. Rauchhaus M, Doehner W, Francis DP, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 2000;**102**:3060–7.
19. Filippatos GS, Kanatselos C, Manolatos DD, Vougas B, Sideris A, Kardara D, Anker SD, Kardaras F, Uhal B. Studies on apoptosis and fibrosis in skeletal musculature: a comparison of heart failure patients with and without cardiac cachexia. *Int J Cardiol* 2003;**90**:107–13.
20. King D, Smith ML, Lye M. Gastro-intestinal protein loss in elderly patients with cardiac cachexia. *Age Ageing* 1996;**25**:221–3.
21. King D, Smith ML, Chapman TJ, Stockdale HR, Lye M. Fat malabsorption in elderly patients with cardiac cachexia. *Age Ageing* 1996;**25**:144–9.
22. Aquilani R, Opasich C, Verri M, et al. Is nutritional intake adequate in chronic heart failure patients? *J Am Coll Cardiol* 2003;**42**:1218–23.
23. Krack A, Sharma R, Figulla HR, Anker SD. The importance of the gastrointestinal system in the pathogenesis of heart failure. *Eur Heart J* 2005;**26**:2368–74.
24. von Haeling S, et al. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. *Cardiovasc Res* 2007;**73**:298–309.
25. Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure. *J Am Coll Cardiol* 2007;**50**:1561–9.
26. Paccagnella A, Calo MA, Caenaro G, et al. Cardiac cachexia: preoperative and postoperative nutrition management. *JPEN J Parenter Enteral Nutr* 1994;**18**:409–16.
27. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001;**345**:1223–9.
28. Filippatos G, Rauchhaus M, Anker SD. Decompensated heart failure and cachexia: is it time to legalize anabolics? *Int J Cardiol* 2006;**111**:185–6.
29. Gheorghiade M, Filippatos GS, Fonarow GC, Anker SD. Nutritional supplementation with amino acids in cardiovascular and metabolic diseases: hypermetabolic syndrome as a therapeutic target. Introduction. *Am J Cardiol* 2008;**101**(11A):1E–2E.
30. Bocchi EA, de Moraes AV, Esteves A, Bacal F, Auler JO, Carmona MJ, Bellotti G, Ramires AF. L-Arginine reduces heart rate and improves hemodynamics in severe congestive heart failure. *Clin Cardiol* 2000;**23**:205–10.
31. Wu G, Meininger CJ. Arginine nutrition and cardiovascular function. *J Nutr* 2000;**130**:2626–9.
32. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;**147**:1151–6.
33. Vermeeren MA, Creutzberg EC, Schols AM, Postma DS, Pieters WR, Roldaan AC, Wouters EF. on behalf of the COSMIC Study Group. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med* 2006;**100**:1349–55.
34. Cano N, Roth H, Court-Ortune I, et al. Clinical Research Group of the Societe Francophone de Nutrition Enteral et Parenteral. Nutritional depletion in patients on long-term oxygen therapy and/or home mechanical ventilation. *Eur Resp J* 2002;**20**:30–7.
35. Bolton CE, Ionescu AA, Edwards PH, Faulkner TA, Edwards SM, Shale DJ. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;**170**(12):1286–93.
36. Gulsvik A. The global burden and impact of chronic obstructive pulmonary disease worldwide. *Monaldi Arch Chest Dis* 2001;**56**:261–4.
37. Hurd S. The impact of COPD on lung health worldwide: epidemiology and incidence. *Chest* 2000;**117**(Suppl. 2):1S–4S.
38. Di Francia M, Barbier D, Mege J, Orehek J, et al. Tumor necrosis factor-alpha and weight loss in chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1994;**150**:1453–5.
39. Congleton J. The pulmonary cachexia syndrome: aspects of energy balance. *Proc Nutr Soc* 1999;**58**:321–8.
40. Farber MO, Mannix ET. Tissue wasting in patients with chronic obstructive pulmonary disease. *Neurol Clin* 2000;**18**:245–62.
41. Schols AM, Wouters EF. Nutritional abnormalities and supplementation in chronic obstructive pulmonary disease. *Clin Chest Med* 2000;**21**:753–62.
42. Thorsdottir I, Gunnarsdottir I, Eriksen B. Screening method evaluated by nutritional status measurements can be used to detect malnourishment in chronic obstructive pulmonary disease. *J Am Diet Assoc* 2001;**101**:648–54.
43. Schols AM, Creutzberg EC, Buurman WA, Campfield LA, Saris WH, Wouters EF. Plasma leptin is related to proinflammatory status and dietary intake in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:1220–6.
44. Takabatake N, Nakamura H, Minamihaba O, et al. A novel pathophysiologic phenomenon in cachexic patients with chronic obstructive pulmonary disease: the relationship between the circadian rhythm of circulating leptin and the very low-frequency component of heart rate variability. *Am J Respir Crit Care Med* 2001;**163**:1289–90.
45. Raguso CA, Guinot SL, Janssens JP, Kayser B, Pichard C. Chronic hypoxia: common traits between chronic obstructive pulmonary disease and altitude. *Curr Opin Clin Nutr Metab Care* 2004;**7**:411–7.
46. Baarends EM, Schols AM, Pannemans DL, Westerterp KR, Wouters EF. Total free living energy expenditure in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**155**:549–54.
47. Schiffelers SL, Blaak EE, Baarends EM, et al. ß-Adrenoceptor-mediated thermogenesis and lipolysis in patients with chronic obstructive pulmonary disease. *Am J Physiol Endocrinol Metab* 2001;**280**:E357–64.
48. Saudny-Unterberger H, Martin JG, Gray-Donald K. Impact of nutritional support on functional status during an acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**156**(3 Part 1):794–9.
49. Koerts-de Lang E, Schols AM, Rooyackers OE, Gayan-Ramirez G, Decramer M, Wouters EF. Different effects of corticosteroid-induced muscle wasting compared with undernutrition on rat diaphragm energy metabolism. *Eur J Appl Physiol* 2000;**82**:493–8.
50. 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**:1435–8.
51. Schols AM. Nutrition in chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2000;**6**:110–5.
52. Schols AM, Slangen J, Volovics L, Wouiters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1791–7.
53. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. *Eur Respir J* 2002;**20**:539–44.
54. Marquis K, Debigare R, Lacasse Y, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;**166**:809–13.
55. Schols AMWJ, Broekhuizen R, Weling-Scheepers CAP, Wouters EFM. Body composition and mortality in COPD. *AJCN* 2005;**82**(1):53–9.
56. Vestbo J, Prescott E, Almdal T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen city heart study. *Am J Respir Crit Care Med* 2006;**173**(1):79–83.
57. Slinde F, Gronberg A, Engstrom CP, Rossander-Hulthen L, Larsson S. Body composition by bioelectrical impedance predicts mortality in chronic obstructive pulmonary disease patients. *Respir Med* 2005;**99**(8):1004–9 [Epub. 2005 April 12].

58. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994;**7**:1793–7.
59. Baarends EM, Schols AM, Mostert R, Wouters EF. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;**10**:2807–13.
60. Mostert R, Goris A, Weling-Scheepers C, Wouters FEM, Schols AMWJ. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000;**9**:859–67.
61. Suchner U, Rothkopf MM, Stanislaus G, Elwyn DH, Kvetan V, Askanazi J. Growth hormone and pulmonary disease. Metabolic effects in patients receiving parenteral nutrition. *Arch Intern Med* 1990;**150**: 1225–30.
62. Aguilaniu B, Goldstein-Shapses S, Pajon A, et al. Muscle protein degradation in severely malnourished patients with chronic obstructive pulmonary disease subject to short-term total parenteral nutrition. *JPEN* 1992;**16**: 248–54.
63. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS, White J. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;**1**:CD000998.
64. Borum ML, Lynn J, Zhong Z, et al. The effect of nutritional supplementation on survival in seriously ill hospitalized adults: an evaluation of the SUPPORT data. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *J Am Ger Soc* 2000;**48**(Suppl.):S33–8.
65. Rose W. Total parenteral nutrition and the patient with chronic obstructive pulmonary disease. *J Intrav Nurs* 1992;**15**:18–23.
66. Iovinelli G, Marinangeli F, Ciccone A, Ciccozzi A, Leonardis M, Paladini A, Varrassi G. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs medium chain triglycerides. *Minerva Anestesiol* 2007;**73**:65–76.