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Case report

Effects of a comprehensive, inpatient pulmonary rehabilitation programme in a cachectic patient with very severe COPD and chronic respiratory failure

Pulmonary rehabilitation (PR) is a comprehensive intervention based on a thorough patient assessment followed by personalised interventions designed to improve the physical and psychological condition of patients with chronic respiratory diseases and to promote the long-term adherence to health-enhancing behaviours [1]. While the clinical importance of physical activity is recognised across all stages of disease, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 strategy for chronic obstructive pulmonary disease (COPD) states that patients that remain highly symptomatic and/or those with a history of moderate or severe exacerbations despite optimal pharmacotherapy are indicated for PR [2]. Improvements in symptoms, increases in quality of life and gains in functional capacity after PR are independent of age, sex or the baseline degree of airflow limitation [3, 4]. However, it is known that patients with higher symptoms of dyspnoea, worse functional capacity and poor health status at baseline are more likely to be good responders to PR [5]. While PR is traditionally applied in clinically stable patients, there is increasing evidence for its beneficial effects following hospitalisations [6] and in those with frequent exacerbations [5]. In patients with very severe disease awaiting lung transplantation significant improvements in exercise capacity and health status were reported after short-term comprehensive PR [7]. Moreover, an increasing number of specific (non-)pharmacological interventions are available and can be combined with PR in the subgroup of patients with very advanced disease, including neuromuscular electrical stimulation (NMES), noninvasive ventilatory support and anabolic agents. Finally, PR may be an appropriate setting to introduce advance care planning (ACP) [8]. The role of these personalised and targeted interventions will be highlighted in this case report.

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Case report

A 47-year-old man with very severe COPD was admitted to CIRO, a tertiary care centre for patients with advanced lung diseases in Horn, the Netherlands. The patient was transferred from a regional hospital, where he had been hospitalised for 20 days for an exacerbation of his disease.

Medical history

- 1990: right-sided pneumothorax, treated with chest tube and drainage
- 2010: left-sided pneumothorax, treated by video-assisted thoracoscopy with pleural rubbing and bullectomy
- 2010: COPD
- 2014: pulmonary hypertension, mean pulmonary artery pressure 55 mmHg, normal left ventricular function

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A cachectic patient with very severe COPD and chronic respiratory failure may benefit from comprehensive and personalised pulmonary rehabilitation including neuromuscular electrical stimulation, noninvasive ventilation and anabolic steroids http://bit.ly/31Ss7WZ

Table 1 *General patient characteristics pre- and post-PR*

Characteristics	Pre-PR	Post-PR
General		
Age years	47	
Height cm	175	
Weight kg	46.8	61.5
Body mass index kg·m^{-2}	15.1	19.8
Dexa scan		
FFM kg	41.1	51.0
FFM index kg·m^{-2}	13.4	16.7
T-score L2-L4	–4.2	
T-score hip	–4.2	
Lung function		
FEV1 L (% pred)	0.37 (10.2)	
FVC L (% pred)	2.23 (47.4)	
FEV1/FVC %	17	
FRC L (% pred)	10.1 (295)	
RV L (% pred)	9.6 (456)	
TLC L (% pred)	11.0 (160)	
Arterial blood gases		
P_{aCO_2} kPa	17.8	11.0
P_{aO_2} kPa	7.7	6.7
Dyspnoea		
mMRC score	4	3

FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension.

The man had been hospitalised for exacerbations of COPD five times in the previous year. Each time, he suffered from acute-on-chronic respiratory failure, for which he was treated with noninvasive ventilation (NIV) three times. When admitted to CIRO, he experienced shortness of breath at rest and had trouble reaching the restroom on his own. He had chronic cough and sputum with purulence. Until admission, he continued to smoke six cigarettes per day and had acquired 40 pack-years. His past was characterised by extensive substance and alcohol abuse, but this was not recent. He was using long-term oxygen therapy, 2 L·min^{-1}. Besides intermittent oedema, he had no cardiac symptoms. Over the past year, he was fed by a percutaneous endoscopic gastrostomy feeding tube and he had gained approximately 10 kg in weight. His appetite was very variable. He lived alone, had a very limited social network and was deemed unfit for work. The man hardly derived any pleasures in his life.

Medication when admitted

Prednisolone 1×30 mg as maintenance therapy, azithromycin 250 mg three times per week, formoterol/budesonide 9/320 dry powder inhaler two times per day, salbutamol/ipratropium 2.5 mg four times per day, and as needed, bumetanide 1×5 mg, enalapril 1×5 mg, pantoprazole 1×40 mg.

Physical examination

A badly attended, cachectic, dyspnoeic and tachypnoeic man. Resting oxygen saturation of 86% with 2 L of oxygen therapy. Central venous pressure was not raised. Over his lungs he had very soft breathing sounds with prolonged expiration. No abnormal heart sounds. Slight pitting oedema of the lower extremities.

Pre-rehabilitation assessment

Patient characteristics before and after PR are presented in tables 1 and 2. At baseline, the man was underweight with low fat-free mass (FFM) and osteoporosis. The degree of airflow limitation was very severe, as was the degree of lung hyperinflation. Blood gas analysis on oxygen supplementation revealed severe hypercapnia and hypoxaemia. Modified Medical Research Council (mMRC) dyspnoea score was high. Exercise tolerance was very limited and he had severe muscle weakness. Health status was poor and the man had depressive symptoms.

Case summary

A relatively young man with very severe COPD with frequent exacerbations and hospitalisations and a high burden of disease (indicated by mMRC, COPD

Table 2 *Outcomes of pulmonary rehabilitation*

Characteristics	Pre-PR	Post-PR
Functionality		
6MWD m (% pred)	83 (10)	319 (38)
Quadriceps peak torque Nm (% pred)	31 (15)	88 (43)
Health status		
CAT points	38	30
CCQ points	5.3	4.1
SGRQ total score points	92.1	74.3
Psychological symptoms		
HADS anxiety points	9	8
HADS depression points	12	7

6MWD: 6-min walking distance; HADS: Hospital Anxiety and Depression Scale.

Assessment Test (CAT), Clinical COPD Questionnaire (CCQ) and St. George's Respiratory Questionnaire (SGRQ)). According to the GOLD classification he was in GOLD grade 4D. In addition, he had severe chronic hypercapnia, severe lung hyperinflation and persistent cigarette use. Also, he had class III pulmonary hypertension, very severe cachexia characterised by low body weight, low FFM and osteoporosis. Functional exercise capacity and peripheral muscle strength were minimal and he suffered from significant psychological symptoms. Finally, there was a complete lack of a social support.

Task 1
Which indications for PR would you define for the presented case, based on the results of the pre-rehabilitation assessment?

Task 2
What are potential indications for NMES, NIV and anabolic steroids during PR?

Answer 1
The potential goals for PR are:

- Smoking cessation
- Optimisation of pulmonary condition
- Tapering the chronic use of oral corticosteroids
- Improving functional performance
- Improving weight and body composition
- Reducing psychological symptoms
- Improving health status
- Increasing societal participation
- Increasing self-management and coping
- Introduce ACP

Answer 2
Potential indications for NMES:

- Peripheral muscle weakness in combination with severe dyspnoea

Potential indications for NIV:

- Chronic hypercapnia

Potential indications for anabolic steroids:

- Very low FFM and body weight
- Combined with high protein supplementation and exercise training

Comprehensive pulmonary rehabilitation

The results of the integrated assessment of his physical and psychological condition were discussed with the patient. He received information about his prognosis and possible disease trajectory. Severity and complexity of his pulmonary condition, smoking behaviour, the systemic manifestations and comorbidities were emphasised. Motivation and urgency of behaviour change were addressed. Although the multidisciplinary team of the centre had serious doubts regarding the possibility of comprehensive PR, resulting from both the severity of disease as well as the patient's motivation, he was given the benefit of the doubt and PR was initiated. Since his exercise tolerance was minimal in combination with severe chronic respiratory failure, he was not a candidate for traditional progressive endurance or interval exercise training on a treadmill or bicycle [9]. Instead, NMES was initiated (two times per day for 18 min, 75 Hz, intensity adjusted to individual toleration [10]) and combined with resistance exercise training, consisting of bilateral leg extension and leg press, chest press and upper back training (three times per week, three sets of ten repetitions, initially at 65% of maximal strength and increasing by 5% every 2 weeks). Nocturnal NIV was initiated to achieve control of nocturnal hypoventilation (Philips Respironics Inc., Murrysville, PA, USA). The protocol and settings for NIV were auto-titrated average volume-assured pressure support (AVAPS-AE), maximum pressure: 26 cmH_2O, pressure support maximum: 18 cmH_2O, pressure support minimum: 10 cmH_2O, expiratory positive airway pressure maximum: 8 cmH_2O, expiratory positive airway pressure minimum: 6 cmH_2O, rise time: 200 ms, AVAPS rate: 5 $cmH_2O \cdot min^{-1}$. A long-acting muscarinic antagonist was added to his pulmonary medications [11] and the maintenance dose of oral glucocorticosteroids (OCS) was carefully tapered, as OCS have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications [12]. Pharmacotherapy for osteoporosis was started [13]. Nicotine replacement therapy (14 $mg \cdot day^{-1}$) and smoking cessation counselling were initiated. This counselling was provided by his coaching respiratory nurse and in weekly group sessions. Based on recent smoking, severe hypercapnia and very poor exercise tolerance, he was considered not to be a candidate for lung volume reduction [14]. The patient participated in educational sessions about COPD, medications and healthy living. One of the educational sessions included information about life-sustaining treatments. Also, his goals of care, preferences regarding life-sustaining treatments and end-of-life care were discussed. Self-management interventions were performed. High-caloric and high-protein nutritional supplementation (Nutrison Energy Multi Fibre, 1.53 $kcal \cdot mL^{-1}$ tube feed enriched with 1.5 g/100 mL of Multi Fibre, 500 mL per night) was given by the feeding tube and anabolic steroids were given (a deep *i.m.* injection of 50 mg of nandrolone decanoate once every 2 weeks [15]). Training in skills to overcome problematic activities of daily living and functional capacity was provided by an occupational therapist. In addition, the patient received individualised psychological support at a frequency of 2–3 times per week, focusing on problem-solving therapy related to his passive coping and depressive symptoms. Finally, a social worker was involved in order to improve the home environment of the patient.

Course of the intervention

Initially, the patient experienced great difficulties complying to the programme, especially with giving up smoking and sleeping with NIV. After ~2 weeks, he started to feel a bit better and he did not smoke anymore. He was less dyspnoeic, his mobility increased and he became less gloomy. During his 8-week inpatient stay, he experienced one exacerbation of COPD, during which *Haemophilus influenzae* was cultured in his sputum and based on sensitivity analysis, he was treated with amoxicillin 3×500 mg and prednisone 1×30 mg for 7 days. The exacerbation did not result in acute worsening of his chronic respiratory failure. The patient completed his inpatient 5 days a week programme of 8 weeks.

Outcomes of treatment

As presented in table 1, the patient gained more than 14 kg in body weight, of which 10 kg consisted of FFM. The degree of dyspnoea and hypercapnia improved, although both remained prominently present. Functional exercise performance and peripheral muscle strength improved to a clinically significant degree (table 2). Also, symptoms of anxiety and depression decreased (table 2). The patient stated that he was satisfied with the results of the treatment and that he had reached his goals (quitting smoking, improving mobility and increasing in body weight). This allowed him to perform important activities of daily living and resulted in strongly improved health-related quality of life as was shown by the results of various questionnaires. To conclude, the PR programme was very successful in the short term. Care for the patient was transferred to his local respiratory physician and general practitioner. In addition, the continuity of care in the home environment was ensured for the various disciplines involved in the treatment. Following discharge from CIRO, the patient was able to reside in his home environment for almost 6 months, a sharp contrast to his frequent hospitalisations in the year prior to PR. Eventually, he was readmitted to the hospital with acute-on-chronic respiratory failure resulting from an exacerbation and died during this event.

Discussion

COPD is one of the most prevalent chronic diseases worldwide and a major cause of mortality [16]. However, within the entire COPD population, the proportion of patients with a very severe degree of airflow limitation is low [17]. Few studies have investigated the effects of pharmacological interventions and PR in patients with very severe COPD. However, it is assumed that also in this population, pharmacotherapy results in symptom reduction and is aimed at reducing dyspnoea and other respiratory symptoms, improving health status and exercise capacity and preventing exacerbations [12]. Beneficial effects on survival rates have not been demonstrated. Also, the optimal setting of PR for patients with very severe COPD has not been studied. There is a large variation in the setting, content, frequency and duration of PR programmes across the world and a need for a standard set of assessment measures to identify patients eligible for PR, taking disease complexity into consideration [18]. This should result in referral to an appropriate intervention setting, provided at home or in the community, in a hospital-based outpatient setting or in an inpatient hospital setting. Indeed, the feasibility of endurance exercise training in patients with very severe COPD often is very limited, as a result of disabling dyspnoea, severe muscle weakness and deconditioning [10]. In addition, in pulmonary hypertension, which may occur in very severe COPD, PR should be carefully supervised and closely monitored [19]. However, there are an increasing number of possible interventions targeted at very severe COPD patients.

Neuromuscular electrical stimulation

NMES involves the application of an electrical current through electrodes placed on the skin over the targeted muscles of the patient, thereby depolarising motor neurons and, in turn, inducing skeletal muscle contractions. The metabolic load of NMES on the impaired respiratory system in COPD is relatively low and the intervention is associated with low symptoms of dyspnoea, fatigue and muscle pain [20]. Sillen *et al*. [10] performed a randomised controlled trial to investigate the effects of high- (75 Hz) and low-frequency (15 Hz) NMES with progressive intensity with the effects of traditional progressive strength training during a comprehensive inpatient PR programme in COPD patients with severe dyspnoea (mMRC 3 and 4) and quadriceps muscle weakness. The increases in muscle strength and exercise performance were comparable in patients treated with high-frequency NMES or strength training, but less pronounced in those randomised to low-frequency NMES. Therefore, we used high-frequency NMES in the current case. In addition, NMES resulted in similar increases in lower-limb FFM [21]. The results of the study indicated that NMES is a good alternative for strength training in this specific severely dyspnoeic patient group with muscle weakness. Previously, Vivodtzev *et al*. [22] demonstrated metabolic and structural improvements in skeletal muscle following NMES at 50 Hz in COPD. As with any exercise training intervention, effects will wear off if no maintenance programme is provided [23].

Nutritional supplements and anabolic steroids

Alterations in body composition, including underweight and low FFM (as a marker of muscle mass), are among the most well-recognised extrapulmonary features of COPD [24]. Although it was long considered that loss of body weight and FFM are part of the progressive nature of the disease, several studies in recent years demonstrated that the longitudinal changes in body composition in COPD are comparable to those in smoking and non-smoking controls [25, 26]. However, frequent exacerbators and patients on maintenance OCS experience a greater decline in FFM compared to infrequent exacerbators [27]. Independent of the cause and timing of alterations in body composition in COPD, it is well-known that being underweight is associated with increased mortality risk [28]. In particular, low FFM contributes to this elevated

risk and is related to muscle weakness [29], poor exercise tolerance and reduced health status [30].

Ferreira *et al*. [31] performed a meta-analysis on the effects of nutritional interventions in patients with COPD and reported a significantly greater increase in body weight with nutritional supplementation compared to placebo. Moreover, significant increases in FFM and 6MWD were observed with nutritional supplementation compared to placebo. A large proportion of the studies in the effects of nutritional supplementation combined this intervention with progressive exercise training, which is considered an anabolic stimulus.

Several small studies investigated the potential benefits of anabolic steroids in COPD. Increase in FFM compared to placebo was mainly observed in depleted patients [32]. Changes were relatively limited, as was the increase in functional capacity. Therefore, anabolic steroids are rarely used in the treatment of underweight and low FFM in COPD [33]. However, especially for very severe patients on maintenance OCS, like the patient in this case, anabolic steroids may be used as a last resource, as there is some evidence suggesting synergistic effects of anabolic steroids and glucocorticoids on muscle recovery and function in COPD [15, 34].

Noninvasive ventilation

Home NIV is increasingly recognised as an additional treatment for patients with very severe COPD and chronic hypercapnia. Köhnlein *et al*. [35] performed a randomised controlled trial investigating the effects of NIV *versus* usual care in clinically stable patients with a baseline P_{aCO_2} of 7 kPa or higher and a pH higher than 7.35. 1-year mortality was 12% in the intervention groups *versus* 33% in the usual care group (p=0.0004). In addition, a significantly prolonged time to readmission or death within 12 months was demonstrated among COPD patients with persistent hypercapnia following an acute exacerbation when home NIV was added to home oxygen therapy [36]. Previously, Duiverman *et al*. [37] investigated the effects of nocturnal NIV as adjunct to PR. While the study was negative regarding its primary outcome, *i.e.* improvement in Chronic Respiratory Questionnaire (CRQ) total score, the study showed a significant decrease in fatigue and daytime P_{aCO_2} and an increase in physical activity level with NIV *versus* usual care. Although some beneficial effects of NIV on the outcomes of PR have been described, there is a lack of evidence supporting the routine use of NIV during PR in hypercapnic COPD patients. In an ultimate effort to improve the integrated health status and to prevent hospital readmission, NIV was initiated at the start of PR in the current patient case.

Advance care planning

PR can provide the opportunity to introduce ACP [8]. In this patient, the physician introduced ACP by discussing the disease, prognosis and possible future disease trajectory. In addition, goals of care, life-sustaining treatment preferences and end-of-life care were discussed. Finally, during an educational session information was provided regarding life-sustaining treatments. Indeed, Heffner *et al*. [38] have shown that patients participating in PR want information about life-sustaining treatments and advance directives. Moreover, ACP education during PR has been shown to increase discussions between patients and physicians about life-sustaining treatments and advance directives and improve patient assurance that their physicians understand their preferences [39].

Conclusion

This case report highlights that a patient with very severe COPD, chronic respiratory failure and severe cachexia can benefit from multidisciplinary and comprehensive PR in the short term. It highlights that PR comprises more than exercise training and when individually tailored is feasible and very effective for the most advanced COPD patients. NMES, anabolic steroids, NIV and ACP are potentially beneficial interventions for this subgroup of extreme patients and are in line with a personalised and integrated approach for patients with complex respiratory failure.

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Conflict of interest

F.M.E. Franssen reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and TEVA, and grants and personal fees from Novartis and MedImmune, outside the submitted work. L.E.G.W. Vanfleteren

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