Pulmonary Rehabilitation, Physical Activity, Respiratory Failure, and Palliative Respiratory Care

Martijn A. Spruit[1,2,3], Carolyn L. Rochester[4,5], Fabio Pitta[6], Klaus Kenn[7,8], Annemie M.W.J. Schols[2], Nick Hart[9,10], Emiel F.M. Wouters[1,2], Stefano Nava[11], Michael Dreher[12], Daisy J.A. Janssen[1,13], Miriam J. Johnson[14], Randall J. Curtis[15,16], Manuel Sastry[17], and Frits M.E. Franssen[1,2]

Affiliations

1. Department of Research and Education, CIRO, Horn, Netherlands
2. Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht, The Netherlands
3. REVAL - Rehabilitation Research Center, BIOMED - Biomedical Research Institute, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium
4. Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA
5. VA Connecticut Healthcare System, West Haven, CT, USA
6. Department of Physiotherapy, Laboratory of Research in Respiratory Physiotherapy (LFIP). State University of Londrina, Londrina, Brazil.
7. Department of Respiratory Medicine and pulmonary rehabilitation, Schoen Klinik Berchtesgadener Land, Schoenau am Koenigssee, Germany
8. Department of Pulmonary Rehabilitation, University of Marburg, Germany
9. Lane-Fox Clinical Respiratory Physiology Research Centre, Guy's and St Thomas' NHS Trust, St Thomas' Hospital, London, UK
10. Lane-Fox Respiratory Service, Guy's and St Thomas' NHS Trust, St Thomas' Hospital, London, UK

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11. Alma Mater University, Dept. of Clinical, Integrated and Experimental Medicine (DIMES), Respiratory and Critical Care Unit, S. Orsola-Malpighi Hospital Bologna, Italy
12. Division of Pneumology, University Hospital RWTH Aachen, Aachen, Germany
13. Centre of Expertise for Palliative Care, MUMC+, Maastricht, The Netherlands
14. Wolfson Palliative Care Research Centre, Hull York Medical School, Hull, UK
15. Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle, US
16. Cambia Palliative Care Center of Excellence, University of Washington, Seattle, US.
17. Academic Sleep Center, CIRO, Horn, The Netherlands

Corresponding author

Prof. dr. Martijn A. Spruit, Fellow of the ERS

Hornerheide 1, 6085 NM, Horn, The Netherlands

Phone number: +31 475 587 601

E-mail address: martijnspruit@ciro-horn.nl

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Abstract

The CIRO Academy in Horn (the Netherlands) organized a two-day meeting to present and discuss the studies published in 2017 pertaining to key priority areas of respiratory and critical care medicine. This report provides a comprehensive review of the studies investigating all aspects of pulmonary rehabilitation and exercise training, physical activity and sedentary behaviour, acute and chronic respiratory failure as well as palliative respiratory care published in 2017.

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Pulmonary Rehabilitation and Exercise Training

In 2017, several studies considered novel aspects of patient assessment before and during pulmonary rehabilitation (PR) in chronic obstructive pulmonary disease (COPD) patients. The target training intensity in the PR exercise prescription is critically dependent on baseline exercise testing (1), which is associated with a learning effect (2). In a large national patient cohort from the UK, only 22.6% of patients had a practice walk test [six minute walking test (6MWT) or incremental shuttle walk test (ISWT)] at the start of PR (3). Moreover, in this cohort, practice walk tests were associated with an increase in PR enrolment and completion (1). The reasons for this are not clear, but merit further investigation. This study suggests that PR programs should be encouraged to perform practice walk tests whenever possible. Notably, a sit-to-stand (STS) test was as a reliable and responsive measure of functional exercise capacity in COPD that correlated strongly with six minute walking test (6MWT) (4). The STS could therefore potentially serve as an additional or alternate test from which to formulate the PR exercise prescription. STS testing also helps to predict long-term patient outcomes including mortality (5), hence its routine measurement in PR may have prognostic value for patients. Furthermore, responsiveness and minimal clinically important difference values for the COPD assessment test (CAT), clinical COPD questionnaire (CCQ) and hospital anxiety and depression score (HADS) have been published (6). Knowledge of these values will help clinicians to evaluate the efficacy of their PR programs regarding these outcomes.

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Although pain (7), fatigue (8), and cognitive impairment (9) are common among COPD patients attending PR, these symptoms are commonly overlooked. Indeed, clinical features typically assessed in PR do not distinguish those COPD patients with and without cognitive impairment (9). Importantly, patients with cognitive impairment were still shown to benefit from PR (10). Cardiac abnormalities (11) and peripheral arterial disease (12) are also prevalent yet remain often undiagnosed among individuals who participate in PR. Although comorbidities do not adversely affect PR outcomes per se (13), screening for each of these comorbidities may be considered among PR participants, since under-diagnosis deprives patients of the opportunity to receive proper medical treatment and in turn poses risk of adverse health outcomes such as episodes of congestive heart failure, cardiac ischemia, claudication and/or limb ischemia.

Likewise, patients who have mild to moderate severity acute exacerbations of COPD (AECOPD) during PR still achieve significant gains in 6MWT, although AECOPD requiring hospitalization are associated with a decline in 6MWT and higher PR dropout rates (14). Furthermore, a cohort study from the UK showed an association between socioeconomic disadvantage and lower adherence to and completion of PR (15). Socioeconomic disadvantage was not, however, associated with lower gains in exercise performance or health status following PR (15). Notably, individuals with COPD who have a spouse or partner caregiver have an 11-fold greater odds of participation in PR than those lacking this social support (16). Importantly, home-based exercise interventions are both safe and beneficial, and may also be helpful for individuals who lack access to or are unable to participate in centre-based PR programs (17, 18).

A multicentre RCT demonstrated benefits of an intensive post-PR maintenance exercise program on 6MWT and the body-mass index, airflow obstruction, dyspnoea, and exercise (BODE) scores up to 2 years post-PR, but without a significant benefit for quality of life (19). Repeat PR programs were also effective, irrespective of the time period between programs (20), hence may be considered according to clinical need. Supporting previous studies, a nationwide Japanese retrospective observational cohort study reduced readmission risk with early PR delivered following hospitalization (21).

Various forms of exercise training are beneficial in PR. Arm strength training leads to gains in upper extremity strength and endurance, with associated improvements in performance of activities of daily living (22). Whole body vibration training improves balance, muscle power output and exercise performance, and may be a particularly suitable training modality for individuals with impaired balance and low exercise capacity (23). Novel work, utilising functional MRI imaging, tested whether neural responses to visual word cues were altered by participation in 6 weeks of outpatient PR among individuals with mild to moderate severity COPD (24). Changes in patients' ratings of breathlessness and anxiety in response to word cues for a range of activities after, as compared to before PR were associated with specific regional changes in brain activity. For example, changes in ratings of breathlessness during activities after PR correlated positively with metabolic activity in the insula and anterior cingulate cortex. Baseline activity in selected brain regions also correlated with improvements in breathlessness and anxiety after PR. This work suggests that aspects of neural signalling can be altered by participation in PR, perhaps by changes in learned associations between environmental stimuli and brain perception. Future use of functional MRI imaging to better understand individuals' neural responses to exercise training and other components of PR may help to develop strategies to target specific aspects of learning that could ultimately optimize individualization and efficacy of PR.

Physical activity and sedentary behaviour

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The degree of airflow limitation is only moderately related to daily physical activity (PA) levels in patients with COPD (25), stressing the importance of searching for extra-pulmonary barriers and enablers that may affect PA (26). Proximity of residence to green or open spaces and neighbourhood deprivation are not determinants of PA, but dog walking and grand parenting are (27). Consequently, encouraging patients to walk the dog and/or take care of grandchildren seems to be a feasible way to boost the PA level of these patients. Moreover, spouses may play an important role in changing PA behaviour in patients with COPD, as patients with a physically active spouse were physically more active themselves (28).

Sedentary behaviour (>8:30 hours/day spent in activities of intensity <1.5 metabolic equivalents) increases the 5-year mortality risk in patients with COPD (29). So, an in-depth assessment PA behaviour (sedentarism *and* the PA) seems of clinical relevance. Furthermore, impaired sleep quality is closely related to less PA (30). Therefore, PA-enhancing interventions need to take sleep quality into consideration .

Changes in PA following different exercise-based interventions showed contrasting results. The amount and intensity of PA increased by using a 12-week semi-automated tele-coaching intervention including a step counter and an app installed on a smartphone (31). In contrast, pedometer-directed step targets were unable to enhance the effects of PR on PA (32). Also after a comprehensive PR program, different response profiles for changes in PA were found (33). Poor responders are likely to be the focus of attention in future PA-enhancing interventions, provided the patient has enough functional capacity in order to reduce sedentary behaviour and increase physical activity levels. Hence, this recent body of evidence justifies the clinical relevance of features such as the value of objectively assessing the degree of sedentarism and the increase in PA derived from factors around the patient (e.g., spouse, grandchildren and pets). Attention should also be drawn to the profile of response to PR (i.e., identifying poor PA responders), as well as to the components and timing of PA interventions.

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Exercise training combined with oxygen supplementation or non-invasive ventilation

The Long-Term Oxygen Treatment Trial (34) showed no effect of LTOT on first hospitalization and death over 6 years in 738 COPD patients with moderate hypoxia. However, the limitations of this trial suggest that further studies are needed before definitive conclusions regarding the benefits of LTOT for individuals with COPD and moderate hypoxia can be drawn. Short-term effects of oxygen supplementation on exercise performance appear more conclusive. Indeed, oxygen supplementation (10 l/min) in 29 non-hypoxemic COPD patients during exercise doubled peak work rates compared to room air (35). This, however, is not a typical real-life approach.

An oxygen supplementation of 2 l/min during 6-minute walk test improved exercise performance and oxygen saturation, and reduced dyspnoea and the number of unintended breaks compared to room air in COPD patients with hypoxia at rest or during exercise (36). Regarding patients with ILD, one small study (n=20) has shown the non-inferiority of two portable concentrators compared to O_2-cylinders (37). Interestingly, an interview based study including 26 Australian respiratory physicians presumed a higher probability of prescribing LTOT in ILD compared to COPD patients (38).

Using NIV to enhance exercise performance in patients with respiratory failure has a reasonable physiological rationale but it has not been shown to improve walking distance (39). The authors, however, combined the results of patients with COPD and kyphoscoliosis, which made it difficult to draw a clear conclusion. Indeed, NIV is not expected to be beneficial in patients with kyphoscoliosis. During a specialized inpatient PR study, 296 of 1044 patients awaiting lung transplantation received nocturnal NIV due to hypercapnia (40). The increase in 6MWD after PR in the NIV group was higher, albeit by only 11 meters. LTOT and NIV are potentially valuable

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therapeutic options, in particular to support COPD patients with severe lung hyperinflation and exercise-induced oxygen desaturation (41) in the context of exercise training as part of a comprehensive PR program. Further well-designed studies are needed to prove these concepts and to enable physicians to identify ideal candidates for these therapeutic options more easily.

Nutritional modulation with(out) exercise training

The latest Cochrane meta-analysis (42) reported moderate quality evidence of nutritional supplementation on body weight, body composition, exercise performance and quality of life in malnourished COPD patients. This conclusion was substantiated by a single blinded RCT conducted in India (43). Unintended weight loss is more frequent in severe disease but in a UK COPD population, Collins and colleagues (44) additionally highlighted the importance of deprivation on malnutrition risk. Most studies to date focused on nutritional intervention in clinical stable disease, but an Australian study showed hospitalization as 'window of opportunity' to start up nutritional modulation, as malnourished COPD patients experienced significantly longer hospital stays at double the cost (45).

A shift in nutritional approaches, from protein-calorie supplementation to maintain body weight and muscle mass, to treating nutrient deficiencies and optimizing plasma nutrient status, to modulate physical function and cardiovascular risk is occurring (46-48). Low muscle mass and abdominal obesity may coexist in normal weight COPD patients with elevated cardiovascular risk profile (49). Next to low muscle mass, a high prevalence of deficiencies in vitamin D, vitamin B12 and iron in hospitalized COPD are reported (46). Calder and colleagues (47) investigated 3 months of multimodal nutritional intervention including high quality protein, vitamin D and n-3 fatty acids *versus* an iso-caloric control, and showed positive effects on blood pressure, blood lipids and on exercise-induced fatigue. A Dutch trial (48) investigated the efficacy of a similar multimodal nutritional intervention as adjunct to 4 months high-intensity exercise training. Muscle mass and physical performance improved in both groups, but the intervention group showed additional effects on nutritional status and physical activity compared to placebo. These data suggest that targeted multimodal nutritional modulation combined with exercise training has an beneficial effect in patients with COPD. Nevertheless, nitrate, which has been proposed as pharmaco-nutrient to modulate extra-pulmonary pathology via multiple pathways, did not influence cycling efficiency, physical performance and cardiac biomarkers in a cross-over, proof of concept RCT (50).

Early rehabilitation during critical illness

Acute skeletal muscle wasting occurs early and rapidly during critical illness (51). The clinical priority is to reduce acute muscle wasting as this is a major driver of long-term disability (52). This has provided the rationale for clinical trials investigating early mobilization and exercise therapy within the ICU with the primary goal of enhancing functional outcome, health-related quality of life and reducing healthcare utilization (53-57).

The outcome from these trials has been inconsistent with three trials demonstrating no benefit from early ICU mobilization (53-55) and two trials demonstrating benefit from early ICU mobilization (56, 57). We must consider the "PICO" approach (target population, intervention delivered, control comparator and primary outcome) to understand the clinical effectiveness differences between the trials. The target populations of the medical ICU trials (53-55, 57) differed with ages ranging from 53 to 62 years with the trials recruiting patients with acute lung injury/acute respiratory distress syndrome and varying frequencies of co-morbidities (Table 1). The mean length of ICU stay was 6 to 16 days across the trials further highlighting the different

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target populations in terms of recovery trajectory. These factors are wholly relevant as recent data has demonstrated that age, ICU length of stay and co-morbidity burden effect the outcome post critical illness (58).

Table 1: Patient Characteristics in the medical early mobilisation trials

	Schweikert et al (57)	**Moss et al (55)**	**Morris et al (54)**	**Wright et al (53)**
Mean Age (years)	56	53	56	62
Matching Gender	No	Yes	Yes	No
Primary Diagnosis	All Medical	ARDS Medical	ARF Medical	Mixed Medical/Surgical
Co-Morbidities Reported	Diabetes	Diabetes, cirrhosis, cancer, renal failure, HIV, organ transplantation	Not reported	Pre-Morbid Katz Index
ICU LOS (Days)	6.9	15.5	7.8	5.5

In regard to the intervention delivered, we must also consider the dose, intensity and timing of an intervention. The trial that demonstrated a benefit in functional outcome delivered 19 minutes per

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day of exercise therapy dose prior to cessation of mechanical ventilation compared to the control group (57), whereas the other trials (53-55) delivered only 10 minutes per day. The within ICU sessions in the Moss et al study (55) was 31 minutes per day in the treatment group vs. 21 minutes per day in the control group, a similar difference to the Wright et al study (53) which demonstrated 23 minutes per day vs. 13 minutes per day. In addition, the exercise therapy was delivered 1.5 days post initiation of mechanical ventilation (57) in this trial, whilst the other trials initiated exercise therapy between 4-8 days. Furthermore, the importance of intensity of the treatment is highlighted by the difference between the study by Morris et al (54), which delivered treatment for only approximately 50% of the intervention days, compared with the Schweickert et al (57) study that provided physical and occupational therapy for 90% of the mechanical ventilator days.

Establishing the barriers and enablers to early mobilization will promote better application of exercise therapy in critically ill patients (59). Early mobilisation needs to be targeted at the appropriate ICU population, with current data supporting application very early in the course of critical illness. The severity of the acute illness determines the degree of muscle wasting (51), with age, ICU length of stay, systemic inflammation and chronic health prior to critical illness determining the trajectory of recovery (58). In addition, decreased mitochondrial biogenesis and dysregulated lipid oxidation contribute to a compromised skeletal muscle bioenergetic status with intramuscular inflammation associated with impaired anabolic recovery (60) and development of ICU acquired weakness(61). Future clinical work will need to focus on these key areas with the establishment of the appropriate timing, dose and frequency of both phramcological and non-pharmacological treatments.

Home-management of chronic respiratory failure

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NIV can be used for long-term treatment of chronic respiratory failure in the home environment. In patients with obesity hypoventilation syndrome, recent data suggests that NIV and continuous positive airway pressure results in a similar improvement in arterial blood gas measurement and health-related quality of life (62). A meta-analysis assessing the efficacy of long-term NIV in COPD patients has shown that the arterial partial pressure of carbon dioxide ($PaCO_2$) can be decreased with NIV with mortality improved with a significant reduction in $PaCO_2$ by NIV (63). This is supported by recent studies that have demonstrated that effective NIV, with the aim of significantly reducing elevated $PaCO_2$, is well tolerated and associated with improvements in quality of life (64) and long-term survival (65). Furthermore, evidence supports the use of home oxygen therapy and home mechanical ventilation (HOT-HMV) in COPD patients following acute respiratory failure and persistent hypercapnia e.g. COPD patients with acute on chronic respiratory failure (66). In the HOT-HMV clinical trial, the addition of home NIV to home oxygen therapy prolonged the time to readmission or death within 12 months (66).

Palliative respiratory care in COPD

Timely integration of palliative COPD care with disease-oriented treatment can improve patient as well as informal caregiver outcomes (67). However, the unpredictable disease trajectory in COPD is a challenge for timely provision of end-of-life care. Indeed, patients with COPD were less likely to die at home than patients with lung cancer (68). Prognostic variables and multivariate scores contributing to an accurate risk assessment for death within 12 months are mostly lacking (69). Identifying patients in need for palliative care thus remains a challenge (70). The initiation of palliative care, therefore, should be based on complexity of symptoms and unmet needs instead of estimation of prognosis (67).

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Two meta-analyses addressed opioid use for breathlessness, a major problem for patients with advanced disease. Ekström and colleagues (71) confirmed that short-term use of opioids are associated with statistically significant as well as clinically relevant reductions in breathlessness severity. Verberkt and colleagues (72) explored respiratory adverse effects of opioids, a frequently mentioned physician-endorsed barrier towards opioid prescription. After exploring 67 studies no evidence was found of significant or clinically relevant respiratory adverse effects of short-term use of opioids for chronic breathlessness.

In 2017 the European Association for Palliative Care published a consensus-based definition as well as recommendations for advance care planning (ACP) (73). Jabbarian and colleagues (74) performed a systematic review of preferences and practices of ACP in chronic respiratory diseases. They showed that a majority of patients are interested in engaging in ACP, but despite this, ACP is rarely done. Moreover, ACP is a continuous process between patients and physicians, in which preferences for specific situations are discussed and that needs to be regularly re-evaluated to deliver high-quality end-of-life care (75). Although clinicians acknowledge the importance of ACP, they are hesitant to initiate ACP. A nurse-led ACP-intervention can increase ACP discussions and completion of advance directives and appointment of a substitute medical decision-maker (76); and can facilitate patient-physician communication about end-of-life care without causing psychological distress in both patients and their loved ones (77). Palliative care can also reduce use of healthcare services (78). When acute respiratory failure ensues in terminally ill patients, NIV may be applied, as recently suggested by the ERS/ATS guidelines, with the sole aim of palliating dyspnoea, and eventually give more time to say goodbye to the loved ones (79).

So, these recent studies show that effective palliative care interventions are available for patients with COPD, for example for symptom management, but also interventions addressing advance care planning needs. Nevertheless, identifying patients in need for palliative care remains a challenge and this should be a focus for future research.

Palliative respiratory care in interstitial lung diseases

Palliative care needs, access to palliative care and symptom management in patients with interstitial lung diseases are presented in a summary paper (80).

A qualitative study of current patients, current and past caregivers confirmed wide-ranging needs and the challenges of advance care planning. Caregivers of decedents reported symptoms and frustration with education provided more frequently indicating re-framing of experience after the patient's death (81). An observational study of patients and caregivers (Netherlands, Germany) attending information/education days including end-of-life care topics showed most wished to know everything about their condition, and that the information had improved feelings of security, belying clinicians' concerns of taking away hope (82). However, study group participants are self-selected information-seekers.

In practice, access to neither general (respiratory and primary care teams) nor specialist (palliative care teams) palliative care is routine (https://www.brit-thoracic.org.uk/document-library/audit-and-quality-improvement/lung-disease-registry/bts-ild-registry-programme-annual-report-201415/). Recent advances include development and validation of the NICE endorsed Needs Assessment Tool for Interstitial Lung Disease (NAT:ILD; http://www.hyms.ac.uk/go/nat-pd-ild) to help respiratory clinicians identify palliative needs of patients and caregivers, and triage referral to specialist palliative care (83, 84). Implementation in practice requires service reconfiguration to allow holistic assessment, training in communication skills and symptom

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management and support from palliative care services (85). Symptoms are burdensome in ILD. Preliminary data show improvement in subjective and objective cough by pirfenidone (86). Breathlessness is of major importance; an Australian IPF registry study showed that breathlessness predicted quality of life explaining over 70% of the variation in the model (87). A primary care study showed increased consultations due to breathlessness by people, some up to five years prior to IPF diagnosis (88). The importance of breathlessness management in addition to ILD-directed treatment is emphasized in a recent consideration of chronic breathlessness as a new clinical syndrome, defined as disabling breathlessness, persistent despite optimized disease-modifying treatment (89). Consistent with this, a systematic review and qualitative synthesis of 101 papers proposed a new concept of "breathing space" – maximum *living* with chronic breathlessness - encompassing patients' coping, help-seeking, and clinicians' responsiveness to breathlessness as a distinct entity (90).

ILDs are therefore identified as a group of diseases which carry a large symptom burden, especially breathlessness which has particularly wide-reaching detrimental effects on quality of life. Holistic assessment with attention to symptom management, information need and planning for the future are key to excellent care but is rarely done systematically. A validated assessment tool is now available but care is needed with implementation with consideration to service reconfiguration to allow sufficient time, resources and training.

Future directions

As outlined above, the fields of PR, physical activity, home management of respiratory failure, and palliative respiratory care have made substantial progress over the last year. Innovative methods to assess the broad needs of individual patients with chronic respiratory diseases have been proposed, novel interventions and/or indications for existing therapies have been evaluated, and new models for providing healthcare have been confirmed. However, several gaps in our knowledge remain and need to be addressed in future research. While PR assessment and interventions are aimed to provide a comprehensive and individualized treatment (91) and recent meta-analysis and guidelines confirmed the overall benefits of PR (1, 92, 93), not all patients improve as a result of this intervention (94, 95). Similarly, systematic reviews of palliative care interventions suggest benefit, but work is needed to identify the best intervention for individual patients (96). Research is needed to help understand the organizational aspects, patient characteristics and interventional factors related to treatment benefit, individualizing treatments to address specific patient needs, and improve cost-effectiveness of interventions. In addition, development of multidimensional and individualized outcome assessment is required to reflect the personalized and comprehensive nature of these treatments (95). Also, the effectiveness and the best approaches to integrate PR with palliative care for patients with advanced and complex chronic respiratory diseases need to be investigated. Furthermore, we need to study the effects of interventions combining traditional PR and palliative care with innovative medical treatments for patients with different but advanced chronic respiratory diseases. Such interventions may include the addition of high-flow oxygen therapy for patients with severe exercise-induced desaturation (97), non-invasive ventilation for patients with pronounced hyperinflation and/or hypercapnia (98), endobronchial interventions for patients with severe emphysema (99, 100), and biologicals for patients with severe obstructive lung diseases (101). Finally, we should aim for (combined) therapies that are supportive for the patient to take the responsibility as specialists of their own lives: patients must become co-creators of value care (102).

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