The pulmonary rehabilitation regimen: a treatment for frailty and 'inflammaging'?

ABSTRACT

Pulmonary rehabilitation is an exercise-based intervention that improves walking endurance, strength, functional independence, wellbeing and the risk of re-admission to hospital. It was developed for patients recovering from acute exacerbations of chronic obstructive pulmonary disease, and sometimes other long-term inflammatory lung diseases. Many other conditions have a chronic inflammatory component, including type 2 diabetes, obesity, osteoarthritis and old age. Such background inflammation is linked to a range of adverse outcomes, including all-cause mortality, sarcopenia and other markers of frailty. Exercise, including pulmonary rehabilitation, has an anti-inflammatory effect on innate immune chemistry, and improves outcomes in a variety of conditions, although for most diagnostic groups there is no consistent structured programme similar to pulmonary rehabilitation. The authors contend that the pulmonary rehabilitation model could be used generically to treat other chronic and post-acute inflammatory states and thereby reduce the risk of frailty and other adverse outcomes.

In the UK, and demographically similar countries with an ageing population, the proportion and absolute number of people living with chronic inflammatory conditions is rising. About 1 in 7 of the UK's population will be over 75 years of age in 2040 and this expanding cohort is frail and have long-term health conditions (Harper et al, 2016), many of which are associated with chronic and/or prolonged sub-acute systemic inflammation. For example, people with conditions such as chronic obstructive pulmonary disease, metabolic syndrome, osteoarthritis, type 2 diabetes and hypertension have raised levels of blood inflammatory markers such as C-reactive protein, interleukin-1-beta (IL-1β), IL-6, and tumour necrosis factor-alpha (TNF-α) as a result of a sustained pro-inflammatory state (Allen, 2015, 2017). Such people have an increased risk of all-cause mortality, frailty, physical dependency, restricted mobility, vascular events, heart failure, sarcopenia and thromboembolism (Aksu et al, 2013).

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As the focus of medicine moves increasingly towards caring for people with chronic conditions, the effects of these pro-inflammatory states will become more noticeable in both clinical and economic terms. There will be an imperative to seek therapeutic strategies that can avoid or ameliorate the impact, and it is likely that drugs and lifestyle adjustments will have roles to play.

Exercise induces a shift in inflammatory markers towards a less inflamed profile. This has been demonstrated in a range of clinical contexts, including age-related inflammation (Geffken et al, 2001; Wannamethee et al, 2002) and in narrowly defined groups such as patients with heart failure (Larsen et al, 2001). This article looks at the positive effects of exercise on the chemistry of inflammation and a number of subsequent patient outcomes. The authors discuss evidence that supports their contention that the established exercise-based intervention generally known as pulmonary rehabilitation can be regarded as a generic model for effective delivery of exercise therapy to patients with chronic or non-resolving post-acute inflammation of a wide range of origins and need not be confined to patients with certain respiratory conditions.

Exercise modifies the chemistry of systemic inflammation

The health benefits of exercise are widely recognized. These include reducing the risk of all-cause mortality, coronary artery disease, ischaemic stroke and some cancers, and improving insulin sensitivity, blood pressure, self-reported wellbeing, mobility and independence (Allen, 2015). The underlying mechanisms for these benefits are complex and appear to involve a mix of humoral, autonomic and psychological factors. However, it has become clear that a key contributing factor is likely to be exercise-induced reduction of systemic inflammation, as measured by background blood levels of C-reactive protein and pro-inflammatory cytokines, such as IL-1β and TNF-α.

The apparent immune-modulating role of post-exercise peak levels of IL-6 released from skeletal muscle is primarily anti-inflammatory and anti-sarcopenic and

probably mediated through IL-6-induced release of IL-10 (Pedersen, 2013). An example of empirical evidence for this is found in the HERITAGE study, a 20-week exercise programme which found that those with a high level of C-reactive protein (>3.0 mg/litre) had a median reduction of 1.34 mg/litre from their baseline level of C-reactive protein (Lakka et al, 2005).

The amount of long-term exercise habitually performed also seems to affect levels of C-reactive protein. After adjusting for multiple confounding factors and having a sedentary group as a control, the odds ratio of having an elevated C-reactive protein level is 0.98 (95% confidence interval 0.78–1.23) for light activity, 0.85 (0.70–1.02) for moderate activity and 0.53 (0.40–0.71) for vigorous activity (Ford, 2002), indicating a dose–response relationship between exercise and suppression of systemic inflammation. Even leisure time activity increased albumin levels and lowered white cell counts and fibrinogen levels.

Several forms of exercise have been shown to reduce baseline levels of C-reactive protein – aerobic dancing, jogging, swimming, cycling and weight lifting all had a measurable effect (King et al, 2003). However, it appears that exercise has to be sustained to maintain the anti-inflammatory effect. Elderly men who were active but became inactive had C-reactive protein levels similar to those who had remained sedentary over a 20-year period, whereas the inverse occurred in those who became active (Wannamethee et al, 2002). The observed reduction of C-reactive protein levels in response to exercise suggests a fall in aggregate inflammation and has been replicated in a number of studies (Taaffe et al, 2000; Elosua et al, 2005; Hamer et al, 2012).

The effects of exercise on specific cytokines is less straightforward. Some have shown a rise in interleukin-1 receptor antagonist (IL-1ra) and a fall in baseline IL-1β and TNF-α levels (Pedersen, 2017). Some are less clear, for example, in 50–70-year-old obese postmenopausal women a regimen of diet and exercise caused a drop in mean TNF-α concentrations, but this trend did not reach statistical significance (You et al, 2004).

Systemic inflammation in chronic obstructive pulmonary disease

The chronic inflammatory state that accompanies chronic obstructive pulmonary disease is systemic and not limited to the lungs. Levels of blood C-reactive protein in stable patients with non-exacerbated chronic obstructive pulmonary disease is higher than those in healthy age-matched controls (7.22±9.84 *vs* 3.14±2.27 mg/litre, $P<0.005$). Additionally, a subgroup of patients with chronic obstructive pulmonary disease who had no smoking history also had a significantly raised C-reactive protein level compared with healthy controls (Aksu et al, 2013). This suggests that there is a pro-inflammatory effect independent of the effects of smoking in patients with chronic obstructive pulmonary disease.

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C-reactive protein levels also have prognostic value. A longitudinal study over 8 years found the incidences of hospitalization and death were significantly increased in those whose baseline C-reactive protein level was >3 mg/litre when compared to those whose level was <3 mg/litre ($P<0.001$) after adjustment for sex, age, spirometry and other comorbidities (Dahl et al, 2007).

Levels of the pro-inflammatory cytokine TNF-α are chronically raised at baseline in patients with chronic obstructive pulmonary disease compared with healthy controls (11.43±11.91 *vs* 5.99±5.29 pg/ml, $P<0.03$), and this correlates with elevated baseline blood IL-6 levels (Karadag et al, 2008). A meta-analysis which reviewed studies of the pro-inflammatory state of patients with chronic obstructive pulmonary disease found baseline blood IL-6 levels to be an average of 13.10 pg/ml higher in patients with chronic obstructive pulmonary disease compared with healthy controls (95% confidence interval 7.23–18.37). Also, IL-8, a pro-inflammatory cytokine released mainly from inflamed airways, was only detectable in those with chronic obstructive pulmonary disease and was undetectable in healthy controls (Gan et al, 2004).

Of key clinical importance, TNF-α seems to have a role in the extra-pulmonary complications of chronic obstructive pulmonary disease, particularly loss of muscle mass and cachexia. A negative correlation has been shown between baseline levels of TNF-α and fat-free mass (Gaki et al, 2011). Increased TNF-α production by blood monocytes has been found in those with chronic obstructive pulmonary disease who had lost >5% of their body weight in the previous year, when compared with both healthy controls and chronic obstructive pulmonary disease patients with stable weight (de Godoy et al, 1996). The mechanism by which TNF-α causes muscle loss is not fully understood, but those with levels of increased TNF-α have increased resting energy expenditure when adjusted for fat-free mass. Further, those with chronic obstructive pulmonary disease who had increased resting energy expenditure had lower fat-free mass and higher baseline blood TNF-α levels (Schols et al, 1996). It appears that chronically raised TNF-α and IL-6 levels have a proteolytic effect, resulting in muscle breakdown and a predisposition to sarcopenia, whereas the peak IL-6 levels induced by exercise in the absence of TNF-α help to preserve muscle integrity.

Muscle mass and strength are important for mobility and function in people with chronic obstructive

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pulmonary disease, and sarcopenia is a predictor of increased mortality in those with severe chronic obstructive pulmonary disease (Swallow et al, 2007). In a study that used computed tomography scans to assess the mid-thigh muscle cross-sectional area, those with decreased mass but similarly impaired spirometry had an increased mortality odds ratio of 13.16 (95% confidence interval 1.74–99.20) compared with 3.37 for those with thigh muscles within the normal range (Marquis et al, 2002).

Chronic obstructive pulmonary disease as a model for chronic inflammation in old age

There appear to be similarities between the inflammatory status of people with chronic obstructive pulmonary disease and those with other chronic inflammatory conditions, many of which have multiple causes especially in old age. Further, many of the consequent comorbidities, such as sarcopenia, low mood, loss of appetite and osteoporosis, found in people with chronic obstructive pulmonary disease are also a feature of other pro-inflammatory disorders associated with frailty, such as heart failure, osteoarthritis and metabolic syndrome (Barnes, 2008; Allen, 2017).

Ageing itself is associated with low-amplitude chronic inflammation in many older individuals, particularly above the age of 80 years, with the same range of comorbid consequences. This phenomenon has been referred to as 'inflammaging' and appears to be detrimental (Franceschi and Campisi, 2014). In that state the innate immune response to stimuli such as infection or injury is altered. As well as approximately 2-fold higher baseline levels of inflammatory markers, there is a prolonged rise in levels of TNF-α, IL-1β, IL-6 and C-reactive protein after an acute stimulus, such as infection, lower levels and reduced activity of IL-10 and a slower return to the pre-stimulus baseline (Bruunsgaard et al, 1999; Krabbe et al, 2001; Allen, 2015).

The mechanism for these age-related dys-immune states is not fully delineated. Whether the chronically elevated baseline levels of inflammatory markers are part of the normal ageing process, and merely reflect a need for enhanced immune surveillance, or are a result of other background pro-inflammatory comorbidities is not clear (Ferrucci et al, 2005). There is, therefore, a strong association between prolonged systemic inflammation and frailty comorbidities in patients with chronic obstructive pulmonary disease and other chronic pro-inflammatory conditions, and in old age.

Evidence for the effectiveness of pulmonary rehabilitation

Pulmonary rehabilitation is one of the cornerstone treatments for chronic obstructive pulmonary disease. It is defined by the American Thoracic Society and the European Respiratory Society as 'a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education and behaviour changes. The intention of pulmonary rehabilitation is to improve the physical and psychological condition of people and to promote long-term adherence of health-enhancing behaviours' (Spruit et al, 2013).

Although the content, scope and delivery methods vary in different localities and institutions, the minimum package for pulmonary rehabilitation as suggested by the British Thoracic Society is supervised twice-weekly personalised aerobic or resistance training. The duration of supervised pulmonary rehabilitation is normally 6–12 weeks, and includes encouraging those participating to take appropriate physical exercise, typically walking or static cycling, for 30 minutes 5 days a week (Bolton et al, 2013). The evidence for benefit from pulmonary rehabilitation regimens is extensive and embedded in current guidelines (Bolton et al, 2013). Further, elderly patients with chronic obstructive pulmonary disease who have markers of frailty and sarcopenia also benefit from pulmonary rehabilitation, to the extent that frailty indices improve in a high proportion (Attwell and Vassallo, 2017).

Patients with chronic obstructive pulmonary disease and other chronic respiratory conditions receiving pulmonary rehabilitation consistently achieve improved exercise tolerance, functional independence, feeling of wellbeing and lower risk of hospitalization (McCarthy et al, 2015; Nguyen et al, 2015). There is also evidence that pulmonary rehabilitation reduces chronic systemic inflammation (Wang et al, 2014; Abd El-Kader et al, 2016; Sciriha et al, 2017). These aspects will now be considered in further detail.

Exercise tolerance and muscle function

In many patients who have chronic obstructive pulmonary disease skeletal muscle mass is decreased. The reduction in quadriceps mass, for example, predisposes to impaired mobility, postural instability and falls, and is associated with subjectively and objectively poor exercise tolerance. Reduced muscle mass and strength in patients with cardiorespiratory disorders was also found to proportionally increase the sense of leg work effort and dyspnoea during exercise and substantially reduced maximum work capacity (Hamilton et al, 1995). A correlation has been found between maximum quadriceps muscle force and the 6-minute walking distance test in individuals (Gosselink et al, 1996). These findings indicate that the effectiveness of pulmonary rehabilitation, which includes both aerobic and resistive exercise, is likely to be at least partly a result of improved muscle strength.

Further, a Cochrane review found a statistically significant mean improvement in the distance walked for those involved in pulmonary rehabilitation of 43.93 m by the end of the programme (McCarthy et al, 2015). The incremental shuttle walking test demonstrated a mean improvement of 39.77 m after a pulmonary rehabilitation programme, a positive trend that did not reach statistical significance (McCarthy et al, 2015). Structured supervised exercise improves muscle mass, strength, mobility and balance in the frail and pre-frail elderly people (de Labra et al, 2015). This parallels the functional improvements gained from pulmonary rehabilitation for patients with chronic obstructive pulmonary disease.

Quality of life, wellbeing and mood

Several studies have examined the effects of pulmonary rehabilitation on quality of life measurements and related disease severity scores, such as the Chronic Respiratory Disease Questionnaire and the St George's Respiratory Questionnaire. The Chronic Respiratory Disease Questionnaire uses a 7-point scale assessing individuals' experiences of dyspnoea, mastery of symptoms, fatigue and emotional function. A change of symptoms greater than 0.5 has been deemed to be the minimal clinically importance difference for that index (Jaeschke et al, 1989). A Cochrane review of the effects of pulmonary rehabilitation on Chronic Respiratory Disease Questionnaire scores showed all four domains were improved with pulmonary rehabilitation and the lower limits of the confidence interval exceeded the minimal clinically importance difference of >0.5 when compared with usual care (McCarthy et al, 2015).

The review also considered the changes in the St George's Respiratory Questionnaire, which has an minimal clinically importance difference of 4 points. It found that total quality of life, symptom burden, exercise and impact upon life improved significantly with pulmonary rehabilitation compared with control groups. There was also a clinically and statistically significant change when reviewing the total effect of pulmonary rehabilitation on the St George's Respiratory Questionnaire in patients with chronic obstructive pulmonary disease (McCarthy et al, 2015).

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Depression and anxiety rates are high both in frail old age and patients with chronic obstructive pulmonary disease (Taylor, 2014; Yohannes and Alexopoulos, 2014). Although the complex interplay of factors causing the mental health conditions may be different in these groups, positive effects of exercise on mood have been demonstrated (Blake, 2012). In elderly patients exercise lowers self-reported depression by 30% (Mather et al, 2002).

Hospitalization rates

The effectiveness of pulmonary rehabilitation on rates of hospitalization has been studied widely (McCarthy et al, 2015). A meta-analysis of the effects of pulmonary rehabilitation on patients who have been discharged from the hospital with a recent diagnosis of an infective exacerbation of chronic obstructive pulmonary disease found a positive effect on rates of hospitalization with the overall post-pulmonary rehabilitation hospitalization rate per person per year (pppy) of 0.39 compared with the control group of 0.47. When focusing on the nine randomized control trials looking at pulmonary rehabilitation, hospitalization rates of 0.62 pppy were found in the pulmonary rehabilitation groups *vs* 0.97 pppy for the controls. The effectiveness of pulmonary rehabilitation before and after rehabilitation was reviewed, with the finding that pre-pulmonary rehabilitation hospitalization rates were 1.24 pppy and post-rehab were 0.47 pppy.

A UK cohort study which trialled a 7-week short course of pulmonary rehabilitation after infective exacerbation of chronic obstructive pulmonary disease found a 37.7% reduction in the incidence of admission to hospital. Similarly reductions of hospital admission risk were shown in a 5-year cohort study in the USA (Nguyen et al, 2015).

The anti-inflammatory effects of pulmonary rehabilitation

As has been found with other forms of exercise, pulmonary rehabilitation has a systemic anti-inflammatory effect. Patients with chronic obstructive pulmonary disease who were included in a pulmonary rehabilitation-based home exercise training programme showed a significant drop in blood C-reactive protein and IL-8 levels over 6 months compared to their baseline levels and those of a control group, although TNF-α levels remained unchanged (Wang et al, 2014). Symmetrical aerobic and resistance exercise in patients with chronic obstructive pulmonary disease led to a significant drop in levels of C-reactive protein and a range of cytokines (TNF-α, IL-2, IL-4 and IL-6), suggesting that exercise has a modulating effect on innate immune chemistry with a shift toward the baseline surveillance phenotype. Aerobic exercise was found to be more effective at lowering pro-inflammatory cytokines (Abd El-Kader et al, 2016).

A study of pulmonary rehabilitation over 12 weeks found a reducing trend in mean C-reactive protein level over the 12 weeks from a baseline of 9.57 to 7.1 mg/litre, with a significant drop from week 8 to 12 of 41%, although there was a slight rise in erythrocyte sedimentation rate and serum amyloid protein A level (Sciriha et al, 2017). Overall, therefore, from the studies reviewed, pulmonary rehabilitation seems to have a dampening effect on systemic inflammation in patients with chronic obstructive pulmonary disease that is likely to be one of the mechanisms by which it reduces

KEY POINTS

- Pulmonary rehabilitation is an effective exercise-based intervention that improves a number of outcomes for patients with chronic obstructive pulmonary disease.
- The beneficial effect of pulmonary rehabilitation is probably mediated, at least in part, by the anti-inflammatory and anti-sarcopenic effects of exercise.
- Many other chronic conditions are accompanied by raised levels of pro-inflammatory markers that are associated with adverse outcomes.
- Exercise reduces systemic inflammation and improves a range of clinical outcomes in a wide variety of diagnostic contexts.
- Most disease-specific exercise interventions are not as well structured or consistent as pulmonary rehabilitation, with the possible exception of cardiac rehabilitation.
- The pulmonary rehabilitation model could be used to organize and deliver exercise treatment for adult patients with single-causation or multiple-causation systemic inflammatory conditions at risk of loss of independence, sarcopenia, reduced mobility and other markers of frailty, irrespective of the underlying pathology.

the disease burden associated with chronic obstructive pulmonary disease.

Conclusion and proposition: pulmonary rehabilitation as a generic intervention for frailty

This article describes the biochemical, physiological and functional similarities between frail and pre-frail elderly people, and patients with chronic obstructive pulmonary disease. One of the most important unifying factors among such patients is the presence of chronic systemic inflammation. While some of the overall beneficial effects of exercise are likely to be mediated through neuro-endocrine, myological and psychological mechanisms, the shift of innate immune status toward a less inflamed phenotype is probably the most ubiquitous factor. There is significant evidence for the benefits of pulmonary rehabilitation, a holistic mix of interventions centred on individually tailored and structured exercise, in patients with chronic obstructive pulmonary disease.

The authors are not suggesting that pulmonary rehabilitation offers any unique form of exercise, only that it is well organized and effectively delivered. It is probable, based on current evidence, that the observed benefits of pulmonary rehabilitation are transferable and not confined to patients with chronic obstructive pulmonary disease. Therefore, a pulmonary rehabilitation-style programme is likely to be beneficial for frail and pre-frail, mainly elderly, patients recovering from other acute illnesses, especially those with chronic or prolonged post-acute systemic inflammation.

The authors contend that pulmonary rehabilitation has a sound evidence framework for a number of key improved outcomes, many of which are not directly related to improvements in respiratory status. Some exercise-based programmes are well defined, for example those for patients with stroke or hip fracture, although the emphasis tends to be on functional targets rather than exercise endurance. On the other hand, general post-acute rehabilitation programmes for elderly patients, normally individually tailored after comprehensive geriatric assessment, vary considerably in design, content, availability and duration, and the evidence for benefit, while not lacking, is less consistent and clear (de Labra et al, 2015). The authors therefore propose that the pulmonary rehabilitation model should be used to provide bespoke post-acute rehabilitation for all ambulant patients who are frail or at risk of becoming frail, irrespective of the cause of the acute episode. At the very least, trials should be conducted to establish the utility and cost-effectiveness of the pulmonary rehabilitation model if used in such a generalized way. BJHM

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