The impact of the meta-analysis of pulmonary rehabilitation by Lacasse and colleagues: transforming pulmonary rehabilitation from "art to science"

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Shareable abstract (@ERSpublications)
#Pulmonaryrehab was transformed in the 1990s into the standard of care for COPD: this article focuses on the impact of the 1996 meta-analysis by Lacasse and colleagues which provided the evidence to silence the sceptics https://bit.ly/3MIntBC

Cite this article as: Gephine S, Simonelli C, Vagheggini G, *et al*. The impact of the meta-analysis of pulmonary rehabilitation by Lacasse and colleagues: transforming pulmonary rehabilitation from "art to science". *Breathe* 2022; 18: 220021 [DOI: 10.1183/20734735.0021-2022].

Received: 16 Feb 2022
Accepted: 28 April 2022

Introduction

The modern definition of pulmonary rehabilitation (PR) [1, 2] and its effectiveness for improving dyspnoea, health-related quality of life (HRQoL) and exercise tolerance in people with chronic respiratory diseases is now well recognised [3–7]. However, this has not always been the case, and the widespread acceptance of PR as a treatment for COPD required robust evidence of its benefits to silence sceptics who saw PR as an "art" rather than science. The meta-analysis of PR for people with COPD by Lacasse *et al.* [3], in 1996, had a major part to play in this transformation (figure 1). This article provides an overview of this landmark study and discusses the impact it had on the respiratory community.

The early years of PR

Although the concepts behind PR can be traced back several centuries, Alvan L. Barach is often regarded as a pioneering physician, who in the 1950s first reported the concept of physiological training and denounced the damaging effects of a sedentary lifestyle in people with pulmonary emphysema [8]. In the 1960s, Thomas Petty and his team, developed a "standardized outpatient program of pulmonary rehabilitation", including what are the essential components of today's PR, such as individualised exercise training and education [9].

After developing the concept, the challenge was to demonstrate evidence of effectiveness. After almost a decade of experience, in 1969 Petty *et al.* [9] published a landmark paper entitled "A comprehensive care program for chronic airway obstruction", which provided some of the first evidence of benefits of PR, improving exercise tolerance and reducing rate of hospitalisation in 124 people with COPD. In 1974, the first definition of PR was published by the American College of Chest Physicians, in which PR was considered "an art of medical practice" and included "an individualized multi-disciplinary program". The definition was then updated in 1981 in an official statement of the American Thoracic Society, in which exercise training was defined as an essential component of PR [10].

Despite the positive effects described by Petty, the 1980s have been described as the "dark ages" of PR [11], with some physicians doubting the benefits of exercise training for people with COPD; PR was still seen as an "art" and more evidence was needed to demonstrate its scientific basis. Doubts were based on a poor understanding of exercise physiology and focused on the lack of improvement in lung function. A paper published by Belman and Kendregan [12], in 1981, strongly influenced scepticism in PR as it

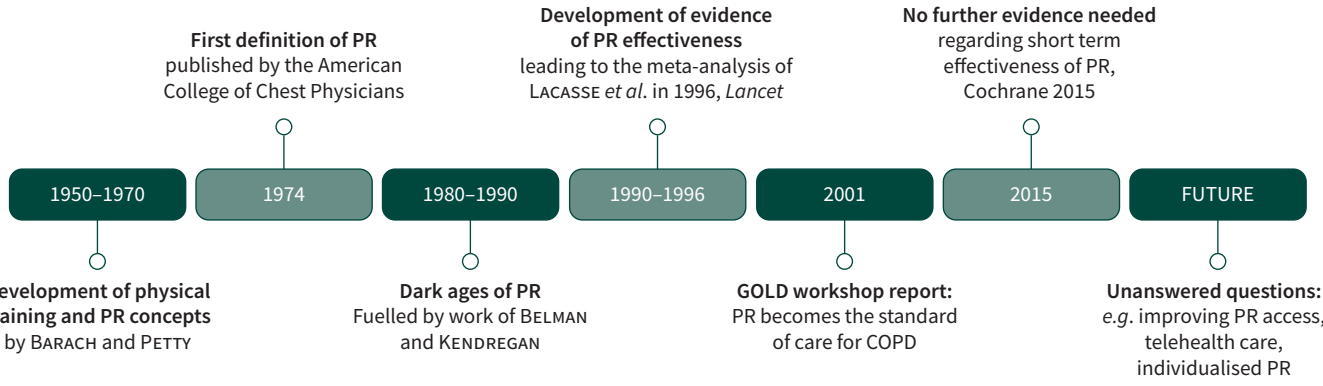

FIGURE 1 Timeline of the history of PR.

failed to show improvements in heart rate and skeletal muscle enzymes following exercise training in people with COPD. However, the study design, specifically the low-intensity training, was challenged later the same year as the reason for a lack of improvement [13].

Understanding began to shift in the early 1990s with landmark studies providing increasing evidence of the benefits of PR. First, Ries [14] provided a review of the scientific basis of the effectiveness of PR on exercise tolerance, dyspnoea and HRQoL. Then strong physiological rationales were developed by Casaburi *et al*. [15, 16] and later by Maltais *et al*. [17] proving that effective exercise training could improve skeletal muscle function in COPD regardless of disease severity. In 1994, Goldstein *et al*. [18] published a landmark trial of PR in the *Lancet* demonstrating improvements in exercise capacity and quality of life. With the publication of an increasing number of controlled trials of PR, it was time for a robust synthesis of the evidence.

The meta-analysis by Lacasse and colleagues: effectiveness of PR on exercise capacity and quality of life

In 1996, the first meta-analysis by Lacasse *et al*. [3] published in the *Lancet* synthesised the evidence investigating the effect of PR on measures of maximal and functional exercise capacity, and HRQoL in people with COPD. It involved a meta-analysis of 14 randomised controlled trials (RCT), comparing at least 4 weeks of PR for people with COPD to usual care.

The 14 RCTs were of moderate methodological quality, with two potential sources of bias: unconcealed randomisation and unblinded study personnel. The PR programmes included were inpatient, outpatient or home-based, lasting between 6 and 18 weeks. Lower-limb exercise was always administered, and other components included breathing exercises, upper-limb training, education, psychological support, postural drainage and inspiratory muscle training. Study sample size varied from 14 to 78, with mean age ranging from 57 to 73 years and heterogeneous disease severity.

Lacasse *et al*. [3] found a significant pooled positive effect of PR on maximal exercise capacity (effect size 0.3, 95% CI 0.1–0.6) in 11 trials (309 patients), equating to 8.3 Watts (95% CI 2.8–16.5 Watts) for studies that used incremental cycling exercise testing. Functional capacity improved with PR with an effect size of 0.6 (95% CI 0.3–1.0) in 11 trials (413 patients), corresponding to an improvement in the 6-min walk test (6MWT) of 55.7 m (95% CI 27.8–92.8 m). The lower limit of the confidence interval fell below the authors estimate for the minimum clinically important difference (MCID) for the 6 MWT of 50 m based on recently published data [19]. The authors found high heterogeneity in the results for functional exercise capacity, with the longest PR programme (6 months) more effective than the shortest one (93.8 m *versus* 39.2 m, p=0.0004).

HRQoL was measured in 12 studies using 10 different methods. Meta-analysis was performed on two of these scales that had been validated at the time: the Transitional Dyspnea Index (TDI) and the Chronic Respiratory Questionnaire (CRQ). These scales were assessed in six studies (126 and 111 patients for TDI and CRQ, respectively) demonstrating a significant improvement in HRQoL following PR compared with usual care. The CRQ revealed an overall effect size higher than the MCID of 0.5 [20] in all the domains investigated (dyspnoea, fatigue, emotion and mastery).

A comprehensive review, but what was missing?

This meta-analysis demonstrated the effectiveness of PR over usual care in improving exercise capacity and HRQoL in people with COPD. Lacasse and colleagues concluded that, given the homogeneity among study results for improvements in maximal exercise capacity and HRQoL, there was no doubt that even PR programmes of short duration were effective.

However, some limitations of the analysis were highlighted. First, the paper demonstrated only the short-term effect of PR at programme completion and suggested further studies were needed to investigate long-term effects and maintenance strategies. Furthermore, despite the homogeneity of the results, the programmes proposed were different in terms of setting, duration and composition, and the contribution given by each single component of the programmes was not investigated. Additional studies were also needed to identify the response to PR in subgroups of COPD with different disease severity or phenotypes, to identify non-responders, as well as improving the tailoring of the programme to the individual. Finally, other methods of evaluation were required to assess the benefits of PR on outcomes other than exercise capacity and HRQoL, such as muscle strength, dyspnoea perception, daily physical activity, healthcare utilisation, hospitalisation rate or mortality, and to investigate the effects for people with chronic respiratory diseases other than COPD.

From research to practice: PR becomes the standard of care for COPD

Publication of the meta-analysis by Lacasse *et al*. [3] was followed by statements from the European Respiratory Society (ERS) [21] and American Thoracic Society (ATS) [22] setting out the clinical benefits of PR and championing further development of PR programmes. In the decade that followed, there was a rapid expansion of PR programmes globally representing a step change in the clinical care of COPD. PR became the standard of care, and in 2001 was included in recommendations for the management of stable COPD [23], and became an integral part of the treatment for a range of chronic respiratory conditions [5–7] although the assumption of the benefits of PR for people with other chronic respiratory diseases was at this stage extrapolated from the data from individuals with COPD.

The Cochrane collaboration published further systematic reviews of PR in 2001 [24], 2006 [25] and 2015 [4], cementing the evidence for improved exercise capacity and quality of life for people with COPD. Indeed, the evidence was so compelling that the 2015 Cochrane review of PR concluded that “additional RCTs comparing pulmonary rehabilitation and conventional care in COPD are not warranted”, thereby firmly closing a chapter in the history of PR development; PR had convincingly transitioned from “art” to scientifically proven treatment.

Where next for PR research?

Although the closing of the Cochrane review was a major moment in PR research, it was not the end of the story. Despite compelling evidence for the effectiveness of PR there remained many unanswered questions regarding the optimal design and delivery of PR programmes across a variety of settings globally [26]. Access, uptake, and completion continue to be major challenges; rate of referrals in some settings are low [27] and once referred many patients do not attend or complete a programme [28], often citing difficulties with transport and competing commitments (including work and caring responsibilities) [29] as reasons for not attending. Alternative models of PR have therefore been developed to address these issues, largely focusing on home-based rehabilitation with varying levels of direct or indirect support. These may provide a useful tool in the PR toolkit, particularly for individuals for whom centre-based PR is unfeasible or undesirable. However, whilst supervised home-based rehabilitation has been shown to be effective [30], the effectiveness of remotely supervised PR remains uncertain [31].

Whilst the work of Lacasse and others has demonstrated the effectiveness of PR in an unselected COPD cohort, it may be possible to further enhance the benefits of PR through an individualised approach to treatment focused on “treatable traits”. A comprehensive PR programme is designed to address multiple physical and psychological aspects of a patient’s condition [32], and whilst the effect of PR on maximal exercise capacity is likely to be primarily mediated through the effect of aerobic exercise training on skeletal muscle dysfunction, other targeted outcomes, such as increased physical activity or reduced healthcare utilisation [33] may not respond to aerobic exercise training in isolation and may require improvements in self-management or knowledge as result of a structured education programme [34]. Therefore, we need a better understanding of how to individualise PR programmes for our diverse group of patients with a range of chronic respiratory diseases, either by stratifying the exercise and education components through targeting of “treatable traits” [35], or providing holistic care through an integrated multidisciplinary approach, before the tale of PR research is truly complete.

Conclusion

Although the concept of multidisciplinary PR was developed in the 1960s, the meta-analysis of Lacasse *et al*. [3] published in 1996 was a major milestone in PR research and facilitated the widespread acceptance of PR as an integral part of the treatment for COPD. The review provided convincing evidence of the effectiveness of PR for improving exercise capacity and quality of life, resulting in the inclusion of PR in international guidelines translating to everyday clinical care for people with chronic respiratory diseases worldwide.

Conflict of interest: C. Simonelli is an unpaid member of the Board of Directors of ARIR Associazione Riabilitatori dell'Insufficienza Respiratoria, Italy, outside the submitted work. G. Vagheggini reports receiving personal fees for a CME course lecture - Provider: Regia Congressi (funded by an unrestricted educational grant from CHIESI Farmaceutici S.p.A) and CME webinar lecture - Summeet Sri (funded by an unrestricted educational grant from A. Menarini Industrie Farmaceutiche Riunite srl). He is president of Fondazione Volterra Ricerche ONLUS (unpaid). All disclosures made outside the submitted work. R. Evans reports receiving grants or contracts from NIHR, UKRI. Payment received from Boehringer June 2021 for speaker bureaus. Support for attending meetings and/or travel received from Chiesi. Leadership or fiduciary role in other board, society, committee or advocacy group for European Respiratory Society as Assembly 01.02 Pulmonary Rehabilitation secretary (unpaid). All disclosures made outside the submitted work. T.J.C. Ward is funded by the NIHR (NIHR Clinical Lectureship (CL-2020-11-004)). The views expressed are those of the authors and not necessarily those ofthe NIHR or the Department of Health and Social Care. The remaining authors have nothing to disclose.

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