

REVIEW

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Pulmonary rehabilitation and cardiovascular risk in COPD: a systematic review



Yousef S. Aldabayan*, Ahmed M. Alrajeh, Arthur Lemson and John R. Hurst

Abstract

Introduction: Pulmonary Rehabilitation (PR) is an effective intervention in COPD however the value of PR in reducing cardiovascular risk in COPD (measured by aortic pulse wave velocity, aPWV) is unclear and there is no existing systematic review.

Objectives: To conduct a systematic review examining whether PR results in alteration of CV risk in COPD (as measured by aPWV).

Methods: An electronic systematic search concordant with PRISMA guidelines was conducted. The search was complete to the 27th of May 2017. Six databases were examined: Embase, Medline, AMED, Web of Science, Cochrane clinical trials, and CINAHL.

Results: This study generated 767 initial matches, which were filtered using inclusion/exclusion criteria. Three studies (201 COPD participants) were included. Our analysis does not confirm that PR affects aPWV but studies were heterogeneous.

Conclusion: There is currently insufficient information on the effect of PR on reducing CV risk in COPD. Therefore controversy remains, with the possibility that there might be some subjects who benefit and others who might experience an increase in CV risk in response to PR. These results will be of value to those interested in gaining a better understanding of the benefits of PR on CV risk in COPD.

Keywords: Pulmonary rehabilitation, Cardiovascular, COPD, Arterial stiffness

Introduction

According to the World Health Organisation (WHO) [1], chronic obstructive pulmonary disease (COPD) is a leading cause of death. In part, the elevated mortality in COPD derives from an enhanced risk of cardiovascular disease (CVD) [2]. Without mitigation, COPD will be the third most common cause of death by 2030 [1].

COPD is defined as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” [3]. Arterial stiffness is a gold-standard predictor of individual cardiovascular risk [4], and a biomarker of elevated cardiovascular risk in COPD patients [5], as it is in healthy populations. It can be measured using aortic pulse wave

velocity [6]. It is known that COPD patients have increased arterial stiffness compared to controls [7, 8], and we have previously reported a relationship between the frequency of exacerbation and arterial stiffness [9].

Interventions to reduce cardiovascular risk in COPD patients are therefore of profound importance, yet existing evidence is not consistent and requires further investigation. Pulmonary Rehabilitation (PR) – a group exercise and education programme - is an evidence-based effective intervention in COPD to reduce symptoms, improve exercise performance and prevent exacerbations [10]. PR is defined by the European Respiratory Society (ERS) and American Thoracic Society (ATS) as “an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities” [11]. Whilst exercise may reduce cardiovascular risk, the effect of exercise training and/or PR programme on cardiovascular risk in COPD remains controversial. The objective

* Correspondence: yousef.aldabayan.15@ucl.ac.uk
UCL Respiratory, Royal Free Campus, University College London, London NW3 2QG, UK

of this systematic review was to summarise and report the effect of PR on cardiovascular risk in COPD.

Review

Method

Search strategy

This systematic review is concordant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The search was complete to the 27th of May 2017. The search was performed using six electronic databases (Excerpta Medica dataBASE (Embase), MEDLARS Online (Medline), Allied and Complementary Medicine Database (AMED), Web of Science database, Cochrane clinical trials database, and Cumulative Index of Nursing and Allied Health Literature (CINAHL)).

All relevant titles and abstracts were read to evaluate eligibility based on our inclusion criteria. After reading the full texts, the first author eliminated non-relevant articles where potentially relevant articles were reviewed by the other authors to confirm eligibility.

Inclusion and exclusion criteria

The included studies met the following criteria:

- 1) Studies of patients with spirometrically-confirmed COPD.
- 2) Patients enrolled on a PR or an exercise training program.
- 3) Patients had cardiovascular risk assessment measured using aPWV before and after the programme to assess change in CV risk.

We excluded books, systematic reviews, non-English manuscripts, conference abstracts with no full-text and non-full text articles.

The primary outcome was change in cardiovascular risk measured using arterial stiffness in response to pulmonary rehabilitation or an exercise-training programme.

Results

Our search strategy (available in the Additional file 1), identified 767 articles, and one additional article was identified by screening reference lists. Of these, only three met all our inclusion and exclusion criteria (Fig. 1). Of the three included studies, two investigated COPD patients who had been enrolled on a PR programme, and one reported outcomes from patients enrolled on an exercise endurance training programme. In summary, with regard to the effect of PR on CV risk in COPD, we found one larger negative study [7] and two smaller positive studies [5, 6].

A detailed description of the three studies is given in Table 1. The sample size and duration of the included

studies varied: 4 weeks, 7 weeks and two years. The sample size ranged from 17 to 330 participants.

Quality assessment

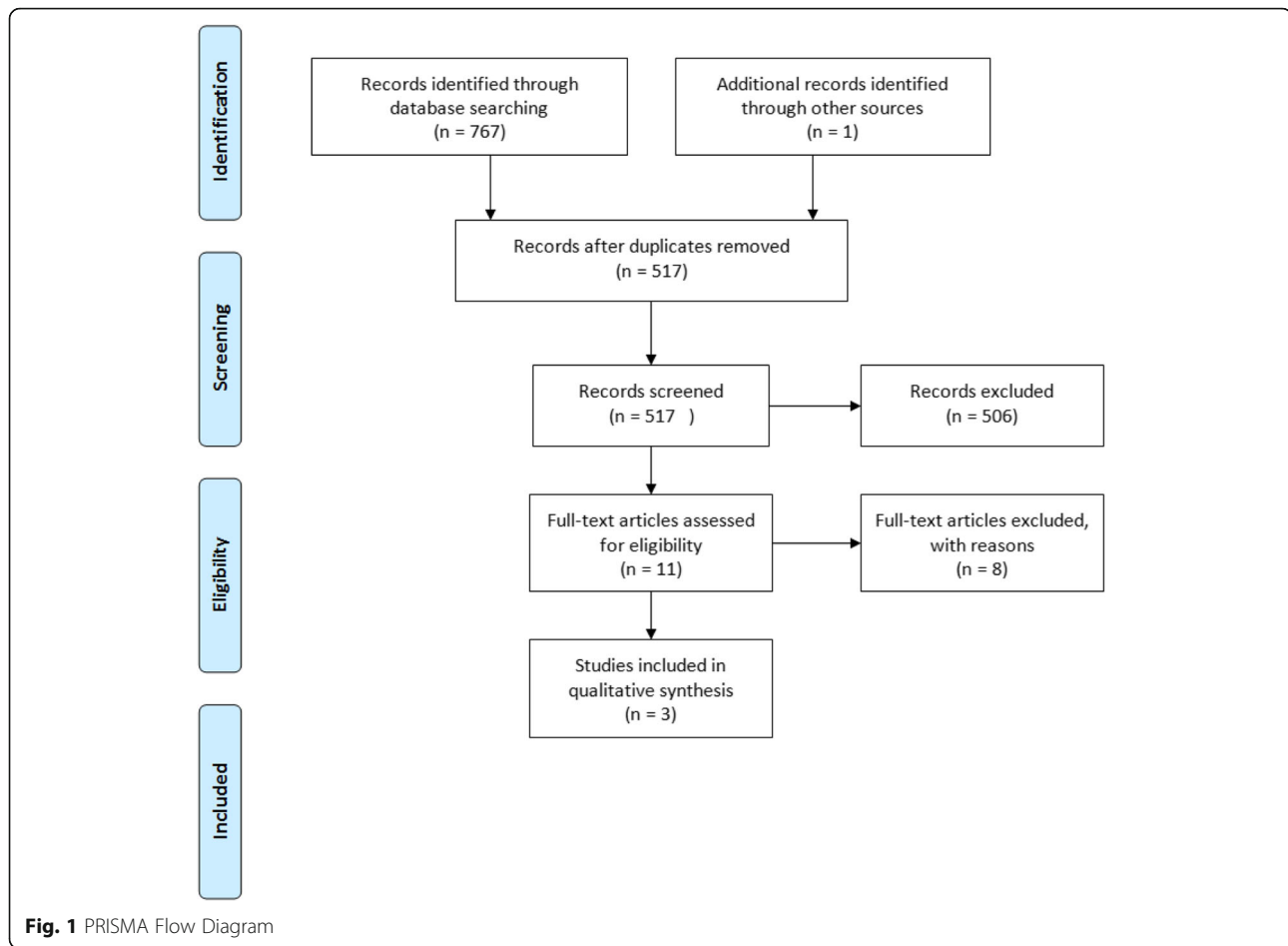
Among the three included studies, two were cohort studies and one was a randomized clinical trial. To assess the quality and the risk of bias of each article, the Newcastle-Ottawa scale (modified) [13] was used for cohort studies as indicated in Table 2 and the Cochrane risk of bias tool (modified) [14] was used for the randomised clinical trial as indicated in Table 3.

Discussion

This systematic review was conducted to evaluate the effects of exercise and/or pulmonary rehabilitation (PR) on cardiovascular risk in COPD as assessed by arterial stiffness. As reported in Table 1, there is one (larger) negative, and two (smaller) positive studies. Controversy remains over the effects of PR on cardiovascular risk. Studies were too heterogeneous to permit meta-analysis. This is the first systematic review to address the important question of whether PR affects cardiovascular risk in COPD.

Vivodtzev conducted a study in 2010 to investigate whether exercise training decreased arterial stiffness in patients with COPD. The randomized trial of aerobic endurance training was run for four weeks in 17 stable patients with moderate to severe COPD free from diabetes and respiratory exacerbation within the preceding three months. The participants were divided into two groups; a trained group ($n = 10$) and an untrained group ($n = 7$). Arterial stiffness was measured blindly by recording the carotid-radial pulse wave velocity (c-r PWV). The baseline measurements of c-r PWV were similar in both groups. After four weeks of an aerobic endurance training programme, c-r PWV readings were stable in the untrained group and significantly reduced in the trained group (from 10.3 ± 0.7 to 9.2 ± 0.8 m/s, $P = 0.001$). c-r PWV reduction correlated with improvements in walking distance ($r = 0.49$), systolic blood pressure ($r = 0.79$), muscle endurance ($r = 0.48$), and fasting glucose ($r = 0.59$) in all patients ($P = < 0.05$), and with changes in maximal heart rate and oxygen consumption ($r = 0.70$, $P = 0.02$) in trained patients. The authors concluded that arterial stiffness appears to be improved following exercise in stable patients with COPD.

Gale conducted a study in 2011 to investigate if pulmonary rehabilitation affected cardiovascular risk factors in patients with COPD. The study was run for seven weeks in the context of a multidisciplinary pulmonary rehabilitation programme on a total of 32 stable COPD participants who were free from ischemic heart disease, cardiac failure, diabetes mellitus or malignancy. These 32 participants were compared with 20 healthy controls at the baseline assessment. In all subjects, aortic pulse



wave velocity was measured before the programme and repeated for those who completed PR. On the initial measurements of aortic stiffness, aPWV was increased in patients compared to the control group ($p < 0.05$). After seven weeks of the multidisciplinary pulmonary rehabilitation programme, 22 patients completed the programme. aPWV was re-measured for those who completed the programme, and was significantly reduced in comparison to the baseline measurement (from 9.8 ± 3.0 m/s to 9.3 ± 2.7 m/s, $p \leq 0.05$). Gale concluded that cardiovascular risk measured by aortic stiffness was significantly improved following multidisciplinary pulmonary rehabilitation in patients with COPD.

Vanfleteren conducted a study in 2014 that aimed to confirm increased arterial stiffness in COPD, evaluate its relationship with systemic inflammation and, most importantly, to examine if the increased arterial stiffness was influenced by PR. The study was run for two years on a total of 168 healthy control participants who had normal pulmonary function tests and 162 COPD patients. Among the COPD group, only 129 patients completed the PR programme and were re-assessed. It was reported that arterial stiffness was increased in COPD

patients at baseline measurement compared to controls. Furthermore, it was reported that systemic inflammatory markers were not related to increased arterial stiffness in COPD. Overall, there was no change in aPWV measurement after PR (10.7 ± 2.7 versus 10.9 ± 2.5 ms, $p = 0.339$). The Authors concluded that changes in arterial stiffness in COPD were not related to markers of systemic inflammation and not influenced by pulmonary rehabilitation.

We noted heterogeneity across the included studies regarding exercise intensity and programme duration (and such heterogeneity prevented meta-analysis). In the Gale study [6], arterial stiffness significantly improved after PR. Additionally, there was a significant reduction in central mean arterial pressure (103 ± 14 to 95 ± 14 mmHg; $p < 0.001$) which may account for the reduction in aPWV. The larger negative study by Vanfleteren [7] was well designed consisting of 40 sessions, twice as many as Gale [6]. There was no effect on reduction of aPWV or on mean arterial pressure. The Vivodtzev study did not include an education component [5].

The available data on the ability of PR to reduce cardiovascular risk in COPD therefore remains contradictory. Importantly, we noted that CV responses to

Table 1 Detailed description of the included studies

| Author (Ref) | Subjects | Study design | Disease severity (mean FEV1% predicted) | CV measures | Detailed description of exercise and/or PR programme | CV response following exercise and/or PR programme. | p. value |
|-----------------|---|------------------------------|---|-------------|---|--|-----------|
| Vivodtzev [5] | COPD patients (n = 17) | Prospective randomized trial | Trained, n = 10 (47 ± 20%) Untrained, n = 7 (54 ± 13%) | (c-r PWV) | Duration: 4 weeks. Session detail: 5 day/wk. (18 ± 8 to 30 ± 12 min exercise time) Intensity training endurance: Intensity was increased depending on the tolerance of the patients (to 6/10 on Borg scale). PWR increased from 38% ± 12% to 65% ± 12% of peak workload at the end of training. | ↓ aPWV in Trained group Baseline measurement (10.3 ± 0.7 m/s) After intervention (9.2 ± 0.8 m/s) | P = 0.001 |
| Gale [6] | Controls (n = 20) COPD patients (n = 32) | Prospective cohort study | (45 ± 20%) | (aPWV) | Duration: 7 weeks. Duration/ sessions: 3 day/wk. (2.25 h exercise time) Intensity training endurance: The ISWT was used to set the intensity of exercise training at 60–70% VO2 peak. | ↓ aPWV Baseline measurement (9.8 ± 3.0 m/s) After intervention (9.3 ± 2.7 m/s) | P = <0.05 |
| Vanfleteren [7] | Controls (n = 168) COPD patients (n = 162) | Prospective cohort study | (51.4 ± 17.4%) | (aPWV) | Duration: 8 weeks Duration/ sessions: 5 day/wk. (duration not specified) Intensity training endurance: Moderate to high intensity. The intensity was increased during the rehabilitation period, based on dyspnoea and fatigue symptom scores. | No change in aPWV Baseline measurement (10.7 ± 2.7 m/s) After intervention (10.9 ± 2.5 m/s) | P = 0.339 |

Date presented as mean (SD). Abbreviations: FEV1 forced expiratory volume in 1 s, CV cardiovascular, PR pulmonary rehabilitation, COPD chronic obstructive pulmonary disease, c-r PWV carotid-radial pulse wave velocity, aPWV aortic pulse wave velocity, PWR peak work rate, ISWT incremental shuttle walk test, VO2 oxygen uptake

Table 2 Risk of bias of the included cohort studies

| First author | Population representative | Sample size adequate | Confounders | Statistical analysis | Missing data | Methodology of the outcome | Objective assessment |
|----------------------|---------------------------|----------------------|-------------|----------------------|--------------|----------------------------|----------------------|
| Gale 2011 [6] | 3 | 2 | 3 | 3 | 3 | 3 | 3 |
| Vanfleteren 2014 [7] | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

0 = Definitely no (therefore high risk of bias), 1 = Mostly no, 2 = Mostly yes, 3 = Definitely yes (therefore low risk of bias)

PR appeared highly heterogeneous in the Vanfleteren paper [7]. This raises the important hypothesis that some patients may benefit and that some patients may be at increased risk from PR in COPD (Fig. 2, derived from the original paper [7]). This may be clinically important.

Cardiovascular co-morbidity is common in COPD. Chen conducted a systemic review and meta-analysis aiming to quantify the magnitude of the association between COPD and increased prevalence of cardiovascular risk-factors and co-morbidity [15]. Twenty seven observational studies were included in the meta-analysis. The pooled odds of cardiovascular disease was higher in subjects with COPD compared to people without (meta-odds ratio OR 2.46, 95% CI 2.02–3.00; $p < 0.0001$). This comprised a two to five-fold higher risk of major cardiovascular disease sub-types (ischemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation and arterial diseases), and a one-third increased risk of hypertension and diabetes. No significant increased risk of cerebrovascular disease, dyslipidaemia, and obesity was detected in patients with COPD.

The papers examined in this systematic review included information on baseline cardiovascular risk. In the Vanfleteren paper, among 162 COPD patients there was no statically significant difference in aPWV after PR ($p = 0.339$) despite the prevalence of recorded cardiac comorbidities including myocardial infraction ($n = 16$ [9.9%]), heart failure ($n = 5$ [3.1%]), peripheral arterial diseases ($n = 30$ [18.5%]), cerebrovascular disease ($n = 14$ [8.6%]), diabetes ($n = 7$ [4.3%]) or any other cardiovascular diseases ($n = 50$ [30.9%]). Furthermore, even after subdividing the patients into subgroups based on cardiovascular risk factors including smoking (ever smoked), hypertension, hyperlipidemia, age and obesity there was no notable difference in response ($p > 0.05$). In the positive studies, Vivodtzev reported that none of the participants had a history of ischemic heart disease or stroke. They reported that the significant reduction

in PWV correlated with systolic BP ($r = 0.79$) and fasting glucose ($r = 0.59$). In the Gale study, none of the participants had reported cardiovascular disease. However, PR did improve some cardiovascular risk factors, including both blood pressure and cholesterol ($p = <0.05$).

None of the three included studies in this review reported data on subsequent risk of hospital admission or mortality following the exercise programme. Puhan conducted a systematic review aiming to compare the effect of PR after COPD exacerbation in reducing hospital admission and mortality [16]. Twenty RCTs (1477 participants) were included in this review. Eight studies including 810 participants contributed data on hospital readmission indicating that PR reduced hospital readmission (pooled odds ratio (OR) 0.44, CI 0.21 to 0.91) but the results were heterogeneous (77%). Six studies contributed data on mortality. The duration of follow-up period ranged from 3 to 48 months with one study showing reduced mortality and four no effect. The quality of evidence was low. None of the trials considered mortality as a primary outcome and the analysis did not show a statistically significant influence of PR on mortality (OR = 0.68, CI 0.28 to 1.67) with significant heterogeneity reported across the studies.

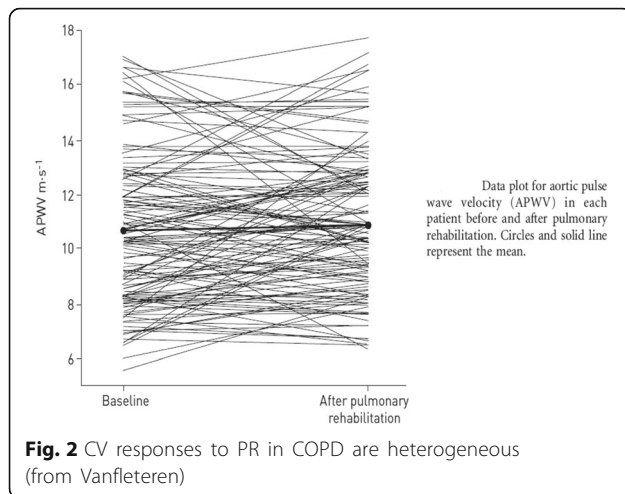
It can be seen from the analysis above that CVD and CVRs are very prevalence among COPD patients, which might be expected to proportionally influence the aPWV. Therefore, the variety of the included patients in terms of CVDs and CVRs might also count to explain the current results' heterogeneity of this systematic review.

The available data on the ability of PR to reduce cardiovascular risk assessed by aPWV in COPD therefore remains contradictory. Interestingly, Oliveira performed a systemic review with the aim of examining the effect of exercise training on arterial stiffness in Coronary Artery Disease (CAD) patients assessed by measuring arterial stiffness or related indexes (eg. indexes of wave

Table 3 Risk of bias in the included randomised trial

| First author | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other sources of bias |
|--------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|---------------------|-----------------------|
| Vivodtzev 2010 [5] | Unclear | Unclear | Unclear | Low | Low | Unclear | Low |

Low: Low risk of bias, High: High risk of bias, Unclear: Unclear risk of bias



reflection or arterial compliance) [17]. Five studies were included in this review with a total of 271 participants varying in age (48–67 years) and exercise programme duration (6 to 20 weeks). Participants were diagnosed with CAD after an acute myocardial infarction, coronary artery bypass graft or coronary angioplasty. Overall, Oliveira found that exercise programs in CAD patients led to improved outcome measures. Specifically, there was a significant reduction in PWV despite use of different measurement methods including brachial-ankle PWV (reduction of 0.120 m/s), carotid-femoral PWV (4.1 m/s to -0.7 m/s) and carotid-radial PWV (0.7 m/s). The authors reported a greater reduction in PWV in CAD patients who completed a 20-week (-1.0 ± 0.3 m/s) versus a 12-week training course (-0.6 ± 0.2 m/s).

In summary, we are unable to conclude whether there is or is not a significant change in aortic pulse-wave velocity in response to PR in COPD. Therefore further work is required to definitively address this question and in particular whether there may be subgroups of patients who do and do not respond. There is an urgent unmet need for evidence-based standardised interventions that reduce the risk of cardiovascular events in patients with COPD. Conducting further studies considering confounding variables such as cardiovascular risk factors and disease, medication, exercise intensity and duration of the programme may better assess the benefits of PR programme on CV risk in COPD.

Strength and limitations

The strength of this work is that there is no previous systematic review on the effect of PR on CV risk in COPD measuring aPWV. A potential limitation of this report was that we excluded non-English studies.

Conclusion

We have systematically searched for and reported those studies that evaluated the effect of PR on CV outcomes in COPD. There is some existing data evaluating the effect of PR on cardiovascular risk in COPD, with one (larger and higher quality) negative study and two smaller positive ones. Study heterogeneity results in continuing controversy in the field. The negative study also reported inter-patient heterogeneity in responses that are unexplained, require further evaluation and may be clinically important. Results generated from this report will be of importance for researchers interested in assessing the benefits of PR on reducing CV risk in COPD.

Additional file

Additional file 1: Search Strategy. (DOC 146 kb)

Abbreviations

AMED: Allied and complementary medicine database; aPWV: Aortic pulse wave velocity; ATS: American thoracic society; BP: Blood pressure; CINAHL: Cumulative index of nursing and allied health literature; COPD CV: Cardiovascular; c-r PWV: Carotid-radial pulse wave velocity; CVD: Cardiovascular disease; CVR: Cardiovascular risk; Embase: Excerpta Medica dataBASE; ERS: European Respiratory Society; FEV1: Forced expiratory volume in 1 second; ISWT: Incremental shuttle walk test; MAP: Mean arterial pressure; PR: Pulmonary rehabilitation; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; PWR: Peak work rate; UK: United Kingdom; VO₂: Oxygen uptake; WHO: World Health Organisation

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Availability of data and materials

Please contact the corresponding author for data requests.

Authors' contributions

YA designed the study and carried out the initial search and data extraction, and drafted the manuscript. AA and JH participated in the design of the study with YA. AL assisted with contributions on PR and cardiovascular risk in coronary artery disease. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

This is a systematic review, ethics approval is not applicable.

Consent for publication

This is a systematic review, consent is not applicable.

Competing interests

The authors declare that they have no competing interests.

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