Heart & Lung 43 (2014) 249–255

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

Pulmonary rehabilitation improves heart rate variability at peak exercise, exercise capacity and health-related quality of life in chronic obstructive pulmonary disease

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ARTICLE INFO

Article history:
Received 22 October 2013
Received in revised form
24 February 2014
Accepted 1 March 2014
Available online 29 March 2014

Keywords:
Chronic obstructive pulmonary disease
Exercise capacity
Health-related quality of life
Heart rate variability
Pulmonary rehabilitation

ABSTRACT

Objective: Patients with chronic obstructive pulmonary disease (COPD) appear to have impaired cardiac autonomic modulation with depressed heart rate variability (HRV). Pulmonary rehabilitation (PR) is recommended as an integral part of the management. However, the effect of PR on HRV at peak exercise remains unclear.

Methods: Sixty-four patients with COPD participated in a 12-week, 2 sessions-per-week, hospital-based PR program. Baseline and post-PR status were evaluated by spirometry, HRV, health-related quality of life (HRQL, St. George's Respiratory Questionnaire, SGRQ), cardiopulmonary exercise test, respiratory muscle strength, and dyspnea Borg's scale.

Results: After PR, there were significant improvements in the time and frequency domains of HRV with increased standard deviation of the normal R–R intervals, difference between adjacent normal R–R intervals within a given time minus one, high-frequency and decreased low-frequency, as well as concurrent improvements in HRQL, exercise capacity, dyspnea score, and respiratory muscle strength (all $p < 0.05$).

Conclusions: PR results in significant improvements in autonomic function, with concurrent improvements in HRQL and exercise capacity.

Introduction

Chronic obstructive pulmonary disease (COPD) is a systemic disease that has been shown to negatively affect the cardiovascular and autonomic nervous systems.[1,2] The withdrawal of parasympathetic tone and increase in sympathetic tone have also been reported in patients with COPD.[3] The possible mechanisms of dysregulated autonomic function in COPD include lung hyperinflation,[3] hypoxia,[4] hypercapnia,[5] systemic inflammation,[6] dyspnea and anxiety.[7] A reduction in lung function and lung hyperinflation may lead to increased adrenergic activation, resulting in increased sympathetic tone.[3] Hypoxia with abnormal oxygen supply to the cardiac sinus node has been reported to facilitate an abnormal response to autonomic stimuli,[4,8] and increased inflammatory state also contributes to autonomic dysfunction.[6] Dyspnea is associated with anxiety and emotional disorders and is frequently

Abbreviations: ANS, autonomic nervous system; BMI, body mass index; BP, blood pressure; CPET, cardiopulmonary exercise test; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LF, low-frequency; PEmax, maximal expiratory pressure; $PETCO_2$, end tidal PCO_2; PImax, maximal inspiratory pressure; HF, high-frequency; HR, heart rate; HRQL, health-related quality of life; HRV, heart rate variability; PR, pulmonary rehabilitation; Rf, respiratory frequency; rMSSD, square root of the mean sum of the squares of the difference between adjacent normal R–R intervals; SDNN, standard deviation of the normal R–R intervals; SGRQ, St. George's Respiratory Questionnaire; SpO_2, hemoglobin saturation by pulse oximeter; VCO_2, carbon dioxide output; VE, minute ventilation; VLF, very-low-frequency; VO_2, oxygen uptake; V_T, tidal volume.

Conflict of interest disclosure: The authors have no financial or other potential conflicts of interest to disclose.

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0147-9563/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.hrtlng.2014.03.002

encountered in patients with COPD and lead to dysregulated autonomic system.[7]

During exercise, patients with COPD are characterized by further withdrawal of parasympathetic tone and increase in sympathetic tone.[3,9] Many possible mechanisms have been postulated regarding autonomic imbalance during exercise in patients with COPD as follows. The development of a rapid shallow breathing pattern during exercise contributes to autonomic dysfunction.[10] Dynamic hyperinflation during exercise results in increased activity of slowly adapting receptors and rapidly adapting receptors fibers, leading to an imbalance in autonomic modulation.[11] Repeated muscular contractions have been shown to increase metabo-reflex-mediated sympathetic excitation during exercise.[12] Oxygen radicals and products of ischemic metabolism generated during muscular contraction can further stimulate local receptors and cause increases in heart rate (HR), blood pressure (BP), and sympathetic activity.[13] These findings therefore suggest that many mechanisms are involved in changes in sympathetic and parasympathetic responses in patients with COPD.

Heart rate variability (HRV), which is a noninvasive tool used to assess HR regulation with the autonomic system is defined as the variation in time differences in milliseconds between consecutive heart beats over a given period of time.[14] By expressing cyclic fluctuations of the HR, HRV reflects autonomic modulation by sympathetic and parasympathetic efferent nervous impulses of heart rhythm.[14] It reflects the balance of sympathetic and parasympathetic nervous systems inputs on cardiac activity.[14] HRV analysis has been used extensively in the clinical setting.[14] Impaired autonomic function has been associated with a worse prognosis in systemic hypertension, congestive heart failure, diabetes, obesity, renal failure, neurological diseases as well as in the healthy population.[14–17] In COPD, many studies have shown that patients with COPD have impaired cardiac autonomic function.[3]

Patients with COPD often have a poor health-related quality of life (HRQL) and exercise capacity.[2,18] Many studies have suggested that pulmonary rehabilitation (PR) is beneficial for improving exercise capacity and HRQL,[19–21] and therefore, PR has been recommended as an integral part of management for these patients.[22,23] Although, there are many studies suggest PR improves exercise capacity and HRQL in COPD,[19–21] the effect of PR on HRV is still not clearly understood. Possible mechanisms regarding autonomic imbalance during exercise include exertional dyspnea, dynamic hyperinflation, and ischemic muscular metabolism.[10–12] Previous studies have reported that PR can improve dynamic hyperinflation, exertional dyspnea, and muscular function, and we therefore hypothesized that PR may improve autonomic dysfunction during exercise.[21,24,25] The present study therefore aimed to investigate the effect of PR on HRV during exercise in patients with COPD. In addition, we investigated the effect of PR on HRQL and exercise capacity concurrently. The results of this study provide a comprehensive understanding of the influence of PR on cardiac autonomic function, exercise capacity and HRQL in such patients.

Methods

Study design

All patients participated in 12-week, 2 sessions per week outpatient-based PRs. The physiological parameters were assessed by HRV, cardiopulmonary exercise test (CPET), spirometry, and respiratory muscle strength testing (maximal inspiratory pressure, PImax; maximal expiratory pressure, PEmax). The HRQL and dyspnea symptom were assessed using the St. George's Respiratory Questionnaire (SGRQ) and dyspnea Borg's scale. All assessments were performed before and after PR. The research protocol was approved by the Ethics Committee of the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and all patients provided informed consent.

Patient selection

Sixty-four patients with COPD were recruited from the outpatient clinic of Taipei Tzu Chi Hospital. The inclusion criteria were (1) a diagnosis of COPD based on the GOLD staging[26]; (2) stable from exacerbations with no worsening of respiratory symptoms (i.e., dyspnea, chest tightness, and cough), no increase in the use of rescue medication, and no unscheduled visits due to worsening COPD for at least three months[27]; and (3) the ability to move independently. The patients with a history of cardiovascular disorders, diabetes, and use of systemic drugs which may have influenced the autonomic nervous system were excluded.

Cardiopulmonary exercise test

The CPET was incremental, symptom-limited exercise testing performed on an electronically braked cycle ergometer (Lode Corival, the Netherlands). The standard bicycle exercise ramp workload protocol was according to the method of Wasserman et al.[28] To stabilize gas measurements, the patients were asked to remain still for at least 3 min before beginning upright graded bicycle exercise testing. The patients then performed unloaded pedaling for 3 min followed by the ramp increase in work rate. The work rate increment (10–20 W/min) was judged for each individual patient by considering age, gender, height, and weight for obtaining an exercise phase of 8–12 min[28]

The patients were asked to maintain a cycling cadence of 60 revolutions per minute and were strongly encouraged to achieve their point of maximal exercise. Indications to stop the test were exhaustion, dyspnea, angina, ST-segment depression $\geqq$3 mm, high-degree atrioventricular block, ventricular tachycardia $\geqq$5 consecutive beats at $\geqq$120 beats min^{-1}, new onset of atrial fibrillation, or systolic BP $\geqq$260 mm Hg, and a progressive decrease in BP. The expired air was continuously analyzed using a MedGraphics cardiopulmonary diagnostic system (Breeze suite 6.1, Medical Graphics Corporation; St Paul, MN, USA) to assess the physiological responses to exercise. Oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE), respiratory rate (RR), tidal volume (V_T), hemoglobin saturation by pulse oximetry (SpO_2), end tidal PCO_2 ($PETCO_2$), electrocardiography (ECG), HR, and BP were measured continuously during the exercise test. Ratings of perceived dyspnea were reported by the patients at rest, every 5 min during exercise and at peak exercise on a 10-point Borg scale for dyspnea.[29] The patient's data at maximal exercise were used if the following criteria were met: (1) 85% of age-predicted HR; (2) respiratory exchange ratio $\geqq$1.09; and (3) a plateau of VO_2.[28] Peak VO_2 was expressed as the highest 30-second average value obtained during the last stage of the exercise test.[28]

Heart rate variability recordings

HRV was measured with a total recording time of 5 min at rest and at peak exercise. Version 3.0 of the "CheckMyHeart (CMH)" HRV analysis software (CheckMyHeart, Taiwan) was used for all transformations and analyses.[30] The CMH system included a single-lead electrocardiography recorder (lead I or lead II). Beat-by-beat R–R interval values (resolution 4 ms) were obtained from the ECG signals using the CMH software. The CMH software rejected irregular R–R intervals (non-NN interval) automatically. The CMH software also allowed for manual filtering of non-NN intervals. Detrended time series were cubically interpolated and re-sampled