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Improvement of heart rate variability after exercise training and its predictors in COPD

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KEYWORDS
Chronic obstructive pulmonary disease;
Heart rate variability;
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Determinants

Summary
Background: Current literature lacks solid evidence on the improvement of heart rate variability (HRV) after exercise training in patients with COPD.
Objectives: We aimed to investigate changes in HRV after two exercise training programs in patients with COPD and to investigate the determinants of these eventual changes.
Methods: Forty patients with COPD (FEV_1 39 ± 13%pred) were randomized into high (n = 20) or low (n = 20) intensity exercise training (3-month duration), and had their HRV assessed by the head-up tilt test before and after either protocols. Baseline spirometry, level of daily physical activity, exercise capacity, body composition, functional status, health-related quality of life and muscle force were also assessed to investigate the determinants of improvement in HRV after the training program.
Results: There was a significant improvement in HRV only after the high-intensity protocol (pre *versus* post; SDNN 29 ± 15 ms *versus* 36 ± 19 ms; rMSSD 22 ± 14 ms *versus* 28 ± 22 ms; $p < 0.05$ for both). Higher values of biceps brachialis strength, time spent walking in daily life and SDNN at baseline were determinants of improvement in HRV after the training program.

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Conclusions: High-intensity exercise training improves HRV at rest and during orthostatic stimulus in patients with COPD. Better baseline total HRV, muscle force and daily physical activity level are predictors of HRV improvements after the training program.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible,[1] and by systemic features such as exercise intolerance, systemic inflammation and nutritional abnormalities.[2] In addition, in recent years, a few studies which focused on the assessment of heart rate variability (HRV) in this population demonstrated a considerable degree of cardiac autonomic dysfunction related to important implications such as physical inactivity.[3,4]

In other populations, it has been recognized that HRV reduction is associated with higher risks of morbidity and mortality.[5,6] Both in individuals with cardiac abnormalities and in healthy elderly, exercise training programs have shown improvement in cardiac autonomic function suggesting a reduction in these risks.[7–9]

Nowadays, exercise training is a well-recognized method to treat symptomatic patients with COPD.[2] Its objective is to improve impaired disease outcomes[10] such as exercise capacity, functional status, health-related quality of life and peripheral muscle force, as well as physical activity in daily life.[11] However, little is known about the effects of exercise training programs on HRV changes in patients with COPD. Recently, a study suggested that only 6 weeks of exercise training could improve HRV in patients with COPD based on changes observed in the time and frequency-domain indexes.[8] However, the indexes which reflect the total HRV (such as SDNN index) were not studied in depth. Therefore, it would be relevant to study the response of other HRV variables to an exercise training program. In addition, the abovementioned exercise training program had a relative short duration and frequency (twice a week) and was composed of treadmill and stretching only, what is generally below the recommended for patients with COPD.[2] Furthermore, controversy exists since a previous study showed that patients with COPD with hypertension were not able to change their HRV after a 12-week cycle-ergometer exercise training program.[12]

So far there are no studies investigating the effects of a low-intensity exercise training program on HRV changes in individuals with COPD. The current lack of solid evidence concerning the best type of exercise training in order to improve HRV in patients with COPD reveals the importance of studying exercise protocols with different training intensities.

Finally, although a previous study showed that certain baseline disease characteristics (e.g., the degree of physical inactivity and muscle dysfunction) are related to worse HRV indexes independently of disease severity in patients not submitted to exercise training,[4] it remains unknown whether these baseline characteristics are able to predict the potential improvement in HRV after an exercise training program.

Therefore, the aim of this study was to investigate changes in HRV concerning time and frequency domains after a 3-month randomized high or low-intensity exercise training program in patients with COPD, as well as to investigate the determinants of the eventual changes.

Materials and methods

Study design

Cardiac autonomic function was longitudinally evaluated by HRV assessment before and after 3 months of either endurance and strength training (high intensity, or HI) or calisthenics and breathing exercises (low intensity, or LI). Baseline data of pulmonary function, maximal and functional exercise capacity, body composition, functional status, health-related quality of life, peripheral muscle force and the level of physical activity in daily life were used to study the outcomes which predict eventual improvement in HRV after the training program.

Subjects

An overview of the study protocol can be seen in Fig. 1. Sixty-three patients with COPD entering an exercise training program at the *Hospital Universitário da Universidade Estadual de Londrina* (HU-UEL, Londrina, Brazil)

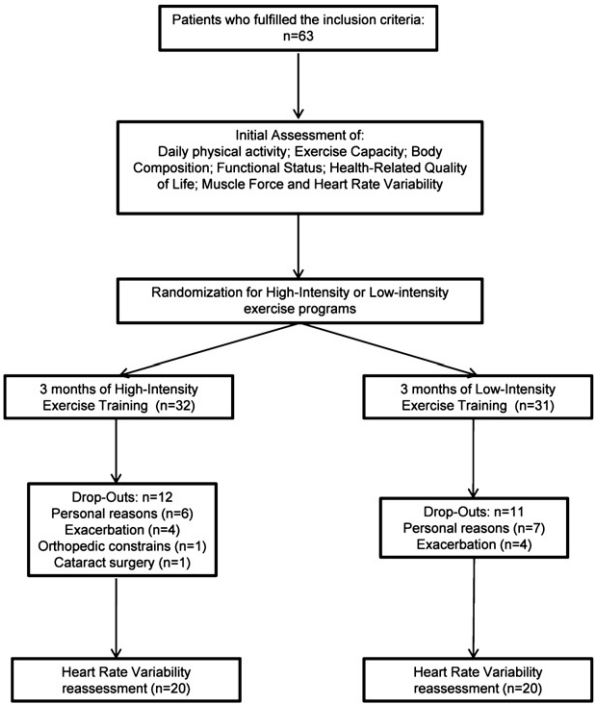

Figure 1 Overview of the study.

were initially included. They were randomized to one of the two study groups (HI or LI) following a concealed envelopes procedure. All patients had diagnosis of moderate to severe COPD according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD).[1] In addition, no patient had severe or unstable cardiac disease, or any underlying comorbidity which could directly interfere with the performance of the aforementioned tests. None of the recruited patients were involved in regular physical activity before participating in study. More details regarding inclusion criteria, patients' comorbidities and pharmacological treatment are found in Supplementary data. Twenty-three patients (11 in LI and 12 in HI) dropped-out during the protocol. Reasons for drop-out were prolonged exacerbations leading to long hospitalization periods (n = 8); consent withdrawal due to personal reasons (n = 13); orthopedic constraints during the protocol (n = 1) and the need to undergo a cataract surgery (n = 1). Forty patients (66 ± 8 years; FEV_1 39 ± 13% predicted; body mass index 27 ± 6 kg/m^2) completed the study (HI n = 20; LI n = 20). However, in the post-training analysis of two patients in the LI group, HRV signals were compromised due to external interference, and could not be used in the analysis. Therefore, final analysis of HRV in the LI group included 18 patients. The study was approved by the Ethic Human Research Committee of HU-UEL (n.04624), and all patients gave formal signed consent.

Exercise programs

In the HI group, circuit training including cycling, walking and strength training was performed based on a protocol previously described.[11] For ergometry cycling, the training intensity was set at 60% of the initial maximal work rate; for treadmill walking, at 75% of the average walking speed during the baseline 6-min walking test (6MWT); and for strength training, at 70% of the baseline 1 repetition maximum test (1RM). Increase in work rates and/or duration was assured on a weekly basis, guided by a predetermined schedule and driven by the patients' perception of their symptoms (Borg-symptom scores).[13] In the LI group, patients progressively performed 5 different sets of exercises including breathing exercises, strengthening of the abdominal muscles (crunches) and callisthenics.[14] Each set consisted of 12 different exercises which were repeated 15 times each. Every 7 sessions, patients began a new set of exercises with an increment on the intensity. Close supervision was provided during both training protocols, which were attended three times per week, for 12 weeks, with 1-h training sessions. Oxygen was routinely offered to patients who had peripheral oxygen saturation levels below 90% during exertion. For more details concerning the exercise protocols see Supplementary data.

Measurements

Spirometry,[15,16] exercise capacity (6MWT and cardiopulmonary exercise test, CPET),[17–19] body composition (bioelectrical impedance),[20,21] peripheral muscle force (femoral quadriceps, brachial triceps and biceps by 1-repetitium maximum [1RM]), functional status (Modified Pulmonary Functional Status and Dyspnea Questionnaire, PFSDQ-M),[22] dyspnea sensation (Medical Research Council scale, MRC),[22] health-related quality of life (Saint George Respiratory Questionnaire, SGRQ)[23] and physical activities in daily life (DynaPort™ activity monitor[24] and SenseWear™ armband multisensor[25]) were assessed at baseline for the patients' characterization. For more details regarding all aforementioned assessments please see Supplementary data.

Heart rate variability measurement and data analysis

Both before and after the protocol, HRV assessment during rest (i.e., supine position) and as a response to an orthostatic stimulus was done using a head-up tilt test (HUTT) following a previous published protocol.[4] In brief, the HUTT was performed with patients positioned on an orthostatic table where they initially stayed for 10 min in supine position; the table was then 75° lifted, and this was followed by a period of more 10 min in orthostatic position. Patients were instructed to breathe at 12 breaths/min according to an audio signal working as a metronome, since the HRV is reproducible in patients with COPD only when the respiratory rate is controlled.[26] All assessments took place in a controlled environment, and the complete description of the HUTT and the HRV assessment protocol can be found in Supplementary data.

The acquisition of heart signals during the protocol was done by a pulse frequency meter (S-810 Polar©, Finland).[27] HRV was analyzed in both time and frequency domains in the two stages of the test (supine and orthostatic position) by the software Kubios HRV version 2.0 (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland). The frequency bands were defined according to previous published recommendations for HRV measurement and interpretation.[28] The main variables used in this study were for the time domain, the standard deviation of the N—N intervals (SDNN, an estimate of total HRV) and the square root of the mean squared difference of the successive N—N intervals (rMSSD — a parasympathetic marker), both routinely measured only during the supine position; and for the frequency domain, the power of low frequency (LF) and high frequency (HF) was described in percentage of total power minus the very low frequency (normalized units – nu). The HF is modulated exclusively by the parasympathetic activity, whereas the LF component is modulated by both parasympathetic and sympathetic activities. The LF/HF ratio was therefore considered as a marker of the sympathovagal balance. Frequency domain variables were measured during both supine and orthostatic positions.

Statistical analysis

Statistical analysis was performed using the SPSS statistical package version 13.0 (SPSS, Inc., Chicago lL). Data were described as mean ± standard deviation. Data distribution was checked by the Kolmogorov—Smirnov test. According to data distribution, the paired t-test or the Wilcoxon test was used to analyze intra-group changes in HRV, as well as changes in variables during the supine and orthostatic

stages of the HUTT. Accordingly, inter-group comparisons were studied with the unpaired t-test or Mann–Whitney test. To analyze the correlation of time domain HRV variables measured during rest (supine position) which changed after the exercise programs (SDNN and rMSSD) and all the other outcomes, the Pearson correlation coefficient was used for continuous variables and the Spearman correlation coefficient was used for ordinal variables or non-normally distributed data. Finally, to verify the determinants of change in HRV after the protocol, a stepwise multiple linear regression model was applied. Only variables with normal data distribution and which showed statistically significant correlation with HRV through Pearson's coefficient were included in the regression models. The level of statistical significance was set at $p < 0.05$ for all analyses.

Results

A summary of both groups' characteristics is provided in Table 1. There were no differences between the groups. All patients had the expected impairments (airway obstruction, impaired peripheral muscle force and maximal and functional exercise capacity). There were no patients with hypoxemia during rest. However, 10 patients (50%) used oxygen during exercise throughout the HI protocol due to desaturation during exertion, whereas no patient in the LI group needed supplemental oxygen during the training.

Head-up tilt test

An overview of the changes concerning the frequency domain variables during the HUTT (i.e., supine and orthostatic position), as well as the changes in time domain variables (only at supine position) for both HI and LI can be observed in Table 2. When comparing before and after the protocol, only HI had significant changes in SDNN and rMSSD (29 ± 15 ms *versus* 36 ± 19 ms and 22 ± 14 ms *versus* 28 ± 22 ms respectively; $p < 0.05$ for both). In the supine position, there were no changes in the frequency domain variables (LFnu, HFnu, LF/HF) when comparing before and after the program for both groups. However, concerning the changes between HUTT positions (supine and orthostatic), there were different responses before and after the training program: at baseline, there were significant differences between supine and orthostatic positions in all frequency domain variables for both groups, what no longer occurred in the HI group after the program (Table 2). A visual depiction of these results in a representative patient is shown in Figs. 2 and 3. When comparing the magnitude of post–pre changes (Δ) in HRV variables between the groups,

Table 1 Patients' characteristics.

	High-intensity	Low-intensity
Age (years)	67 ± 7	65 ± 10
Gender (M/F)	10/10	11/9
Smoking history (pack × years)	43 [23–64]	44 [18–83]
Arterial Pressure (systolic/diastolic)	$123/80 \pm 14/11$	$121/80 \pm 13/11$
MRC score (1–5)	3 (2–4)	4 (3–4)
SGRQ – total score (0–100)	57 (41–66)	60 (52–65)
Pulmonary function		
FEV_1 (% predicted)	40 ± 13	39 ± 14
FEV_1/FVC	48 ± 14	47 ± 14
Muscle force		
Quadriceps force (kg)	12.4 ± 5.3	10.4 ± 7.2
Triceps force (kg)	11.5 ± 3.3	10.5 ± 5.1
Biceps brachial (kg)	10.4 ± 3.8	9.2 ± 4.7
Exercise capacity		
6MWT (m)	442 ± 82	392 ± 108
Wmax (watts)	29 ± 22	30 ± 27
Body composition		
Fat-free mass (kg)	45 ± 9	44 ± 8
BMI (kg/m^2)	27 ± 6	26 ± 15
Physical activity in daily life (DynaPort)		
Time spent walking per day (min/day)	57 ± 32	54 ± 28
Time spent standing per day (min/day)	248 ± 95	270 ± 139
Physical activity in daily life (SenseWear)		
Total daily energy expenditure (kcal/day)	1295 ± 635	1331 ± 596
Daily energy expenditure in activities demanding > 3 METs (kcal/day)	408 ± 620	428 ± 620
Number of steps per day (steps/day)	4539 ± 5314	4553 ± 5968
Time spent per day in activities demanding > 3 METs (min/day)	75 ± 88	75 ± 99

Data are presented as mean ± standard deviation or median (interquartile range). M = male; F = female; MRC = Medical Research Council scale; PFSDQ-M = modified pulmonary functional status and dyspnea questionnaire; SGRQ = Saint George's respiratory questionnaire; FEV_1 = forced expiratory volume in the first second; 6MWT = 6-min walking distance test; Wmax = maximal workload; BMI = body mass index; METs = metabolic equivalents. $p > 0.05$ for all variables.

Table 2 Heart rate variability before and after 3 months of high or low-intensity exercise training program (HI and LI, respectively).

	Pre-training		Post-training	
	Supine	Orthostatic	Supine	Orthostatic
Time domain				
SDNN (MS) – HI	29 ± 15	–	36 ± 19*	–
SDNN (MS) – LI	25 ± 12	–	22 ± 10	–
rMSSD (MS) – HI	22 ± 14	–	28 ± 22*	–
rMSSD (MS) – LI	22 ± 22	–	19 ± 14	–
Frequency domain				
LFnu (%) – HI	44 ± 15	55 ± 21**	42 ± 24	50 ± 20
LFnu (%) – LI	48 ± 19	58 ± 15**	43 ± 19	62 ± 20**
HFnu (%) – HI	56 ± 15	44 ± 21**	58 ± 24	50 ± 20
HFnu (%) – LI	51 ± 19	41 ± 15**	56 ± 19	37 ± 20**
LF/HF ratio – HI	0.9 ± 0.8	2.3 ± 3.1**	1.3 ± 1.5	1.3 ± 0.9
LF/HF ratio – LI	1.2 ± 0.9	1.7 ± 1.0**	1.1 ± 1.2	2.8 ± 2.8**

Data are presented as mean ± standard deviation. HI = high-intensity exercise training; LI = low-intensity exercise training. For clarification purposes, HI outcomes are presented in grey lines, and LI outcomes are presented in white lines. * = $p < 0.05$; paired t-test, pre *versus* post; ** = $p < 0.05$; paired t-test, supine *versus* orthostatic position. SDNN = standard deviation of N–N intervals; rMSSD = square root of the mean squared difference of the successive N–N intervals; LFnu = low frequency in normalized units; HFnu = high frequency in normalized units.

there was significant difference in ΔSDNN (6.3 ± 6.1 ms HI *versus* −3.7 ± 8.9 ms LI; $p = 0.0001$) and a statistical trend in ΔrMSSD (6 ± 9.6 ms HI *versus* −6.2 ± 28 ms LI; $p = 0.08$).

Correlations and regression analyses

For HI, delta post–pre SDNN (ΔSDNN) was significantly correlated with biceps and triceps brachialis muscle force ($r = 0.61$ and $r = 0.56$, respectively; $p < 0.01$ for both) and baseline SDNN ($r = 0.49$; $p < 0.01$). Additionally, there was significant correlation between delta post–pre rMSSD (ΔrMSSD) and baseline SDNN ($r = 0.61$; $p < 0.01$), MRC scale, all PFSDQ-M domains ($-0.45 < r < -0.48$; $p < 0.05$ for all) and time spent walking per day measured by the DynaPort ($r = 0.47$; $p < 0.05$). No further significant correlations were found, including in the LI group. Multiple regression models in the HI group showed that baseline SDNN and biceps muscle force were the only determinants of ΔSDNN (model $R^2 = 0.51$; $p < 0.01$), as seen in Fig. 4, whereas ΔrMSSD was determined by time spent walking per day and baseline SDNN (model $R^2 = 0.49$; $p = 0.002$) as seen in Fig. 5.

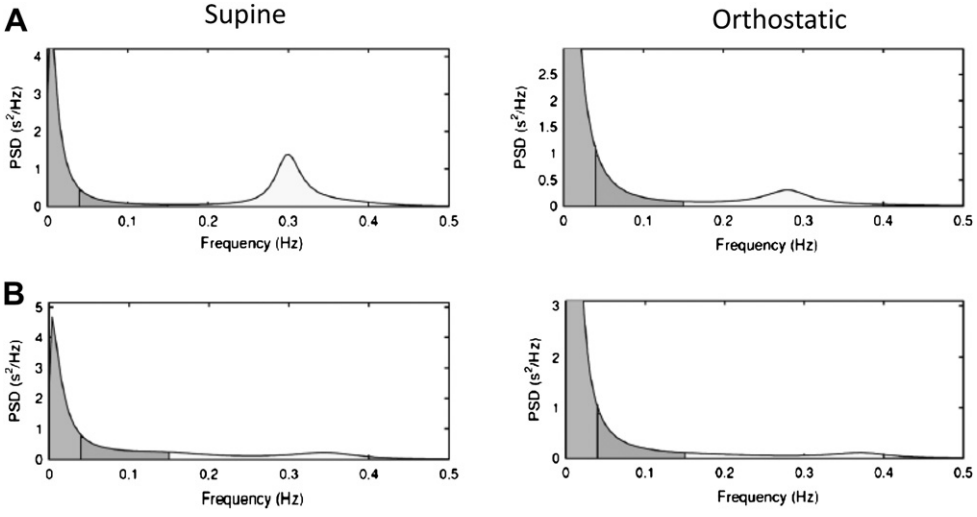

Figure 2 Visual representation of the band frequencies in heart rate variability during the supine and orthostatic position before (A) and after (B) a 3-month high-intensity exercise training program. The figure depicts one representative patient. In line A (pre-training program), significant decrease in high frequency (HF) and increase in low frequency (LF) occured after an orthostatic stimulus ($p<0.05$ for both taking into account the whole group), whereas in line B (post-training program) there were no longer differences in HF and LF between the supine and orthostatic position ($p>0.05$ for both in the whole group). PSD = Power Spectral Density.

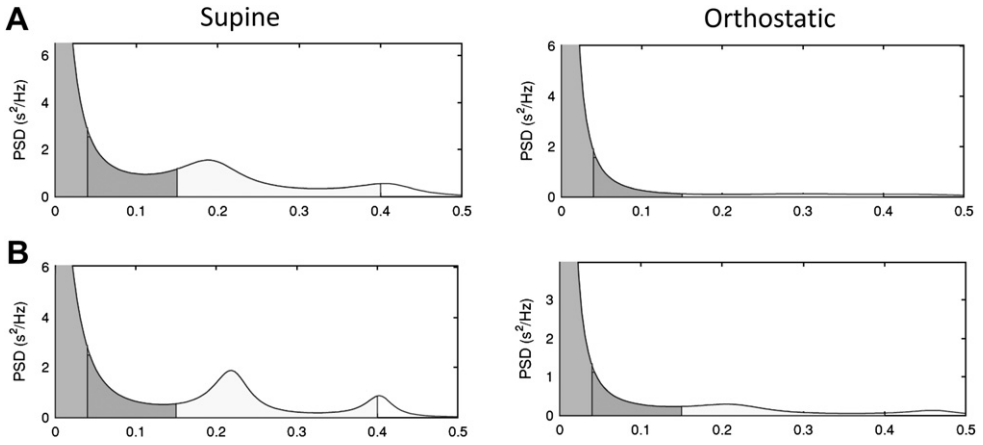

Figure 3 Visual representation of the band frequencies in heart rate variability during the supine and orthostatic position before (A) and after (B) a 3-month low-intensity exercise training program. The figure depicts one representative patient. In line A (pre-training program), significant decrease in high frequency (HF) and increase in low frequency (LF) occured after an orthostatic stimulus ($p<0.05$ for both taking into account the whole group), at the same way in the line B (post-training program) there were differences in HF and LF between the supine and orthostatic position ($p<0.05$ for both taking into account the whole group). PSD = Power Spectral Density.

Oxygen use

The group of patients who performed the high-intensity exercise program was split into two according to the need of oxygen supplementation during the exercises. The minimum accepted value of peripheral oxygen saturation was set at 90% for oxygen supplementation during the exercise training. Ten patients (50%) routinely used oxygen during training sessions (7 male). The paired t-test (SDNN, rMSSD, LFnu and HFnu) or the Wilcoxon tests (LF/HF) between patients who used or did not use oxygen after the exercise training program did not show differences in the responses ($p > 0.05$ for all variables). In the low-intensity calisthenics and breathing exercises program, no patient used oxygen during the training sessions since no desaturation during exercise was observed.

Discussion

The present study showed that a 12-week high-intensity exercise training program including endurance and strengthening exercises was able to improve HRV outcomes such as the rMSSD and SDNN variables, whereas a low-intensity program of similar duration was not. Our results are in accordance with a previous study by Borghi-Silva et al., which showed that an aerobic training program was

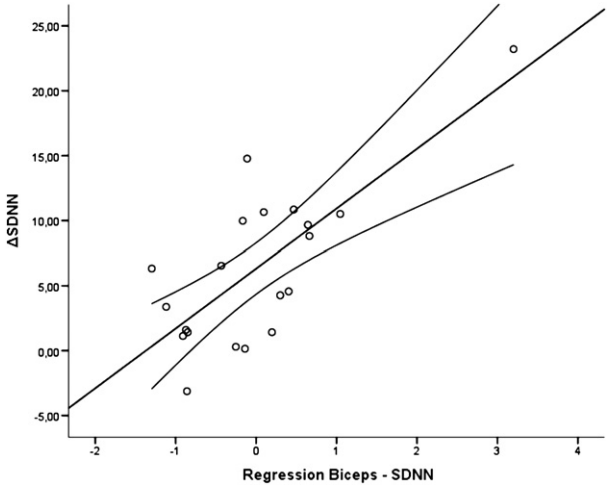

Figure 4 Scatter plot of each subject's influence and regression line of a stepwise multiple regression model of ΔSDNN before and after training in the high-intensity exercise group. Dependent variable = SDNN = standard deviation of the N—N intervals; independent variables = biceps muscle force and SDNN (pre-training). $R^2 = 0.51$, $p < 0.05$.

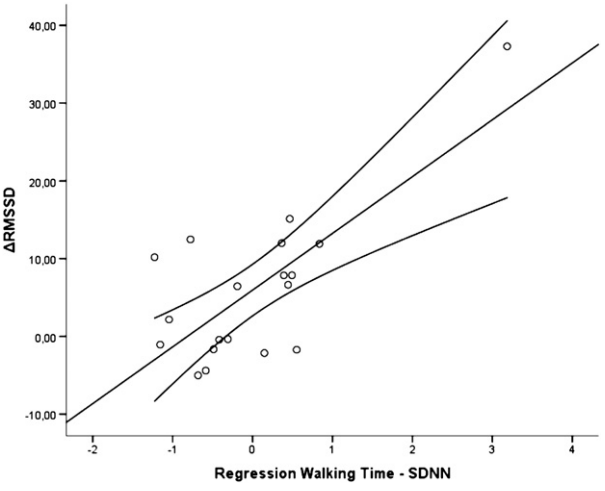

Figure 5 Scatter plot of each subject's influence and regression line of a stepwise multiple regression model of ΔrMSSD before and after training in the high-intensity exercise group. Dependent variable = rMSSD = square root of the mean squared difference of the successive N—N intervals; independent variables = walking time and SDNN (pre-training). $R^2 = 0.49$, $p < 0.05$.

also able to improve variables of the time and frequency domains of HRV.[8] Despite these benefits, the study from Borghi-Silva et al. included a somewhat limited training protocol (just treadmill and stretching exercises), and it was composed by 18 sessions, which is below the recommended.[10] Another potential limitation of that study is the lack of controlled breathing during the assessment of HRV, since it is not possible to be absolutely sure whether the observed changes were due to real improvement or due to methodological bias. Furthermore, our baseline values of rMSSD are higher than those observed by Borghi-Silva et al., showing that the influence of controlled breathing in parasympathetic baseline values does not interfere in its changes after an exercise protocol.

Regarding the frequency domain variables in the supine position, this study showed no differences after high-intensity training. This is in contrast with the study by Borghi-Silva et al., which showed improvements in these variables after a 6-week program.[8] A possible explanation for this apparent discrepancy is that, in the latter study, the group of patients had decreased parasympathetic activity and increased sympathetic activity during rest, whereas our group of patients had exactly the opposite. This better autonomic control found in the patients of the present study may justify the less pronounced changes in frequency domain variables.

Previous studies showed discrepancies concerning the capacity of patients with COPD to alter their autonomic control during an orthostatic stimulus.[4,29] To our knowledge, this study was the first to show differences in autonomic nervous control during an orthostatic stimulus through a significant reduction in the imbalance of LFnu, HFnu (and therefore LF/HF ratio) after an exercise training program. Based on these results, it can be confidently stated that autonomic control is improved in patients with COPD after a 3-month high-intensity exercise training program.

Until the present date, there are no studies in patients with COPD or other populations showing correlation of changes in SDNN after exercise training and baseline muscle force. A previous study from our group[4] showed modest but significant correlation between strength of quadriceps and biceps brachial muscles and the SDNN index, implying that an impaired muscle force is related to impaired cardiac autonomic function. Moreover, the present study reinforces these previous results and expands them by concluding that upper limbs muscle force is a predictor of improvement of HRV. Furthermore, our study also found a significant relation between baseline SDNN and its improvement after training, and showed that baseline muscle force and SDNN together are able to determine 51% of the obtained changes in the total cardiac autonomic function. Due to the known close relationship between cardiac autonomic function and mortality risk,[6] it is useful to predict which patients are more prone (or less prone) to improvement in HRV. This information may help identifying which patients are not expected to improve HRV after training, and therefore are preferable main targets for future intervention studies in this field.

The significant correlation of changes in rMSSD with the MRC scale and PFSDQ-M domains is not particularly surprising. Once exercise limitation in COPD is mainly due to ventilatory limitation (i.e., dyspnea)[10] and patients with lower levels of dyspnea usually present higher exercise capacity (therefore, train at a higher intensity), it could be hypothesized that an increase in parasympathetic cardiac tone was more evident in these patients due to their higher training workload during the program. In the same line, improvement in rMSSD is more pronounced in patients with lower levels of functional status limitation and higher levels of physical activity in daily life before training (expressed by higher time spent walking per day). These findings also confirm previous results which showed that HRV and physical activity level are correlated.[4] Regression analysis showed that baseline physical activity level in daily life and SDNN were responsible for 49% of the observed changes in rMSSD, which once again may be a useful information in helping to identify which patients are preferable main targets for future studies in this field. Out of all outcomes from both activity monitors, we only found time spent walking per day (DynaPort) influencing post-training changes in rMSSD, together with upper limbs muscle force. These are intriguing results and surely merit future investigation. For example, concerning the relationship between biceps muscle force and HRV, we believe this is a reflection of the relation between HRV and muscle force in general, and relation with other muscle groups (e.g., quadriceps) could be found in case a larger sample size was studied.

Finally, a novelty of our results was the absence of differences of changes in HRV between patients who used or did not use oxygen during the high-intensity training program. A previous study showed that chronic hypoxemia is associated with HRV reduction.[30] Moreover, long-term oxygen therapy was described to counteract this reduction in patients with COPD.[31] However little is known about the oxygen supplementation during exercise in patients non-hypoxemic at rest, as well as its influence on HRV changes after a training protocol. Although this is a relatively small sample, our study showed that patients who used oxygen during the exercise program had the same responses in SDNN and rMSSD indexes than patients who did not. Due to ethical considerations, it was not studied whether the same responses would be observed in patients not submitted to oxygen supplementation during exercise in case of desaturation. This finding merits future studies to explain the mechanisms involved in changes of HRV patterns in patients hypoxemic during exertion who used supplementary oxygen during exercise.

It should to be noticed that a potential limitation of the present study was that unfortunately there was no strict control for the use of β-blockers or pulmonary pharmacologic agents. However, two factors may counteract this limitation. Firstly, patients were included in the study only if they did not present severe or unstable cardiac disease (see Methods). Secondly, patients were strictly instructed not to use any pulmonary pharmacologic agents on the HRV assessment days. Although this does not rule out the chronic effects of these agents, at least the acute effects were reduced by taking this measure. Furthermore, one can argue that the absence of a typical control group might be another limitation of this study. However, the low-intensity group included in this study did not present any changes after training, and therefore the presence of a control group was unlikely to provide any further useful

results in addition to those currently described here. Moreover, since scientific evidence of benefits from exercise training in COPD is compelling, randomized controlled trials involving exercise training in patients with COPD may be considered as unethical.

Conclusions

Three months of high-intensity exercise training enable an important improvement in post-training cardiac autonomic function in patients with COPD showed through better values in the time-domain analyses in supine position and in the frequency-domain analyses after an orthostatic stimulus. Whether this improvement is related to a lower mortality risk in the long term remains to be studied. In addition, better baseline values of upper limbs muscle force, physical activity in daily life and total heart rate variability may help predicting those patients who will more likely improve their cardiac autonomic function after a high-intensity exercise training program.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.rmed.2011.01.014.

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