New tools in Pulmonary rehabilitation

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Abstract

In patients with more severe COPD the benefits of rehabilitation might be less clear and therefore new treatment options have been developed to increase the benefits of rehabilitation. This paper provides an overview of new approaches being developed as an adjunct to exercise training. Successively the benefits of adding ventilatory support, oxygen, anabolics or neuromuscular stimulation to a rehabilitation programme will be discussed. While positive benefits for a number of these approaches have been found many questions remain unsolved. Therefore, until now we can not recommend these new tools as part of routine management in patients with COPD who start a rehabilitation programme.

New tools in Pulmonary rehabilitation

Pulmonary rehabilitation has shown in many papers that it is effective in patients with Chronic Obstructive Pulmonary Disease (COPD) by improving dyspnoea, exercise tolerance and quality of life.[1-3] However, in patients with more severe COPD the benefits of rehabilitation might be less and therefore new treatment options have been developed to attenuate rehabilitation results. In this paper we will provide an overview of these new approaches being an adjunct to exercise training.

Ventilatory support during exercise or exercise training

Advanced COPD is generally characterized by severe airflow limitation being frequently associated with hyperinflation. This will become worse especially during exercise when the absence of any flow reserve requires the subject to breath at a higher lung volume to adjust to the increased ventilatory requirements. The work of breathing will be increased, primarily to
overcome the intrinsic positive end expiratory pressures. As during exercise the increased ventilatory requirements are difficult to sustain, new approaches are needed to assist the patients with the mechanical output during exercise. The last decades a number of studies have investigated this topic by applying different types of ventilator support during exercise. Petrof showed in 1990 that CPAP reduced inspiratory muscle effort, as indicated by the pressure-time integral of transdiaphragmatic and oesophageal pressure.[4] In addition they found that dyspnea improved with CPAP in five of the eight patients and that the amelioration of dyspnea was directly related to the reductions the pressure-time integral of the oesophageal pressure. O'Donnell showed that by applying 4-5 cmH₂O of Continuous Positive Airway Pressure (CPAP) to patients with COPD (mean FEV₁ 1.2 L) less breathlessness was experienced during their steady-state submaximal exercise.[5] In addition they showed that similar levels of CPAP administered to patients with even more severe COPD (mean FEV₁ 0.9L) did improve their endurance capacity during constant power cycle exercise by 48% [6]. A study comparing inspiratory pressure support (IPS: mean airway pressure 12-15 cmH₂O), CPAP (6 cm H₂O), and oxygen (2 L/min) during exercise showed that only IPS increased walking distance compared with control (62% increase, range +14m to +533m, p=0.01).[7] Patients experienced less breathlessness at iso-time during IPS than during control exercise. A newer technique is proportional assist ventilation (PAV) which is a form of synchronised ventilatory assistance with the specific characteristic that the ventilator generates pressure in proportion to the patient's instantaneous effort. This means that if the patient pulls more, the machine will generate more pressure. Thus, in case of PAV the ventilator amplifies the patient's inspiratory effort without any preselected target volume or pressure. The aim of PAV is to allow the patient to attain whatever ventilation and breathing pattern seems to fit their ventilatory control system. The influence of proportional assist ventilation (PAV) has been compared with pressure support ventilation (PSV) and CPAP in 15 stable patients with COPD (FEV₁ 32% pred, mean PaO₂ 52 mm Hg mean PaCO₂ 52 mm Hg. [8] The patients underwent randomized submaximal cycle endurance at 80% of their maximal workload receiving either: sham ventilation (1 cmH₂O), CPAP (6 cm H₂O), PSV (IPAP 12-16 cmH₂O, EPAP 1 cmH₂O), or PAV (8.6±3.6 cmH₂O and 3±1.3 cmH₂O of volume and flow assistance, respectively and EPAP 1 cmH₂O). CPAP, PSV, and PAV were all able to increase endurance time over sham ventilation (9.6, 10, and 12 minutes versus 7.2 minutes respectively). In addition PAV increased endurance capacity more than the other interventions. More recently a study of Dreher showed that by applying high inspiratory pressures the walking distance could be increased in patients with severe COPD.[9] In this study it was remarkable that the high
inspiratory pressures needed by the patients during the night did not have to be adjusted during walking. If this is really the case this would be a big step forward as it is for the patients in this way easy to use the ventilator during exercise.

A recent study has brought some insight into the mechanism of improved exercise with ventilatory support by showing that IPS delayed the rise of serum lactate during exercise in patients with severe COPD. [10] Lactate increased at 2.96 mmol/L during unassisted walking while with IPS at 2.42 mmol/L (P<0.01). The duration of exercise was increased with IPS (13.6 min versus 5.5 minutes control, p<0.01). This latter observation may be relevant to the application of exercise rehabilitation for patients with severe COPD. Two studies are relevant to mention in this respect. In 2002 Hawkins investigated the effects of exercise training with and without PAV during a 6 week programme.[11] Nineteen patient with COPD with a mean FEV\textsubscript{1} 0.8 L (26% predicted) were included in this study: 10 patients were randomised for training with PAV while 9 trained without PAV. After the programme the mean training intensity at maximal cycle test was 15% higher in the PAV group compared to the other group. The lactate concentration at identical workload in the PAV group was 18% lower compared to the non-PAV group. In addition they found a significant relation between the reduction in plasma lactate at an equivalent workload and the increase in peak workload after training (r=–0.6; p<0.01). This all means that true physiological adaptions can be achieved by applying PAV during training. The study of van ’t Hul is also interesting in this respect: [12] Twenty-nine patients with COPD (mean FEV\textsubscript{1} 1.1 L (41% predicted) with a ventilatory limitation during exercise completed an 8-week cycle exercise programme. They showed that IPS of 10 cm H\textsubscript{2}O significantly increased training intensity compared to IPS of 5 cm H\textsubscript{2}O giving an improved shuttle walking distance and cycle endurance capacity.

In summary, ventilatory support during exercise may decrease dyspnea and improve exercise capacity among patients with COPD. However, current evidence comes from studies with small sample size. Applying ventilatory support during training also showed physiological benefits, which means that this can be used as an additional tool to improve the well-known benefits of rehabilitation. However, this has only been shown in small studies and its long-term benefits have not been elucidated. Therefore, before widespread use of ventilatory support during training could be advocated, larger clinical trials are needed in order to identify the most effective means of ventilatory support during exercise training and which patients benefit most.
Nocturnal ventilatory support in addition to exercise training

One of the first studies investigating the additional value of nocturnal NIPPV next to rehabilitation was published in 2000 by Garrod.[13] Forty-five patients with severe stable COPD (mean FEV₁ 1.0 L) were either randomised to the combination of domiciliary non-invasive positive pressure ventilation (NIPPV) and exercise training (ET) (n = 23) or to ET alone (n = 22). After an 8 week training programme they found a mean significant improvement in mean shuttle walk test (SWT) in the NPPV + ET group compared to the ET group of 72 m. In addition they found a mean significant improvement between both groups for the Chronic Respiratory Disease Questionnaire (CRDQ) of 12.3 which is clinically significant. They concluded that domiciliary NPPV can be used successfully to augment the effects of rehabilitation in severe COPD. Remarkable in this study was that NIPPV was applied to patients who were normocapnic suggesting that ventilation was not the primary limitation during exercise. In addition the compliance for NIPPV was low as the mean number of hours of usage was 2.1 and only 50% of the patients used NIPPV for less than 2 hours. Although we do not know what the minimal effective time is, 2 hours is generally considered as too low.

In a more recently published study, we investigated the benefits of nocturnal ventilatory support in addition to rehabilitation in hypercapnic patients.[14] Seventy–two patients with COPD were randomly assigned to nocturnal NIPPV in addition to rehabilitation (n = 37) or rehabilitation alone (n = 35). Outcome measurements were assessed before and after the 3-month intervention period. While the primary outcome Chronic Respiratory Questionnaire (CRQ) total score improved 15.1 points with NIPPV + rehabilitation, the CRQ improved to 8.7 points with rehabilitation alone, the difference of 7.5 points being not statistically significant between groups (p = 0.08). On the other hand compared with rehabilitation alone, the difference in the fatigue domain of the Maugeri Respiratory Failure questionnaire (MRF-28) was greater with NIPPV + rehabilitation (mean difference 3.3 points, p<0.01), as was the improvement in total score (mean difference -10%, p<0.03) and its cognition domain (mean difference -22%, p<0.01). Furthermore, the addition of NIPPV improved daytime arterial carbon dioxide pressure (mean difference -0.3 kPa; p<0.01) and daily step count (mean difference 1269 steps/day, p<0.01). This was accompanied by an increased daytime minute ventilation (mean difference 1.4 l; p<0.001). This study is unique as it has a long-term follow-
up (to be published) and included only patients who were hypercapnic at rest. A number of other issues are also important to mention:

1) Patients were ventilated with relatively high inspiratory pressures (20 cm H₂O). While these are lower than the pressures used by Windisch[15] they are higher than the pressure used in the older RCT’s [16]. This might explain why the present study did find a significant improved gas exchange which was not the case in the older studies.

2) The drop in PaCO₂ was related to the time patients were using the ventilator: more hours of nocturnal ventilation lead to a significant drop in PaCO₂ during daytime, so without ventilation.

3) Probably the most important part of this study was the monitoring of gas exchange during the night which is crucial to be able to individually adjust ventilator settings and to achieve an effective nocturnal ventilation.

Another study in this field with a comparable design was set up by Kohnlein[17]. This was a prospective observational non-randomized study carried out in COPD GOLD stage 4. Forty patients combined nocturnal NIPPV with rehabilitation for a mean of 29 days and their results were compared with 40 matched control patients who underwent the same rehabilitation programme. Patients in the NIPPV group received pressure support ventilation for around 8 hours with a mean inspiratory pressure of 17.5 cm H₂O and a mean expiratory pressure of 4.5 cm H₂O. Significant between groups differences were found for 6-minute walking test, FEV₁ and lung hyperinflation, while significant within groups differences were found for blood gasses and quality of life in the NIPPV group. Remarkably these positive effects were also found for patients who were normocapnic, so the authors suggest that NIPPV should be started early in the course of COPD.

In conclusion, nocturnal non invasive-ventilation might be an effective tool in increasing the benefits of rehabilitation as positive benefits have been found in several clinically relevant outcomes. However, several issues are still open for discussion: 1) for which type of patient (hypercapnic versus normocapnic) is NIPPV useful; 2) what is the minimal time on NIPPV needed for positive effects; 3) what is the underlying mechanism of the positive effects of NIPPV (improved gas exchange, muscle rest or sleep quality). As long these questions remain
unsolved in combination with the lack of adequately powered studies NIPPV can not been advocated as part of routine management in patients with COPD who start a rehabilitation programme.

Oxygen

Hyperoxia increases endurance time in patients with COPD, probably due to an increase of inspiratory capacity or, in a different way stated, a decrease of dynamic hyperinflation at a certain level of exercise.[18][19] In addition, hyperoxia reduces hyperinflation during recovery after exercise [20] and may prevent hypoxic vasoconstriction[21]. COPD-patients with low fat free mass show lower levels of oxidative stress with supplemental oxygen.[22] It has therefore been hypothesized that patients with COPD are able to achieve higher work rate during exercise training, which will positively affect training results after weeks. It is generally recommended that COPD-patients who are already hypoxemic in rest should use oxygen during exercise, aiming at a rather arbitrary SO$_2$ > 90%. As far as we know, six RCT’s have been published on the effect of oxygen in COPD-patients with or without desatuation during exercise training [23][24-28] (see Table 1).
It can be concluded that hyperoxia has no clear effect on results of exercise training in COPD-patients with or without documented desaturation during exercise. Only in the Emtner-study a significant, and clinically relevant, improvement could be seen, which is associated with a nicely demonstrated higher work load during the rehab.[27] Whether the intensity of training in this study really differed from the other studies cannot be answered from the papers. It should be mentioned that the total number of studied subjects is only small. In addition, it may be that COPD-phenotypes repond differently to hyperoxia. In this respect, it was recently shown that comparable correction of exercise-induced desaturation resulted in different effects on exercise responses, such as endurance time, minute volume or heart rate[29]. The overall disappointing results of hyperoxia in exercise training are in line with the absent effect of supplemental oxygen in daily life. Moore et al recently studied in a randomized controlled trial the effect of oxygen suppletion of 6 l/min during activities and exercise for 12 weeks in 143 COPD-patients (PO$_2$> 7.3 kPa, MRC score ≥ 3).[30] They found no effect of oxygen therapy on dypsnea, functional status and health status. Moreover, no prognostic factors for a beneficial effect of oxygen could be demonstrated, including desaturation (≤88%) during exercise. More studies are definitely needed on the role of supplemental oxygen, for instance on the oxygen concentration, on intensity of exercise programs and on effects in different COPD-phenotypes.

Heliox

A mixture of helium and oxygen (Heliox) has beneficial effects on pulmonary mechanics such as improved lung emptying, reduced flow turbulence and reduced airflow obstruction, and improved gas exchange. Heliox results in an increase of exercise time in constant work rate tests, which is associated with delayed dynamic hyperinflation and lower work of breathing.[31][32] The effect of Heliox during exercise training in rehab setting was studied in two studies . Johnson et al included 32 COPD-patients with an FEV1 < 50%pred, with a mean DLCO of 39%pred, in a randomized three-arm study.[33] Subjects trained 6 weeks, twice a week on the treadmill with air, Heliox (79/21%) or NIPPV. Endurance time and peak work load improved in all treatment arms, with no difference between the arms. Scorsone et al. studied 30 COPD-patients, FEV1<60%pred, with a mean DLCO of 85%pred. Subjects underwent cycling training, for 8 weeks, 3 times per week with either room air, 40% oxygen or Heliox 60/40%.[28] Endurance time and peak oxygen consumption significantly improved
in the three treatment arms, with no difference between the arms. The use of Heliox appeared safe and was well tolerated. Despite these positive studies, it can be concluded that more studies are needed to define the position of Heliox in routine practice.

Anabolics

COPD-patients show changes in hormonal status and in particular low levels of testosterone may be prevalent, which may negatively affect muscle mass and strength. [34,35] In healthy young men a positive effect of testosterone 600 mg weekly for 10 weeks was found on fat free mass, thigh circumference and strength, alone or in combination with strength training. [36] Several randomized controlled trials have been performed in COPD following a rehabilitation programme.[37][38][39][40][41] [42]. They are summarized in Table 2. The subjects in the study of Svartberg did not follow a rehab program, but the study is added as it yields useful data on specific aspects of quality of life.[41]

In their 3-arm study, Schols et al. showed after a post-hoc analysis that the response on anabolics depends on the body composition.[37] Depleted subjects (low weight and/or low FFM) showed increase in arm circumference by nandrolone /nutrition vs placebo, but not vs nutrition alone, whereas in the subjects with normal body composition the nutrition/nandrolone and nutrition alone arms gained more weight than the placebo-arm. They suggested that anabolic steroids may in particular be relevant for subjects with low FFM, but the improvements in outcomes were small. It is suggested that anabolics are particularly effective in patients using oral glucocorticosteroids, [39] but no RCT is present as yet. Although anabolics are potentially hazardous, as they may increase hemoglobin concentrations, induce liver function disorders, or exaggerate prostate cancer, no serious side effects have been reported in the abovementioned studies. Finally, it should be noted that most studied included only men.

In summary, anabolics in combination with training appear to increase lean body mass, but not consistently increase muscle strength. So far, no effect has been found on exercise tolerance or quality of life, except in one study for sexual quality of life.
Neuromuscular electrical stimulation (NMES)

Neuromuscular electrical stimulation (NMES) is a technique aiming at externally stimulating contractions of peripheral muscles to improve peripheral muscle function in patients with severe COPD. It has been tested in COPD-patients with severe peripheral muscle weakness and in bed-bound patients. Until now 5 small controlled studies have used this technique in patients with COPD. NMES consisted in the study of Neder of a symmetrical biphasic square pulsed current at 50 Hz with pulses of 300–400 µs using the highest tolerable amplitude (starting with 10–20 mA at the start of the training session increasing up to 100 mA) [43]. In the first week it was done during 2 s on and 18 s off (10%), while at the end it was for 10 s on and 30 s off (25%). This training protocol was applied in each leg (15 minutes in the first week and 30 minutes thereafter), five times per week for 6 weeks (a total of 30 sessions). After a 6-weeks home based programme patients showed significant improvements in muscle function, maximal and endurance exercise capacity, and dyspnoea. In addition the improvements in muscle performance and exercise capacity correlated well with a decrease in perception for leg effort. Bourjeily-Habr used a similar training programme of NMES consisting of sessions of 20 minutes, 3 times a week for 6 weeks. They found a significant improvement in both quadriceps and hamstrings muscle strength compared to the sham group. While there was no change in lung function and peak workload, the training group showed a significantly better shuttle walking distance. [44] Zanotti et al. investigated in a study of 28 days the additional benefits of NEMS on top of exercise training in bed bound COPD patients receiving mechanical ventilation due to chronic respiratory. [45] Adding NEMS resulted in an increase in muscle strength, a reduced respiratory rate and a decrease in the number of days needed to get out of bed on the chair. Vivodtzev showed that the combination of exercise training and NEMS lead to a greater improvement in quadriceps strength and dyspnoea during performance of daily tasks in patients with very severe COPD with low body mass index. [46] Dal Corso investigated in 17 patients with COPD (FEV₁ 50% predicted) the effects of 6 weeks high frequency NMES (50 Hz) compared with sham treatment in the quadriceps femoris. [47] A modest increase in type II cross sectional area was found which was not associated with an increased muscle strength or walking capacity. Recently a systematic review on the effects of NMES was carried out based on the above 5 mentioned studies. [48] While significant increases were found for the muscle peak torque and walking distance, the
authors conclude that modest effect sizes after NMES in combination with small number of included patients preclude firm evidence to apply this therapy as a standard therapy in COPD. They also conclude that the patients with less severe COPD might have less benefit by applying NMES.

In conclusion, until now there is not enough evidence to start NMES routinely in patients with COPD and further studies should focus on the optimal parameters of the NMES and to know which type of patient will have the most benefit by NMES. Nevertheless, the practice guideline of the ERS /ATS suggests that NEMS may have beneficial effects in addition to exercise training especially in those COPD patients who have weak muscles. [49]
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<td>Rooyackers $^{23}$</td>
<td>12/12</td>
<td>PO$_2$&gt;8.5 kPa, nocturnal SO$_2$&gt;90%, SO$_2$ max exercise&lt;90%, ΔAaO$_2$ rest-max.exerc &gt; 2 kPa</td>
<td>4 l/min</td>
<td>Strength+endurance (cycling), SO$_2$&gt;90%, 10 wks, 5 d/wk, 80 min/day</td>
<td>CWRT, 6MWD, CRQ</td>
<td>ns</td>
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<tr>
<td>Fichter $^{24}$</td>
<td>5/5</td>
<td>35%</td>
<td>Cycling, 4 wks, 5 d/wk</td>
<td>W$_{max}$, cycle ergometry</td>
<td>ns</td>
<td></td>
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<tr>
<td>Garrod $^{25}$</td>
<td>11/11</td>
<td>FEV$_1$&lt;40%, SO$_2$ exer &lt; 90% and ASO$_2$ &gt;4%</td>
<td>4 l/min</td>
<td>Cycling/walking, 6 wks, 3 d/wk, 1 h/day</td>
<td>ISWT, CRQ</td>
<td>ns</td>
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<td>Wadell $^{26}$</td>
<td>10/10</td>
<td>SO$_2$, 6MWD &lt; 92%, PO$_2$ &gt; 7.8 kPa</td>
<td>5 l/min</td>
<td>Walking, 8 wks, 3 d/wk, 30 min/day. SO$_2$&gt;90%</td>
<td>6MWD</td>
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<tr>
<td>Emtner $^{27}$</td>
<td>14/15</td>
<td>FEV$_1$&lt;50%, PO$_2$&gt;7.3 kPa, SO$_2$, CWRT&gt;88%</td>
<td>3 l/min</td>
<td>Cycling, 7 wks, 3 d/wk, 45 min/day.</td>
<td>CWRT</td>
<td>14.5/10.0 min *</td>
</tr>
<tr>
<td>Scorsone$^{28}$</td>
<td>7/9</td>
<td>40%</td>
<td>Cycling, 8 wks, 3 days/wk, 40 min/day.</td>
<td>W$_{max}$, cycle ergometry, CWRT</td>
<td>ns</td>
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</table>

$^*$ 3-arm study: 40% O$_2$, Heliox 60/40% and air, presented results 40% O$_2$ vs air.  * p<0.05. ns: nor statistically significant. #CWRT: constant work rate test, CRQ: Chronic Respiratory Questionnaire, ISWT: Incremental Shuttle Walk Test. 6MWD: 6-minutes walking distance.
<table>
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<td>Schols$^37$</td>
<td>N=213, numbers per treatment arm and sex not reported.</td>
<td>Nandrolone decanoate, 50 mg (m), 25 mg (f), every 2 wks, 8 wks.</td>
<td>Endurance training, 8 wks, 5 d/wk</td>
<td>FFM (BIA), weight, Pi max, arm circumference,</td>
<td>FFM and Pi max (NN vs P).</td>
<td></td>
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<td>Ferreira$^38$</td>
<td>10 m/7m BMI&lt;20 kg/m2, Pi max &lt; 60%pred</td>
<td>Testosterone 250 at start, then stanozolol orally 12 mg/day, 27 wks.</td>
<td>0-9 wks: none, 9-18 wks: inspiratory muscle training, 18-27 wks: endurance training</td>
<td>BMI, LBM (DEXA), extremity circumference, Pi max, 6 MWD, VO2 max.</td>
<td>LBM 3/0 kg *, Thigh circumference 2/0% *, other ns.</td>
<td></td>
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<tr>
<td>Creutzberg$^39$</td>
<td>33 m/30 m &lt; 70 y, PO2&gt;7.3 kPa.</td>
<td>Nandrolone decanoate 50 mg, every 2 wks, 8 wks.</td>
<td>Endurance training, 8 wks, 5 d/wk</td>
<td>FFM (deuterium method), isometric leg strength, Pi max, SGRQ, Wmax and VO2 max.</td>
<td>FFM 1.7/0.3 kg *. Other ns. Posthoc: oral corticosteroid users larger effects on Wmax, Pi max</td>
<td></td>
</tr>
<tr>
<td>Casaburi $$^40$$</td>
<td>12 m/11 m FEV1&lt;60 %pred, serum testosterone &lt; 400 ng/dl</td>
<td>Testosterone enanthate 100 mg, 1/wk, 10 wks.</td>
<td>Resistance training, 10 wks, 3 d/wk.</td>
<td>LBM (DEXA), 1RM leg press</td>
<td>Total LBM 3.3/0.2 kg , Leg lean 1.4/0.5 kg <em>, 1 RM 27/17%</em></td>
<td></td>
</tr>
<tr>
<td>Svartberg$^41$</td>
<td>15 m/14 m FEV1&lt;60%pred</td>
<td>Testosterone enanthate, 250 every 4 wks, 29 wks.</td>
<td>none</td>
<td>6MWD, FFM (DEXA), SQRQ, sexual QoL</td>
<td>FFM 1.1/-0.8 *, sexual QoL improved, other outcomes ns.</td>
<td></td>
</tr>
<tr>
<td>Sharma$^42$</td>
<td>8 (5m,3f)/8 (4m,4f) FEV1&lt;50 %pred</td>
<td>Nandrolone decanoate 50 mg (m) or 25 mg (f), every 2 weeks, 16 weeks.</td>
<td>Resistance/endurance training, 16 wks, 3 d/wk, unsupervised</td>
<td>CRQ, LBM(DEXA), 6MWD</td>
<td>ns</td>
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</table>
1: m=male, f=female. 2: FFM fatfree mass, LBM Lean body mass, SGRQ Saint George’s Respiratory Questionnaire, 1RM 1 repetition maximum, CRQ Chronic Respiratory Questionnaire, 6MWD 6 minutes walking distance, VO$_2$$_{max}$ maximal oxygen uptake on cycle ergometry. $: 3$ arm study: placebo (P), nutrition (420 kcal/d, N), nutrition+nandrolone (NN). $$: 4$-arm study: placebo/no training, testosterone/no training, placebo/training, testosterone/training. Comparison between the training arms * $p<0.05$