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Title: Prescribing exercise in advanced COPD: Training smart, not just hard!

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Body: The high-intensity paradigm is prevailing in COPD training. Individualising training variables is considered the gold standard. Nonlinear periodized exercise (NLE) uses variation of the training variables (mode of exercise, work phase, rest phase, intensity, number of repetitions) to individualize training. The aim of this study was to compare the effects of NLE with traditional endurance and progressive resistance training (EPR) on cycle endurance time (CWT) at 75%Wmax. Methods Patients with severe COPD (N=110, FEV₁ 32%pred, 61 yrs) were stratified on normal or depleted fat-free mass index (depleted FFMi; male FFMi<15 kgFFM/m²; female FFMi<16). Per FFMi-group, patients were randomly assigned to NLE or EPR (3-times/week for 12 weeks). Difference in change was tested with intention-to-treat analysis using linear mixed-effects modeling. Trial number NTR 1045. Results NLE showed more improvement in cycle endurance at 12 weeks: NLE_{Depleted} (N=33, Δ569s = +143%) compared to EPR_{Depleted} (N=34, Δ262s=+66%), difference in change (307s, 95% CI: 162-425) and NLE_{NonDepleted} (N=22, Δ528s = +123%) compared to EPR_{NonDepleted} (N=21, Δ198s = +46%), difference in change (329s, 95%CI: 182-477). During the training, patients in the NLE groups had significantly more repetitions, lower % 1-repetition maximum load, shorter cycle time and lower Borg dyspnea, fatigue and exertion scores than the patients in EPR groups. Conclusion Nonlinear periodized exercise results in >5min more improvement in cycle endurance than traditional endurance and resistance training in patients with advanced COPD and depleted or normal FFM. Applying principles of nonlinear exercise training in athletes to the COPD population is feasible and worthwhile.