BRIEF RESEARCH REPORT

Cardiopulmonary Exercise Testing for Patients With Neuromuscular Disease and Limited Mobility

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ABSTRACT

Background: Patients with neuromuscular disease (NMD) have progressive muscle weakness and limited mobility that contributes to a sedentary lifestyle. A sedentary lifestyle often leads to deconditioning and decreases cardiorespiratory fitness (CRF). Cardiopulmonary exercise testing (CPX) is the gold standard for the evaluation of CRF but has not been widely applied in patients with NMD.

Methods: Patients with NMD were recruited from the Neuromuscular Clinic at the Stanford Neurosciences Health Center at Stanford University. Matched controls were recruited by staff from the local community by word of mouth. All participants performed CPX using a wheelchair-accessible total body trainer and a wearable metabolic cart system to volitional exhaustion.

Results: Participants with NMD and limited mobility (n = 37) were able to perform high-quality CPX with no adverse events or safety concerns of comparable quality to controls. Average respiratory exchange ratio for NMD patients was 1.08 ± 0.16, and average rating of perceived exertion was 18 ± 2 compared with 1.16 ± 0.12 and 18 ± 2 for controls, respectively ($P = 0.17$ and $P = 0.78$, respectively). Patients with NMD on average showed markedly reduced percent predicted VO_2max and impaired ventilatory efficiency.

Conclusion: High-quality CPX in patients with NMD may reveal distinct physiological profiles that may lead to a better understanding of pathology in these individuals. CPX on total body trainers may be a viable method for improving exercise prescription for patients with NMD. *J Clin Exerc Physiol*. 2023;12(1):12–17.

Keywords: CPX, CPET, wheelchair, ventilation, peak VO_2

INTRODUCTION

Patients with neuromuscular disease (NMD) present with specific muscle weakness and fatigue and are largely sedentary and deconditioned (1). This sedentary lifestyle driven by progressive muscle weakness and barriers to accessible means of exercise leads to additional weakness, fatigue, and loss of function (2). This deconditioning cycle results in reduced cardiorespiratory fitness (CRF), which is strongly related to increased risk for cardiovascular and pulmonary diseases (3). Furthermore, people with NMD are living

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longer with a chronic progressive disease, which may further increase risk of developing these comorbidities over the lifespan (4). These largely preventable comorbidities are the leading causes of morbidity and mortality for those with and without NMD, and the risk for developing them is independently correlated to level of CRF (5). The standard for the assessment of CRF is peak oxygen consumption (peak VO_2), determined with cardiopulmonary exercise testing (CPX). Several small studies have suggested a role for CPX for patients with NMD, and hyperventilatory and hypercirculatory patterns have been observed, but very few have reported on CPX for those with NMD who have more motor impairments or are nonambulatory (1,6–8). CPX is applied by clinical exercise physiologists for exercise prescription as the standard of care, with variables such as percent of peak VO_2 and VO_2 reserve favored for exericse prescription development (9). We report on a specific CPX protocol on a total body trainer for patients with NMD and low mobility.

METHODS

This study was approved by the Institutional Review Board of Stanford University. All research staff were trained in good clinical practice, and all participants provided written informed consent or assent before any study procedures. Patients with NMD were prospectively recruited from the Stanford Neurosciences Health Center at Stanford University. Patients with any NMD and limited mobility were included. *Limited mobility* was defined as the inability to safely perform treadmill ambulation. Patients were excluded if they could not provide informed consent and assent where appropriate, had performed treadmill or upright cycle ergometry exercise within the last 6 months, or if they were deemed unable to exercise vigorously by the study physicians. Participants in the control group were recruited from the local community, did not have medical diagnoses which would prohibit maximal exercise testing performance, and efforts were made to match for age and sex. Cardiopulmonary exercise tests were performed using a CosMed K5 wearable metabolic system (COSMED USA Inc, Concord, California) and a Keiser wheelchair-accessible total body trainer (Keiser Corporation, Fresno, California) that allowed patients to use lower limb strength in an elliptical pattern with the lower limbs and a rowing pattern with the upper limbs. Additionally, the total body trainer allowed patients who were in wheelchairs to perform the testing without transfering to a bike. Respiratory gas data were collected and analyzed after applying a 30 second rolling average (every 10 seconds) filter. All CPXs were performed by clinical exercise physiologists and physical therapists and monitored by a physician familiar to the patients and the study protocols.

Peak VO_2 and all other respiratory gas metrics were calculated as the highest 30 second average during the last phase of the CPX. Percent of predicted peak VO_2 was calculated using the Fitness Registry and Importance of Exercise National Database (FRIEND) Registry (10). Peak heart rate (HR; $b \cdot min^{-1}$), rating of perceived exertion (RPE; 6–20), and workload (Watts) were calculated as the highest number recorded during exercise. Oxygen uptake efficiency slope (OUES) was calculated as $VO_2 = a \log V_E + b$, where a = OUES (11). Exercise oscillatory breathing (EOB) was assessed visually by 2 independent investigators with an additional investigator used as a tiebreaker (12). The V_E/VCO_2 slope was calculated for the entire exercise bout (13,14) and to the respiratory compensation point (RCP) to account for nonlinearity, which has been shown to be driven by both CO_2 output and decrease in plasma pH and is related to a decrease in pulmonary perfusion (15–17).

Statistical Analysis

To observe clinical and statistical significance between the groups, the current study was powered to detect a 10 $mL \cdot kg^{-1} \cdot min^{-1}$ difference in peak VO_2. This difference represents the best estimate of the expected difference between the mean peak VO_2 of patients with NMD and limited mobility compared with able-bodied controls. Assuming a power of 80% and using independent-samples t tests (Group A versus Group B) at the 5% significance level revealed a need for a total of 48 participants (24 in each group). We did not expect any dropouts due to the nature of the study.

Data were tested for normalcy using the Shapiro-Wilk test due to small sample size and for group differences using analyses of variance and t tests for independent groups and presented as means ± SD for parametric data. For nonparametric data, Mann-Whitney tests and medians and confidence intervals were used. Categorical data are presented as frequencies and percentages.

RESULTS

We recruited 37 patients with NMD and 8 non-NMD-affected control participants to the study (see Figure 1, Table 1). Patients were included with facioscapulohumeral muscular dystrophy (n = 12), spinal muscular atrophy type 3 (n = 9), myotonic dystrophy type 1 (n = 9), myotonic dystrophy type 2 (n = 1), Pompe disease (n = 3), limb-girdle muscular dystrophy (n = 2), Duchenne muscular dystrophy (n = 2), dysferlinopathy (n = 1), and dystrophinopathy (n = 1).

We were able to perform high-quality CPX with all participants with no adverse events or safety concerns. Average respiratory exchange ratio (RER) and RPE were 1.08 ± 0.16 and 18 ± 2 compared with 1.16 ± 0.12 and 18 ± 2 for controls, respectively (Table 2). Individuals with NMD presented with reduced exercise performance compared with controls as measured by peak workload (66.0 ± 45.5 W versus 198.6 ± 58.9 W, $P < 0.001$) and peak VO_2 (20.6 ± 7.10 $mL \cdot kg^{-1} \cdot min^{-1}$ versus 37.5 ± 11.9 $mL \cdot kg^{-1} \cdot min^{-1}$, $P < 0.001$). Disturbed hemodynamic and ventilatory patterns were noted for the NMD group, with borderline chronotropic incompetence and low O_2 pulse, marked ventilatory inefficiency and severely reduced OUES, and a high proportion of patients displaying EOB.

The mean V_E/VCO_2 slope for the NMD group was 36.3 ± 7.2, indicating ventilatory inefficiency using a threshold abnormal value of 34 (18). The V_E/VCO_2 slope was also

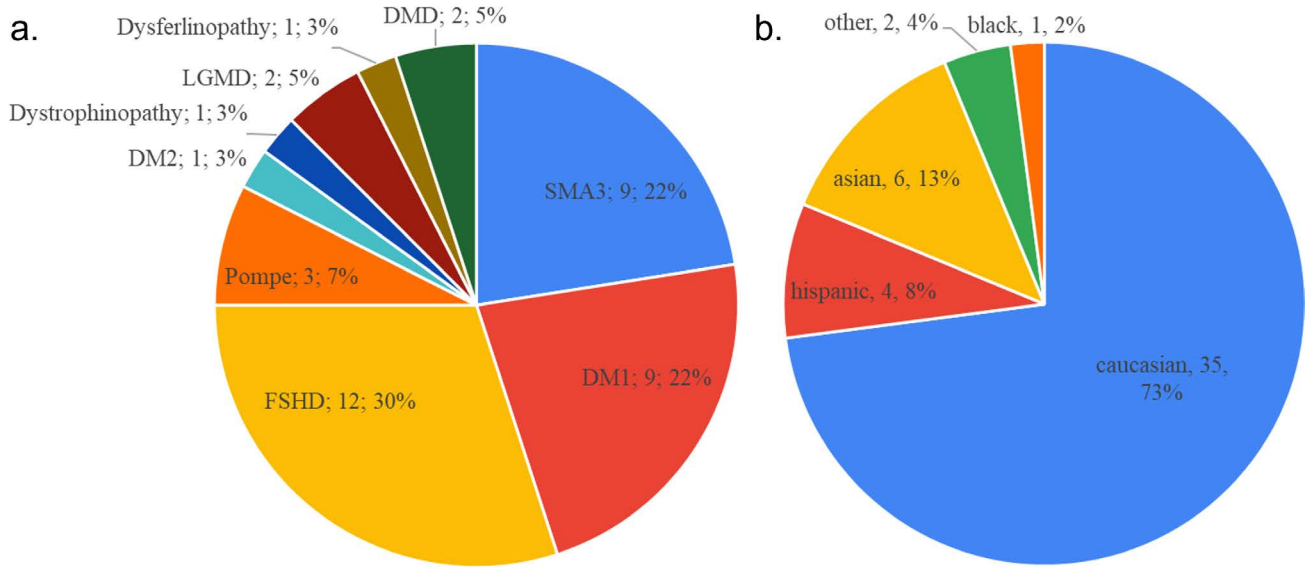

FIGURE 1. (a) Breakdown of types of NMD within the sample. DM1 = myotonic dystrophy type 1; DM2 = myotonic dystrophy type 2; DMD = Duchenne muscular dystrophy; FSHD = facioscapulohumeral muscular dystrophy; LHMD = limb-girdle muscular dystrophy; Pompe = Pompe disease; SMA3 = spinal muscular atrophy type 3. (b) Breakdown of ethnicities within the sample of patients with NMD. Vales are n; %.

relatively high in the control group (32.2 ± 5.3) and not significantly different from the NMD group ($P = 0.13$). The use of the entire CPX resulted in higher V_E/VCO_2 slope values due to the inclusion of hyperventilatory data after the RCP (15). There were significant differences noted between the groups (NMD = 31.9 ± 5.6 versus control = 27.0 ± 2.3, $P = 0.02$), whereby both groups are under the threshold of 34 suggested as the normal hyperventilatory response to high-intensity exercise (16). Importantly, we observed that relative effort as illustrated by equivalent RPE and RER was not significantly different between the groups.

DISCUSSION

This is one of the first reports of quality CPX in patients with a range of NMD from nonambulatory to ambulatory with decreased mobility. We observed significant differences in CPX performance between those with NMD and healthy controls. Patients with NMD had lower peak HR, workload, VO_2, O_2P, and OUES and higher V_E/VCO_2 slope and number of participants presenting EOB. Groups were not significantly different for peak RPE, RER, and %HR.

Some patients with NMD (e.g., patients with spinal muscle atrophy) are not able to safely exercise on a treadmill or cycle ergometer due to muscle weakness and imbalance along proximal and distal muscular distributions. The mode of exercise used in this study is unique as it allowed for indivduals with limited mobility to perform testing safely, including while in a wheelchair. Difficulties with CPX testing for NMD include inability to maximally stress the cardiorespiratory system due to muscle fatigue. The total body trainer allows for push and pull exercise which is easier for patients who have shoulder weakness and may not be able to pedal an arm ergometer. Additionally, combining upper and lower body movement allows those with severe proximal weakness to use both upper and lower limbs to attain maximal testing.

Our study is an important contribution to the literature on exercise testing in NMD where there is a need for more studies about the feasibilty of CPX for nonambulatory patients (8). Studies using novel exercise devices may offer an alternative and should be considered in the design of specific CPX protocols for patients with severe motor

TABLE 1. Patient characteristics.

	NMD (n = 37)		Control (n = 8)		*P* Value
	Mean ± SD	Range	Mean ± SD	Range	
Age (y)	41.5 ± 18.1	10.7, 78.0	44.8 ± 15.5	27.6, 70.1	0.641
Height (cm)	168.4 ± 13.5	137.2, 195.6	177.2 ± 7.9	165.1, 193.0	0.085
Weight (kg)	68.3 ± 21.3	40.9, 146.8	79.1 ± 17.7	55.5, 96.8	0.188
Sex (n; % female)	13; 35%	–	4; 50%	–	0.437

NMD = neuromuscular disease

TABLE 2. Results of cardiopulmonary exercise testing.[a]

	NMD (n = 37)	Control (n = 8)	*P* Value
Peak RPE (6–20)	18.4 ± 2.1	18.1 ± 2.0	0.78
Peak workload (Watt)	66.0 ± 45.5	198.6 ± 58.9	<.001
Peak VO_2 ($L \cdot min^{-1}$)	1.42 ± 0.60	2.86 ± 0.83	<.001
Peak VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	20.6 ± 7.10	37.5 ± 11.9	<.001
Percent of predicted peak VO_2 (%)	55.6 ± 24.9	113.4 ± 29.4	<.001
Peak RER (VCO_2/VO_2)	1.08 ± 0.16	1.16 ± 0.12	0.17
Peak HR ($b \cdot min^{-1}$)	152.5 ± 21.4	169.1 ± 8.07	0.04
Percent of predicted peak HR (%)	83.7 ± 17.7	96.9 ± 5.42	0.05
Peak O_2P ($VO_2/b \cdot min^{-1}$)	9.44 ± 4.15	17.0 ± 4.87	<.001
V_E/VCO_2 slope at RCP	31.9 ± 5.60	27.0 ± 2.28	0.02
V_E/VCO_2 slope	36.3 ± 7.21	32.2 ± 5.30	0.13
OUES ($mL \cdot min^{-1} \cdot log(L \cdot min^{-1})^{-1}$)	1527.8 ± 849.7	2902.6 ± 732.9	<.001
Percent of predicted OUES (%)	65.2 ± 31.3	116.7 ± 23.9	<.001
HR recovery at 1 min ($b \cdot min^{-1}$)	28.4 ± 11.8	22.6 ± 9.51	0.20
EOB (N; %)	17, 46%	0, 0%	–

EOB = exercise oscillatory breathing; HR = heart rate; NMD = neuromuscular disease; O_2P = oxygen pulse; OUES = oxygen uptake efficiency slope; RCP = respiratory compensation point; RER = respiratory exchange ratio; RPE = rating of perceived exertion (6–20 scale); VCO_2 = carbon dioxide production; V_E = minute ventilation; VO_2 = oxygen uptake
[a]All values mean ± SD, except EOB

impairments to allow for adequate testing of CRF. The ability to measure CRF will help improve exercise prescription development and promote an active lifestyle for individuals with NMD, many of whom are at higher risk of other diseases of a sedentary lifestyle (3).

Patients with NMD in the current study had a significantly higher V_E/VCO_2 and lower OUES and O_2P than the control group, and a significantly higher percentage of patients with NMD presented with EOB. These are independent risk factors for poor prognosis of other patient populations, and EOB is a very strong predictor of mortality in heart failure (18). Currently, it is unknown what the relationships of these variables may be on outcome in NMD, and thus, further investigation is warranted to discover their impact (19–24).

Importantly, we were able to show it is possible to perform high-quality CPX, including assessment of peak VO_2, HR, RPE, and ventilatory thresholds in patients with NMD and limited mobility. In addition to investigating its prognotic value, CPX could also be an effective method for prescribing exercise in this population. Establishing effective methods for exercise promotion for patients with NMD has been elusive (25). However, exercise prescription is more effective when combined with CPX, whereby researchers have shown that using ventilatory thresholds adds precision to matching metabolic demands during exercise defined by ventilatory thresholds (26–29). The CPX protocol designed for patients with NMD has the potential to improve on current exercise prescription methods. This is especially important given the ventilatory and hemodynamic limitations in this population, which result in traditional methods of prescription being less effective than in other populations (1). Endurance exercise prescription is inherently difficult in this group; furthermore, specific exercise modes (e.g., Keiser ergometers) and a wide range of diagnoses with large heterogeniety in muscle function require personalization. The traditional barriers to exercise for individuals with NMD may be overcome by the performance of this novel approach to CPX. In the few studies which have assessed the effect of endurance exercise on stronger patients with NMD, training has been observed to increase peak VO_2, workload, and muscle strength by up to 47%, 80%, and 40%, respectively, without causing muscle damage (30–32). As suggested by Siciliano et al. (33,34), proper exercise may improve motor performance in adaptation and response to homeostatic imbalance observed in some patients with NMD. High-quality CPX designed for patients with NMD and lower mobility may promote effective exercise prescriptions.

Limitations

Although CPX has been applied to patients with cardiac and pulmonary disease for many years, there is minimal literature on the use of CPX in NMD. We used conventional reference data (FRIEND Registry) to this sample, and further study is needed to define normal values in different NMD patient populations. Our sample size was small, but we believe these data support our hypothesis that CPX can be safely performed in NMD patients with

the appropriate mode of testing and should be expanded on in future studies. Having performed this study during the COVID-19 pandemic with restrictions in place was an unexpected challenge which limited our ability to recruit participants.

CONCLUSION

Our data demonstrate that high-quality CPX can be conducted in patients with a broad range of NMD and motor dysfunction. Performing CPX in patients with NMD will delineate distinct physiological profiles that may lead to a better understanding of cardiopulmonary and metabolic pathology in these individuals and improvement in the development of exercise prescription.

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REFERENCES

1. Weisman IM, Jorge Zeballos R. Clinical exercise testing. Basel: S. Karger AG; 2002.
2. Phillips M, Flemming N, Tsintzas K. An exploratory study of physical activity and perceived barriers to exercise in ambulant people with neuromuscular disease compared with unaffected controls. Clin Rehabil. 2009;23:746–55.
3. Maquet D, Demoulin C, Croisier J-L, Crielaard J-M. Benefits of physical training in fibromyalgia and related syndromes. Ann Readapt Med Phys. 2007;50:356–68.
4. Rose L, McKim D, Leasa D, Nonoyama M, Tandon A, Bai YQ, Amin R, Katz S, Goldstein R, Gershon A. Trends in incidence, prevalence, and mortality of neuromuscular disease in Ontario, Canada: a population-based retrospective cohort study (2003–2014). PLoS One. 2019;14:e0210574. doi:10.1371/journal.pone.0210574
5. Ahmad FB, Anderson RN. The leading causes of death in the US for 2020. JAMA. 2021;325:1829–30.
6. Bankolé L-C, Millet GY, Temesi J, Bachasson D, Ravelojaona M, Wuyam B, Vergas S, Ponsot E, Antoine J, Kadi F, Féasson L. Safety and efficacy of a 6-month home-based exercise program in patients with facioscapulohumeral muscular dystrophy: a randomized controlled trial. Medicine. 2016;95:e4497. doi:10.1097/MD.0000000000004497
7. Voet NB, van der Kooi EL, Riphagen II, Lindeman E, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev. 2010;CD003907. doi:10.1002/14651858.CD003907.pub3
8. Barroso de Queiroz Davoli G, Bartels B, Mattiello-Sverzut AC, Takken T. Cardiopulmonary exercise testing in neuromuscular disease: a systematic review. Expert Rev Cardiovasc Ther. 2021;19(11):975–91.
9. Marini CF, Sisti D, Leon AS, Skinner JS, Sarzynski MA, Bouchard C, Rocchi ML, Piccoli G, Stocchi V, Federici A, Lucertini F. HRR and O_2R fractions are not equivalent: is it time to rethink aerobic exercise prescription methods? Med Sci Sports Exercise. 2021;53(1):174–82. doi:10.1249/MSS.0000000000002434
10. Kaminsky LA, Arena R, Myers J, Peterman JE, Bonikowske AR, Harber MP, Inojosa JRM, Lavie CJ, Squires RW. Updated reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the Fitness Registry and the Importance of Exercise National Database (FRIEND). Mayo Clin Proc. 2022;97(2):285–93.
11. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, Niskibata K. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol. 1996;28:1567–72.
12. Cornelis J, Beckers P, Vanroy C, Volckaerts T, Vrints C, Vissers D. An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation—a systematic review. Int J Cardiol. 2015;190:161–9.
13. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, Fletcher G, American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology, American Heart Association Council on Cardiovascular Nursing. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation. 2007;116:329–43.
14. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M. Development of a ventilatory classification system in patients with heart failure. Circulation. 2007;115:2410–7.
15. Tabet J-Y, Beauvais F, Thabut G, Tartière J-M, Logeart D, Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO_2 slope in chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2003;10:267–72.
16. Sophie É, Collins SE, Devin B, Phillips DB, Andrew R, Brotto AR, Zahrah H, Rampuri ZH, Michael K, Stickland MK. Ventilatory efficiency in athletes, asthma and obesity. Eur Respir Rev. 2021;30:200206. doi:10.1183/16000617.0206-2020
17. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO_2 and VE/VCO_2 slope in patients with heart failure: a prognostic comparison. Am Heart J. 2004;147:354–60.
18. Myers J, Arena R, Oliveira RB, Bensimhon D, Hsu L, Chase P, Guazzi M, Brubaker P, Moore B, Kitzman D, Peberdy MA. The lowest VE/VCO_2 ratio during exercise as a predictor of outcomes in patients with heart failure. J Card Fail. 2009;15:756–62.
19. Sato T, Yoshihisa A, Kanno Y, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh SI, Ishida T, Takeishi Y. Cardiopulmonary exercise testing as prognostic indicators: comparisons among heart failure patients with reduced, mid-range and preserved ejection fraction. Eur J Prev Cardiol. 2017;24(18):1979–87.
20. Dhakal BP, Lewis GD. Exercise oscillatory ventilation: mechanisms and prognostic significance. World J Cardiol. 2016;8:258–66.
21. Alba AC, Adamson MW, MacIsaac J, Lalonde SD, Chan WS, Delgado DH, Ross HJ. The added value of exercise variables in heart failure prognosis. J Card Fail. 2016;22:492–7.
22. Coeckelberghs E, Buys R, Goetschalckx K, Cornelissen VA, Vanhees L. Prognostic value of the oxygen uptake efficiency

slope and other exercise variables in patients with coronary artery disease. Eur J Prev Cardiol. 2016;23:237–44.
23. Cohen-Solal A, Barnier P, Pessione F, Seknadji P, Logeart D, Laperche T, Gourgon R. Comparison of the long term prognostic value of peak exercise oxygen pulse and peak oxygen uptake in patients with chronic heart failure. Heart. 1997;78(6):572–6. doi:10.1136/hrt.78.6.572
24. Lavie CJ, Milani RV, Mehra MR. Peak exercise oxygen pulse and prognosis in chronic heart failure. Am J Cardiol. 2004;93:588–93.
25. Jones K, Hawke F, Newman J, Miller JA, Burns J, Jakovljevic DG, Gorman G, Turnbill DM, Ramdharry G. Interventions for promoting physical activity in people with neuromuscular disease. Cochrane Database Syst Rev. 2021;5(5):CD013544. doi:10.1002/14651858.CD013544.pub2
26. Anselmi F, Cavigli L, Pagliaro A, Valente S, Valentini F, Cameli M, Focardi M, Mochi N, Dendale P, Hansen D, Bonifazi M, Halle M, D'Ascenzi F. The importance of ventilatory thresholds to define aerobic exercise intensity in cardiac patients and healthy subjects. Scand J Med Sci Sports. 2021;31:1796–808.
27. Anselmi F, Cavigli L, Pagliaro A, Valente S, Mondillo S, Focardi M, Cameli M, Bonifazi M, D'Ascenzi F. [Cardiopulmonary exercise testing: an essential tool for a tailored exercise prescription in patients with cardiac disease]. G Ital Cardiol. 2021;22:716–26.
28. Wolpern AE, Burgos DJ, Janot JM, Dalleck LC. Is a threshold-based model a superior method to the relative percent concept for establishing individual exercise intensity? A randomized controlled trial. BMC Sports Sci Med Rehabil. 2015;7:16. doi:10.1186/s13102-015-0011-z
29. Voet NBM. Exercise in neuromuscular disorders: a promising intervention. Acta Myol. 2019;38:207–14.
30. Oorschot S, Brehm M-A, Daams J, Nollet F, Voorn E. Efficacy of aerobic exercise on aerobic capacity in slowly progressive neuromuscular diseases: a systematic review and meta-analysis. Ann Phys Rehabil Med. 2022;66(1):101637. doi:10.1016/j.rehab.2022.101637
31. Voorn EL, Koopman FS, Nollet F, Brehm M-A. Individualized aerobic exercise in neuromuscular diseases: a pilot study on the feasibility and preliminary effectiveness to improve physical fitness. Phys Ther. 2021;101(3):pzaa213. doi:10.1093/ptj/pzaa213
32. Sveen ML, Jeppesen TD, Hauerslev S, Kober L, Krag TO, Vissing J. Endurance training improves fitness and strength in patients with Becker muscular dystrophy. Brain. 2008;131(Pt11):2824–31. doi:10.1093/brain/awn189
33. Siciliano G, Chico L, Lo Gerfo A, Simoncini C, Schirinzi E, Ricci G. Exercise-related oxidative stress as mechanism to fight physical dysfunction in neuromuscular disorders. Front Physiology. 2020;11. doi:10.3389/fphys.2020.00451
34. Siciliano G, Simoncini C, Lo Gerfo A, Orsucci D, Ricci G, Mancuso M. Effects of aerobic training on exercise-related oxidative stress in mitochondrial myopathies. Neuromuscular Disord. 2012;22:S172–7. doi:10.1016/j.nmd.2012.10.005