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ORIGINAL RESEARCH

Validity of Cardiopulmonary Exercise Testing for Assessing Aerobic Capacity in Neuromuscular Diseases

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Abstract

Objectives: To determine the content validity of cardiopulmonary exercise testing (CPET) for assessing peak oxygen uptake (VO_{2peak}) in neuromuscular diseases (NMD).

Design: Baseline assessment of a randomized controlled trial.

Setting: Academic hospital.

Participants: Eighty-six adults (age: 58.0±13.9 y) with Charcot-Marie-Tooth disease (n=35), postpolio syndrome (n=26), or other NMD (n=25).

Intervention: Not applicable.

Main Outcome Measures: Workload, gas exchange variables, heart rate, and ratings of perceived exertion were measured during CPET on a cycle ergometer, supervised by an experienced trained assessor. Muscle strength of the knee extensors was assessed isometrically with a fixed dynamometer. Criteria for confirming maximal cardiorespiratory effort during CPET were established during 3 consensus meetings of an expert group. The percentage of participants meeting these criteria was assessed to quantify content validity.

Results: The following criteria were established for maximal cardiorespiratory effort: a plateau in oxygen uptake ($VO_{2plateau}$) as the primary criterion, or 2 of 3 secondary criteria: (1) peak respiratory exchange ratio (RER_{peak}) ≥1.10 (2), peak heart rate ≥85% of predicted maximal heart rate; and (3) peak rating of perceived exertion (RPE_{peak}) ≥17 on the 6-20 Borg scale. These criteria were attained by 71 participants (83%). $VO_{2plateau}$, RER_{peak} ≥1.10, peak heart rate ≥85%, and RPE_{peak} ≥17 were attained by 31%, 73%, 69%, and 72% of the participants, respectively. Peak workload, VO_{2peak}, and knee extension muscle strength were significantly higher, and body mass index was lower (all *P*<.05), in participants with maximal cardiorespiratory effort than other participants.

Preliminary results of this study were presented at the Dutch Congress of Rehabilitation Medicine, s-Hertogenbosch, 9 november 2023; the Amsterdam Movement Sciences Congress, Amsterdam, 23 March 2023 ; and the International Annual Congress of the World Muscle Society, Charleston, 6 October 2023.

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Data used for this study was collected as part of a randomized controlled trial registered at the Dutch Trial register (NL7344).

Disclosures: none

List of abbreviations: CMT, Charcot-Marie-Tooth disease; CPET, cardiopulmonary exercise testing; CRE, cardiorespiratory effort; MRC, Medical Research Council; NMD, neuromuscular diseases; PPS, postpolio syndrome; RER, respiratory exchange ratio; RER_{peak}, respiratory exchange ratio at peak exercise; RPE, rating of perceived exertion; RPE_{peak}, rating of perceived exertion at peak exercise; VO_2, oxygen uptake; VO_{2peak}, oxygen uptake at peak exercise; $VO_{2plateau}$, plateau in oxygen uptake.

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Conclusions: Most people with NMD achieved maximal cardiorespiratory effort during CPET. This study provides high quality evidence of sufficient content validity of VO_{2peak} as a maximal aerobic capacity measure. Content validity may be lower in more severely affected people with lower physical fitness.

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Aerobic capacity, defined as the ability of the respiratory and cardiovascular systems to deliver oxygen to the muscles and to use this oxygen to generate energy during exercise,[1] is an important health marker.[2] It is strongly associated with functional performance in daily living and independence at older age.[3,4] People with neuromuscular diseases (NMD) often have reduced aerobic capacity caused by the underlying disease and an inactive lifestyle.[5,6]

Oxygen uptake (VO_2) at peak exercise (VO_{2peak}), the highest rate at which an individual can consume oxygen during exercise, is considered the best physiological marker of aerobic capacity.[7] VO_{2peak} is measured through cardiopulmonary exercise testing (CPET), and it is often used as a primary outcome in aerobic exercise studies in NMD.[8] The validity of CPET could be limited in NMD because the weakened skeletal muscles may prevent the cardiorespiratory system from reaching its maximal capacity.[9] A recent systematic review on measurement properties of aerobic capacity measures in NMD found sufficient content validity of VO_{2peak} assessment, but the quality of evidence was low.[10] The main reasons for downgrading the quality of evidence to low were inconsistent results and risk of bias, because of small sample sizes (<50), lack of experienced test supervisors, and inadequate criteria for confirming maximal cardiorespiratory effort (CRE) during CPET.[10,11]

In the context of VO_{2peak} assessment during CPET, an important aspect of content validity is to check certain physiological and psychological criteria for confirming CRE. There are currently no uniform criteria in NMD, and consequently, a wide variety of criteria have been applied in previous studies in different types of NMD, like Pompe disease, muscular dystrophies, and Charcot-Marie-Tooth (CMT) disease.[10,12] The occurrence of a plateau in VO_2 ($VO_{2plateau}$) is historically viewed as the best criterion for maximal CRE.[13] In addition, different secondary criteria are used, such as following: (1) the respiratory exchange ratio (RER), the ratio between the volume of CO_2 being produced by the body and the amount of O_2 being consumed, at peak exercise (RER_{peak}); (2) the heart rate at peak exercise relative to the age-predicted maximal heart rate; and (3) the rating of perceived exertion (RPE), a subjective outcome measure scale for exercise intensity, at peak exercise (RPE_{peak}). The applied criteria were often based on studies in other (clinical) populations without considering the distorted muscle function in NMD, which can affect exercise test performance and physiological responses during exercise.[12]

The aim of this study was to improve the quality of evidence on the content validity of VO_{2peak} assessment by addressing the main factors that caused risk of bias in existing literature: using a larger sample size (>50), an experienced test supervisor, and adequate criteria for confirming maximal CRE. The physiological load corresponding to frequently applied criteria for maximal CRE was evaluated in terms of percentage VO_{2peak} when reaching these criteria. Using this information and based on consensus, criteria were selected to determine the content validity of VO_{2peak} assessment in NMD. Differences in characteristics and CPET outcomes between people that achieved maximal and submaximal CRE were also explored.

Methods

Participants

Data of the baseline assessment of a randomized controlled trial were used that evaluated the efficacy of a physical activity program, including aerobic exercise to improve physical fitness in NMD, registered at the Dutch Trial register (NL7344).[14] Data were collected between September 2018 and April 2022. Participants were recruited from hospitals and rehabilitation centers in the Netherlands and through the patient organization for NMD, the Dutch Association for Neuromuscular Diseases.

Potentially eligible participants were screened by a rehabilitation physician and a cardiologist. Adults diagnosed with postpolio syndrome (PPS), CMT, or other NMD who were motivated to improve their reduced physical fitness were eligible. Exclusion criteria included contraindications for physical activity according to the American College of Sports Medicine guidelines.[15] More details about the inclusion and exclusion criteria are reported in the published study protocol.[14] Additionally, for the current study, only participants that performed CPET on a cycle ergometer were selected.

The Ethics Review Committee of the Amsterdam Medical Center approved the study protocol (NL75019.018.20), and all participants provided informed consent. Study reporting followed the STrengthening the Reporting of OBservational studies in Epidemiology guidelines.[16]

Cardiopulmonary exercise testing

CPET was performed in the morning on an electromagnetically braked cycle ergometer[a] using MasterScreen CPX,[b] executed according to international guidelines[17] and supervised by the same experienced, trained assessor. After a 3-minute rest phase while sitting on the ergometer, participants started with 3 minutes of unloaded cycling followed by a ramp protocol with workload increments of 5-20 Watts per minute, depending on the participant's estimated physical fitness level, at the discretion of the test supervisor and aiming for an incremental phase duration between 8 and 12 minutes. Participants were instructed to cycle at a pedaling rate of 60-70 rpm. The exercise test was terminated in case of exhaustion, if the pedaling rate dropped <50 rpm, or if one of the stop criteria according to the American College of Sports Medicine guidelines was met.[15]

A calibrated breath-by-breath respiratory gas exchange system[c] was used for gas exchange and respiratory volume measurements. Heart rate was registered continuously using 12-lead electrocardiography.[b] Participants scored their perceived exertion every minute on the 6-20 Borg scale.[18]

Content validity of CPET

According to the COSMIN taxonomy, content validity is the degree to which the content of an instrument is an adequate reflection of the construct to be measured.[19] In the present study, content validity was defined as the degree to which VO_{2peak} assessed through CPET is an adequate reflection of maximal aerobic capacity. This was assessed by determining if certain criteria were attained during CPET for it to be considered a true test of maximal aerobic capacity.[10,20]

Establishing criteria for maximal CRE in NMD

Procedures

To establish an adequate set of criteria for maximal CRE, a group of experts was formed. The panel consisted of researchers and clinicians (ie, physicians) with expertise in exercise testing and in neuromuscular rehabilitation. The initial panel consisting of the 5 experts that were involved in the design of the study were all active in neuromuscular rehabilitation. Two additional experts with extensive expertise in the field of clinical exercise physiology were added to the panel.

Three meetings were held to reach consensus. The first meeting was to establish a subset of frequently applied criteria for maximal CRE.[15,21,22] In the second meeting, it was evaluated if these criteria were achieved at exercise intensities approximating maximal exercise; for each participant, the VO_2 at which each of the selected criteria occurred was determined and plotted relative to the measured VO_{2peak}. A mean relative exercise intensity of >80% at the group level was established as a minimal requirement for a criterion to be an adequate reflection of maximal CRE. The plots (fig 1) were used to select threshold values for each criterion (eg, RER, heart rate, and RPE), based on majority of votes in the panel. In the third meeting, based on all gathered information, the expert group decided on the selection of primary and secondary criteria, as well as the number of criteria that had to be attained, to confirm maximal CRE.

Criteria for maximal CRE

The following criteria were considered:

VO_2 plateau at peak exercise: Assessment of $VO_{2plateau}$ was done independently by 2 experienced raters (TV and EV) through visual inspection of the VO_2 vs time plots. A $VO_{2plateau}$ was present if both of the following criteria were met, according to the raters' clinical judgment: (1) a noticeable deceleration in the rise of oxygen uptake near the end of the test, despite increasing workload, which is distinct from the linear VO_2 increase under increasing workload prior to the deceleration; and (2) a rise in VO_2 under approximately 150 mL/min for the last minute of exercise.[23] Disagreement between raters was resolved by discussion to reach consensus, and if consensus was not reached, by a third rater (SO).

RER at peak exercise: RER_{peak} cutoff points of ≥1.00, ≥1.10, and ≥1.15 have been frequently used as criteria[10] and were evaluated in this study.

Heart rate at peak exercise: A peak heart rate ≥85% and ≥90% of the predicted maximal heart rate was evaluated. Predicted maximal heart rate was determined as $208 - (0.7 \times \text{age})$.[24]

RPE at peak exercise: The 6-20 Borg scale is widely used to subjectively measure exercise intensity.[25,26] In the current study, an RPE_{peak} ≥17 and ≥18 on the 6-20 Borg scale were evaluated.

Outcomes

Demographic data were collected (ie, age and sex), height, weight, and disease characteristics (ie, diagnosis, muscle strength, and use of walking aids). Muscle strength of the lower limbs was obtained by trained rehabilitation physicians by manual muscle testing according to the Medical Research Council (MRC) Scale.[27] The MRC scores of 4 major muscle groups involved during cycling were combined (ie, hip extensors, knee flexors, knee extensors, and ankle plantar flexors[28]) for both legs to form an MRC sum score of 8 muscle groups.

In addition, muscle strength of the knee extensors was assessed isometrically at a knee angle of 60 degrees with a fixed dynamometer[d] and was quantified as the sum score of the maximal voluntary torque of the knee extensors of both legs. Three repetitions

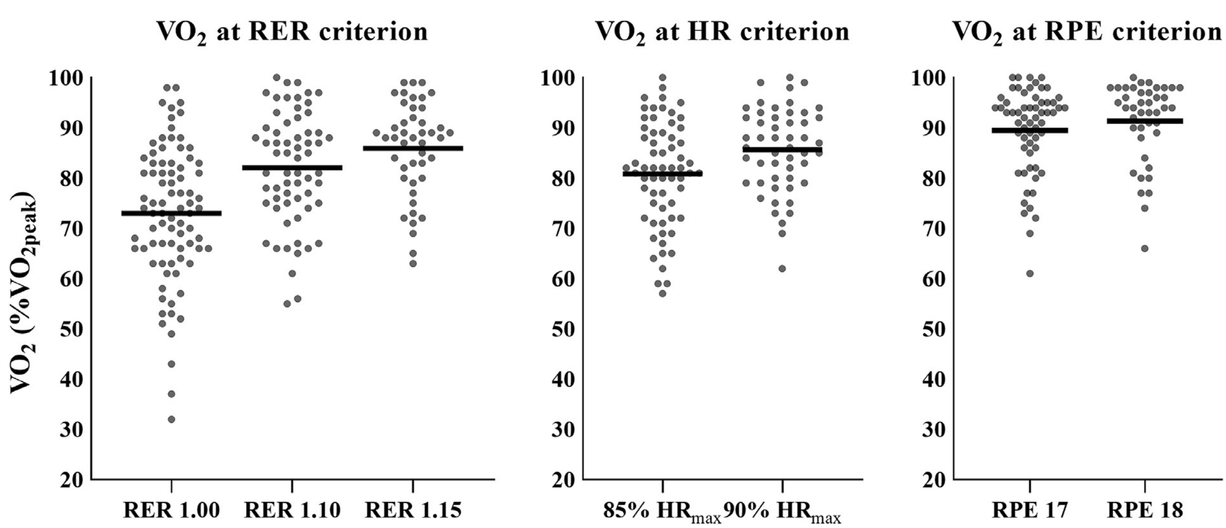

Fig 1 The exercise intensity at which frequently used criteria for maximal cardiorespiratory effort were reached, expressed as the VO_2 relative to the VO_{2peak}. The percentage of VO_{2peak} is shown at (1) an RER_{peak} of 1.00, 1.10, and 1.15; (2) 85% of predicted HR_{max} and 90% of predicted HR_{max}; and (3) RPE_{peak} 17 and RPE_{peak} 18. Each dot represents a single participant (n=86). HR, heart rate; HR_{max}, maximal heart rate.

were performed, and absolute peak torque in Newton-meters (Nm) and peak torque normalized for body weight (Nm/kg) were used for analyses. Only muscle groups with scores >3 on the MRC scale were measured. For MRC scores ≤3, we used 10 Nm as conservative estimation.

Data analysis

Analysis of CPET data was done using a self-developed MATLAB script. Outliers in the breath-by-breath respiratory gas exchange data (>2 SD from the 10-breath moving average) were removed. Breath-by-breath data were converted to second-by-second data using previous neighbor interpolation. The VO_{2peak}, RER_{peak}, and peak heart rate were then determined as the highest 15-second moving average achieved during maximal CPET.

Statistical analysis

Histogram inspection was used to test normality of the data. Data are presented as mean ± SD for normally distributed data and median (range) for nonnormally distributed data. Baseline characteristics (demographic data, anthropometric data, and disease characteristics) are reported using descriptive statistics, and differences in baseline characteristics between groups of NMD were analyzed with one-way analysis of variance or the Kruskal-Wallis H test as a nonparametric alternative, and Fisher exact tests, as appropriate. Content validity of VO_{2peak} assessment was expressed as the percentage of participants meeting the criteria for maximal CRE. Differences between the groups that achieved maximal and submaximal CRE were analyzed with independent samples *t* tests or Mann-Whitney *U* tests as nonparametric alternative, and Fisher exact tests, as appropriate. Differences between diagnosis groups were determined by one-way analysis of variance. An α level of 0.05 was used for all tests of statistical significance. Analyses were performed using SPSS version 28.0.[e]

Results

Participants

Ninety-one participants performed CPET. Exercise tests of 5 participants could not be used for this study for the following reasons: CPET was not performed on a cycle ergometer (n=2), missing raw data (n=2), and premature termination of the exercise test because of electrocardiographic abnormalities (n=1). Therefore, data of 86 participants were included in the current study. Demographic data, anthropometric data, and disease characteristics are shown in table 1. In addition to PPS (n=26) and CMT (n=35), the other NMD group (n=25) consisted of diseases originating in the muscle: congenital myopathy (n=7), myotonic dystrophy type 1 (n=4), limb girdle muscular dystrophy (n=4), inclusion body myositis (n=3), Becker muscular dystrophy (n=1), congenital muscular dystrophy (n=1), myotonic dystrophy type 2 (n=1), nemaline myopathy (n=1), and oculopharyngeal muscular dystrophy (n=1), except for myasthenia gravis (n=1) and chronic idiopathic axonal polyneuropathy (n=1).

Final set of criteria for a maximal CRE

Following the consensus meetings, the occurrence of a $VO_{2plateau}$ was chosen as primary criterion. Although the presence of a $VO_{2plateau}$ is generally indicative of maximal CRE, its absence does not necessarily mean that an individual has not reached maximal CRE.[29,30] Therefore, a set of secondary criteria was established for maximal CRE when a $VO_{2plateau}$ was not present.

Figure 1 and table 2 show that the evaluated criteria for maximal CRE occurred at intensity levels >80% of VO_{2peak}, except for RER_{peak} ≥1.00, (mean, 73% of VO_{2peak}). RER_{peak} ≥1.10, peak heart rate ≥85%, and RPE_{peak} ≥17 occurred at high intensity levels (means of 82%, 81%, and 89% of VO_{2peak}, respectively). Using stricter criteria (eg, RER_{peak} ≥1.15 instead of RER_{peak} ≥1.10) did not result in considerably higher intensities (ie, higher relative VO_2). Therefore, RER_{peak} ≥1.10, peak heart rate ≥85%, and RPE_{peak} ≥17 were considered as secondary criteria. Two of

Table 1 Characteristics of participants with PPS, CMT, or other NMD

	All Participants	PPS (n=26)	CMT (n=35)	Other NMD (n=25)
Demographic data				
Age (y)	58.0±13.9	66.9±6.9*,†	56.14±12.5*	51.4±16.7†
Sex (female)	51 (59%)	20 (77%)	20 (57%)	11 (44%)
Anthropometric data				
Height (cm)	172.1±9.8	166.0±10.0*,†	173.9±9.2*	175.8±7.4†
Weight (kg)	77.0±13.4	76.5±13.2	76.7±14.9	78.1±11.6
BMI (kg/m^2)	26.1±4.6	27.8±4.7	25.4±4.9	25.3±3.7
Disease characteristics				
Walking aid (Yes)	31 (36%)	13 (50%)	13 (37%)	5 (20%)
MMT sum score legs‡	35.2 (19-40)	31.9 (19-40)*,†	36.3 (26-40)*	37.0 (24-40)†

NOTE. Data are frequencies, mean ± SD for normally distributed data, or median (range) for nonnormally distributed data. Differences in baseline characteristics between groups of NMD were analyzed with Fisher exact tests for frequencies, one-way analysis of variance for normally distributed data, and the Kruskal-Wallis H test for nonnormally distributed data.

Abbreviations: MMT, manual muscle testing.

* $P<.05$, PPS vs CMT.

† $P<.05$, PPS vs other NMD.

‡ Sum score for muscle strength of the legs was calculated by adding 8 muscle groups, of which each muscle group had a score between 0 and 5; therefore, the sum score ranged from 0-40.

Table 2 Criteria for confirming maximal cardiorespiratory effort

Criterion	Criterion Attained, n (%)	Relative VO_2 ($\%VO_{2peak}$)
$VO_{2plateau}$	27 (31%)	-
RER_{peak} ≥1.00	82 (95%)	73 ± 14
RER_{peak} ≥1.10	63 (73%)	82 ± 11
RER_{peak} ≥1.15	47 (55%)	86 ± 9
HR_{peak} >85% of predicted HR_{max}	67 (69%)	81 ± 10
HR_{peak} >90% of predicted HR_{max}	42 (49%)	86 ± 8
RPE_{peak} ≥17	62 (72%)	89 ± 9
RPE_{peak} ≥18	43 (50%)	91 ± 8

NOTE. Data are frequencies (%) or mean ± SD.
Abbreviations: HR_{max}, maximal heart rate; HR_{peak}, heart rate at peak exercise.

these secondary criteria needed to be attained to confirm maximal CRE. A flowchart of the validity assessment for maximal CPET is shown in fig 2.

Content validity of maximal CPET

The criteria for confirming maximal CRE were attained in 71 of all 86 participants (83%). Table 2 shows the percentage of participants attaining each criterion. Of all participants, 3 (3.5%), 16 (18.6%), 33 (38.4%), and 34 (39.5%) attained none, 1, 2, and all 3 of the secondary criteria, respectively. Of the 15 participants that did not attain the established set of criteria, 8 (53%) did not reach an RER_{peak} ≥1.10, 12 (80%) did not reach a peak heart rate ≥85% of the predicted maximal heart rate, and 13 (87%) did not reach an RPE_{peak} ≥17.

Participant characteristics and CPET outcomes: maximal vs submaximal CRE

Table 3 shows characteristics and CPET outcomes for participants that attained maximal and submaximal CRE. Peak workload, VO_{2peak} and absolute and normalized median knee extensor muscle strength were significantly higher in participants achieving maximal CRE compared with participants reaching submaximal CRE (P<.05). The proportion of participants with submaximal CRE was significantly higher in the group with PPS (53%) compared to the group with CMT (13%), P=.014. Normalized knee extensor muscle strength was significantly lower in participants with PPS (1.62 Nm/kg) than in those with CMT (2.99 Nm/kg), P<.001.

Discussion

The following criteria were established to determine the content validity of VO_{2peak} assessment during CPET in NMD: a $VO_{2plateau}$ as the primary criterion, or 2 of 3 secondary criteria, namely RER_{peak} ≥1.10, peak heart rate ≥85%, and RPE_{peak} ≥17 (see fig 2). These criteria were attained by 71 of 86 participants (83%), indicating sufficient content validity. Peak workload, VO_{2peak}, and knee extension muscle strength were significantly higher in participants who attained maximal CRE compared to participants with submaximal CRE.

This study used actual CPET data and expert opinion to establish a set of criteria for confirming maximal CRE in NMD. A $VO_{2plateau}$, used as primary criterion, was found in only 31% of participants. This corresponds with findings in healthy and other clinical populations, where a $VO_{2plateau}$ occurred in <50% of the participants.[31-33] Therefore, as in other populations, secondary criteria were deemed necessary for confirming maximal CRE during CPET in NMD.

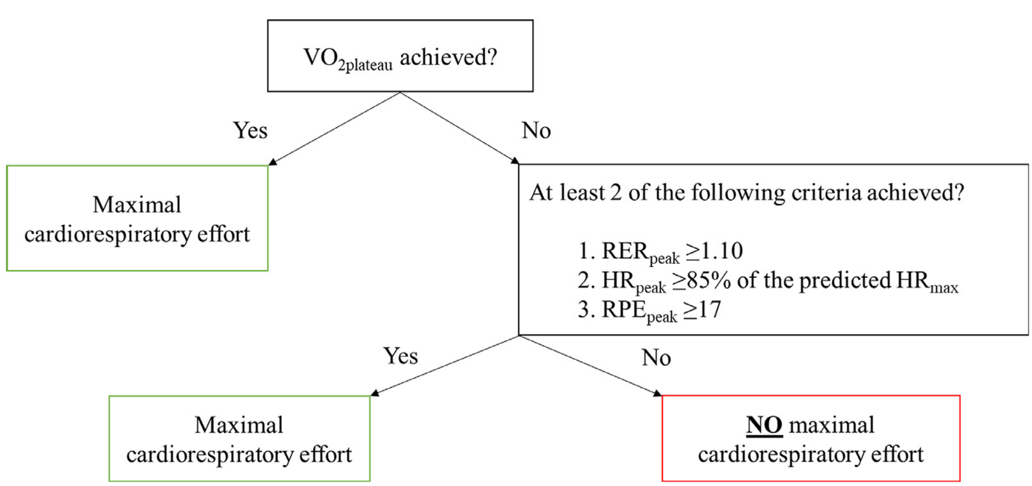

Fig 2 Flowchart of the assessment of maximal cardiorespiratory effort. Cardiorespiratory effort was considered maximal if the primary criterion ($VO_{2plateau}$) or 2 of the secondary criteria were achieved. Abbreviations: HR_{max}, maximal heart rate; HR_{peak}, heart rate at peak exercise.

Table 3 Participant characteristics and cardiopulmonary exercise testing outcomes: maximal versus submaximal cardiorespiratory effort during cardiopulmonary exercise testing

Variable	Maximal Cardiorespiratory Effort (n=71)	Submaximal Cardiorespiratory Effort (n=15)	*P*
Participant characteristics			
Age (y)	63.0 (23.0-79.0)	67.0 (41.0-77.0)	.156
Sex, female	39 (55%)	12 (80%)	.088
Height (cm)	173.2 (151.5-193.9)	167.5 (152.0-175.0)	.006†
Weight (kg)	77.0 (47.9-124.2)	77.8 (52.4-94.8)	.900
BMI (kg/m^2)	24.5 (16.8-42.9)	28.2 (17.5-33.5)	.009†
Walking aid, Yes	24 (34%)	7 (47%)	.384
MMT sum score legs*	37.3 (19.0-40.0)	33.0 (20.0-40.0)	.049†
Knee extensor strength (Nm)	186.3 (20.0-358.0)	95.5 (37.3-252.4)	.009†
Knee extensor strength (Nm/kg)	2.5 (0.3-4.5)	1.3 (0.4-3.6)	.004†
Exercise test outcomes			
Peak workload (W)	133.0 (37.0-266.0)	82.0 (39.0-135.0)	<.001†
Peak workload (W/kg)	1.7 (0.5-4.0)	1.0 (0.5-1.9)	<.001†
VO2peak (mL/kg/min)	21.0 (11.5-43.9)	16.6 (10.0-25.3)	.013†

NOTE. Data are frequencies (%) or median (range). Differences between the groups that achieved maximal and submaximal cardiorespiratory effort were analyzed with Fisher exact tests and Mann-Whitney *U* tests, as appropriate.

Abbreviations: CMT, Charcot-Marie-Tooth disease; MMT, manual muscle testing; PPS, post-polio syndrome; VO_{2peak}, oxygen uptake at peak exercise.

* Sum score for muscle strength of the legs was calculated by adding 8 muscle groups, of which each muscle group had a score between 0 and 5; therefore, the sum score ranged from 0-40.

† Statistical significance.

The RER_{peak} is a key secondary criterion in evaluating maximal CRE in exercise testing and also in NMD. The present study findings indicate that an RER_{peak} cutoff value of 1.00 is too low in NMD, as it typically occurred at exercise intensities <80% VO_{2peak}. An RER cutoff of 1.10 more accurately reflects high-exercise intensity and is thus recommended as criterion. It is important to realize though that the RER_{peak} is not applicable for certain NMD that were not part of the present study cohort; in metabolic myopathies, such as McArdle disease, RER_{peak} is known to be decreased,[34] whereas RER_{peak} during CPET is generally increased in mitochondrial myopathies.[35]

The use of peak heart rate as a criterion for valid VO_{2peak} assessment in NMD is often debated. A recent review stated that a low peak heart rate is expected when muscle metabolism is the primary limiting factor in CPET, because the test is terminated before maximally stressing the cardiovascular system.[12] However, the results of the present study suggest that, in the types of NMD studied, peak heart rate is a useful criterion, indicated by the consistent high-exercise intensities at which participants reached 85% of the predicted maximal heart rate. RPE_{peak} ≥17 was also included as secondary criterion; despite its subjective nature and a potential risk of distortion by noncardiopulmonary factors such as local muscle fatigue or pain,[36] the results of the present study suggest that an RPE_{peak} ≥17 accurately reflects near-maximal exercise in most of the participants.

The finding that 83% of the study cohort attained the established criteria for maximal CRE implies that CPET can be applied for valid assessment of maximal aerobic capacity (ie, VO_{2peak}) for most people with NMD. The value of 83% was within the range of 64%-100% reported in a recent systematic review on measurement properties for content validity of aerobic capacity measures in NMD.[10] Because types of NMD and CPET protocols differ between studies, the different (numbers of) criteria to confirm maximal CRE likely contributed to the wide range. In a study in which 100% of the participants attained maximal CRE, an RER_{peak} ≥1.00 was regarded sufficient for maximal CRE.[37] A study in which 64% of the participants attained maximal CRE considered 4 criteria: RER_{peak} ≥1.10, $VO_{2plateau}$, RPE_{peak} ≥7 on the 1-10 Borg Scale, and a peak heart rate ≥85% of the predicted heart rate reserve. Maximal CRE was confirmed when 3 of the 4 criteria were met.[38] The low prevalence of $VO_{2plateau}$ and the high number of criteria used in the study likely caused low-content validity. The present study further shows that the number of criteria that must be attained strongly affects the percentage of participants achieving maximal CRE. This underscores the importance of developing a standardized set of criteria to assess the content validity of VO_{2peak} assessment during CPET.[10,12] With the set of criteria used in the present study, together with the large sample size (>50) and an experienced trained CPET assessor, the main reasons for the increased risk of bias of earlier studies were avoided. The outcomes of this study strongly contribute to the quality of evidence for sufficient content validity of VO_{2peak} assessment in NMD.[10]

Participants who attained maximal CRE appear to have higher physical fitness levels and lower disease severity than participants with submaximal CRE. They had a significantly higher peak workload, VO_{2peak}, and knee extension muscle strength, and a lower body mass index. The lower knee muscle strength in participants with submaximal CRE likely contributes to the lower peak exercise values achieved by these participants.[39] Also, the proportion of participants with submaximal CRE was significantly higher in the group with PPS than those with CMT. This may be explained by the difference in distribution of muscle weakness between NMD. People with PPS typically develop proximal atrophy of the lower limbs, such as the quadriceps, reducing knee extensor strength.[40] This is also shown in table 1. In contrast, people with CMT often develop distal atrophy of the lower limbs, affecting smaller muscles less important for cycle exercise performance.[41]

Study limitations

A limitation to the study findings is that all participants had to be able to cycle on an ergometer and to follow the physical activity program. This limits the generalizability of the results to more severely affected people with NMD, for example, those that are wheelchair-bound and cannot be tested on a cycle ergometer. Furthermore, because of the relatively low number of the participants with submaximal CRE, and because multiple statistical tests were performed, increasing a potential type 1 error, the evaluation of between-group differences should be considered as exploratory.

Clinical implications

The present study findings indicate that CPET can be used for a valid assessment of maximal aerobic capacity in most people with NMD but that the validity is lower in more severely affected people. For this subgroup, alternative, submaximal, aerobic capacity measures may be considered, such as the first ventilatory threshold[42] and the oxygen uptake efficiency slope.[43] Next steps may be to identify determinants for attaining maximal CRE during CPET in a large study cohort including more severely affected people with NMD and to develop and evaluate clinimetric properties of submaximal aerobic capacity measures.

Conclusions

In general, persons with NMD attained maximal CRE during CPET. This study provides high quality evidence of sufficient content validity of VO_{2peak} as a maximal aerobic capacity measure. However, the validity of VO_{2peak} assessment was lower in more severely affected individuals, who had lower physical fitness. The criteria for valid VO_{2peak} assessment in this study (ie, $VO_{2plateau}$ as the primary criterion and RER_{peak} ≥1.10, peak heart rate ≥85% of the predicted maximal heart rate, and RPE_{peak} ≥17 as secondary criteria) can be used in future studies to improve standardization and comparison between CPET outcomes.

Suppliers

a. Lode Excalibur; Lode BV.
b. 12-lead electrocardiography monitor; CareFusion.
c. Oxycon Pro; Jaeger.
d. System 4; Biodex.
e. SPSS Statistics for Windows, version 28.0; IBM Corp.

Keywords

Aerobic exercise; Cardiorespiratory fitness; Maximal exercise test; Measurement properties; Neuromuscular disorders; Rehabilitation; VO_{2max}

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