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REVIEW

Cardiopulmonary exercise testing in neuromuscular disease: a systematic review

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ABSTRACT

Introduction: Cardiopulmonary exercise testing (CPET) is increasingly used to determine aerobic fitness in health and disability conditions. Patients with neuromuscular diseases (NMDs) often present with symptoms of cardiac and/or skeletal muscle dysfunction and fatigue that might impede the ability to deliver maximal cardiopulmonary effort. Although an increasing number of studies report on NMDs' physical fitness, the applicability of CPET remains largely unknown.

Areas covered: This systematic review synthesized evidence about the quality and feasibility of CPET in NMDs and patient's aerobic fitness. The review followed the PRISMA guidelines (PROSPERO number CRD42020211068). Between September and October 2020 one independent reviewer searched the PubMed/MEDLINE, EMBASE, SCOPUS, and Web of Science databases. Excluding reviews and protocol description articles without baseline data, all study designs using CPET to assess adult or pediatric patients with NMDs were included. The methodological quality was assessed according to the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) recommendations.

Expert opinion: CPET is feasible for ambulatory patients with NMDs when their functional level and the exercise modality are taken into account. However, there is still a vast potential for standardizing and designing disease-specific CPET protocols for patients with NMDs. Moreover, future studies are urged to follow the ATS/ACCP recommendations.

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KEYWORDS
Exercise test; exercise modality; feasibility; muscle disease; rehabilitation; aerobic fitness

1. Introduction

Neuromuscular diseases (NMDs) are a heterogeneous and complex group of inherited or acquired disorders involving one or more components of the motor unit (motor neuron, peripheral nerve, neuromuscular junction, and skeletal muscle) [1,2]. Because of the disease-specific muscle weakness and fatigue, these patients exhibit limited physical activity, contributing to deconditioning and creating a 'vicious cycle' of activity discouragement and overall deconditioning [3]. In addition to that, some subtypes of NMDs, such as patients with muscular dystrophy, also suffer from cardiomyopathy and conduction disorders, which also prevent them from fully engaging in exercise [3,4].

Cardiopulmonary exercise testing (CPET) is an incremental test with gas exchange measurement and is performed up to the tolerance limit or until indications for termination [5]. It provides the investigator with information on the integrative exercise response of multiple physiological systems (cardiovascular, pulmonary, hematopoietic, neuropsychologic, and skeletal muscle) to meet the increased metabolic demand for oxygen uptake and carbon dioxide production of the active muscles during exercise [5,6]. This is possible because the pattern of oxygen uptake (VO_2), ventilation (VE), and carbon dioxide output (VCO_2) measured breath by breath reflects the efficiency of the heart, lungs, blood circulation blood, pulmonary blood flow, and peripheral oxygen [5]. Therefore, the use of CPET is possible to distinguish the dominant physiological system that limits exercise performance (cardiac, pulmonary, muscle metabolism, or deconditioning), optimizing the therapeutic decision-making process [7].

The noninvasive feature of CPET and its usefulness lead to an increased interest in using it to assess exercise limiting factors and the efficacy of interventions in patients with NMDs. For example, Rapin et al. [8] were able to identify peripheral factors as the main limitation to exercise in adults with muscular dystrophies, metabolic myopathies, and hereditary peripheral neuropathies. Crescimanno et al. [9] observed a slight increase in the aerobic fitness of patients with glycogen storage disease type II in 36 months of enzyme replacement therapy, and Wiesinger et al. [10] prescribed and assessed the efficacy of a six-week aerobic training for adults with inflammatory myopathy.

Despite those informative findings using CPET in NMDs, no previous study has assessed the safety, quality, and applicability of CPET for this group. The study of such aspects is important because CPET is an intense stress test first developed to assess patients with cardiovascular and pulmonary diseases [6]. Most patients with NMDs have high levels of fatigue and present weaker muscles, more susceptible to contraction-induced muscle fiber injury, than patients with cardiac or

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Supplemental data for this article can be accessed here

Article highlights

- Standardization in CPET protocols is needed because of low adherence to ATS/ACCP recommendations;
- High completion rates and few adverse events support the feasibility of CPET in pediatric and adult patients with NMD;
- Low cardiopulmonary stress (e.g. low peak heart rate), despite high metabolic demand (e.g. peak respiratory exchange ratio >1), might be a feature of NMDs, except for patients with glycogen storage disease or motor neuron disease;
- The upright cycle ergometer with ramp-wise increments is advisable to assess various ambulatory adults and some pediatric patients with NMD;
- On the treadmill, the Naughton and the Dubowy protocols are alternatives for some adults and the young patients with NMD when an upright cycle ergometer is not available.

pulmonary disease. Therefore, an intense test as the CPET could be detrimental for some NMDs.

Regarding that, this review has four aims: (1) to identify and synthesize evidence about the available CPET protocols for NMDs, (2) to evaluate the quality and feasibility of these protocols, (3) to assess the aerobic fitness of patients with NMDs and (4) to provide recommendations about the use of CPET for this group. We are investigating these properties because the technical quality and delivered effort's quality guarantee the appropriate interpretation of CPET outcomes in clinical practice and research. Moreover, information about completion rate and adverse events can address whether the CPET protocols are practical and suitable for this group or if adaptations are needed. We hypothesize that the available CPET protocols are feasible for patients with a high functional level, such as ambulatory patients, and that innovations and adaptations are needed to use this test in weaker patients.

2. Methods

This systematic review of the literature is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11], and it was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) under the number CRD42020211068.

2.1. Data source and search strategy

Following the approach of Bramer et al. [12], we created a systematic search strategy for the databases MEDLINE using the MESH thesaurus terms for 'NMD' and 'CPET.' NMDs included muscular dystrophies, congenital myopathies, spinal muscular atrophies, amyotrophic lateral sclerosis, post-poliomyelitis, polyneuropathies, Guillain-Barre syndrome and myasthenia gravis. Consecutively, this search strategy was adapted to the databases EMBASE, SCOPUS, and Web of Science. An example of this search strategy is shown in Supplementary Material A.

Between September and October 2020, one reviewer (GD) independently searched all databases and selected the relevant articles based on titles and abstracts. Subsequently, the full-text articles of selected studies were checked for compliance with the selection criteria described below. If there was doubt, a second reviewer (TT) was consulted for the decision on the included articles. Relevant reference lists were also hand-searched to identify additional records. The selection process was supported by an online version of Endnote software (Endnote Clarivate Analytics®).

2.2. Selection criteria for eligible articles

2.2.1. Study design and language

Cross-sectional observational studies, cohort-studies, case-reports or control studies, randomized or quasi-randomized clinical trials, and protocol descriptions of clinical trials with baseline data written in English, Portuguese, Spanish, Dutch, German, or French, were included. Narrative literature reviews, systematic reviews, protocol descriptions of clinical trials without baseline results, or studies of which the full text was not available, were excluded.

2.2.2. Participants

Patients with NMD, without restriction to sex and age, were included.

Studies that evaluated patients with diabetic or compression neuropathies, chronic fatigue syndrome or fibromyalgia, radiculopathy, spinal cord injuries, complex regional pain syndrome, or additional diagnoses to the NMD reported on the study's inclusion and exclusion criteria were excluded.

2.2.3. Methodology

Studies that performed a CPET on patients with NMDs to assess aerobic fitness or intervention effects on aerobic fitness (e.g. training program, diet or medication), or studies that assessed the psychometric properties of CPET in this group, were included. Studies that did not describe the exercise modality, the interval and/or workload increments, or the velocity and/or grade increments of the CPET protocol, were excluded; likewise, studies, reporting submaximal exercise tests, field tests, electronically assisted tests, or anaerobic tests, were excluded.

2.3. Data extraction

Using a standard form, one reviewer (GD) extracted data from the included studies about (1) characteristics of the population (Tables 1 and 2), (2) characteristics of the CPET (Tables 3 and 4), (3) the quality and feasibility of CPET (Tables 5 and 6) and (4) aerobic fitness of the patients (Tables 7 and 8). If there was doubt, a second reviewer (TT), was consulted. The percentages of the predicted peak oxygen uptake (VO_{2peak}) and peak heart rate (HR_{peak}) were calculated following reference values for exercise modality and age [7,13–15].

2.4. Methodological quality

The recommendations of the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) for CPET methodology, which include standard information about equipment, modality, protocol, conduct of the test, monitoring, safety and personal issues, were used to determine the methodological quality of included studies [6].

Table 1. Study population characteristics – Adults.

Exercise Modality	NMD sub classification	Disease	Studies (n)	Patients (n)	Sex (M/F)	Age (Mean-SD)	Range
UPC	GSD	GSD II, V, VII	19	114	65/49	39.0 (11.4)	16–70
	MitoD	MELAS, PEO, RRFD, CPTD	29	325	139/186	38.0 (10.7)	13–96
	GSD, MitoD	_*	1	9	6/3	49.0	28–66
	IHM	MD, FSHD, LGMD, CMyo, CCD, NM, HMM Dystrophies, Myopathies	8	111	74/37	35.1 (8.6)	21–65
	IM	DM, PM	6	78	23/55	51.2 (11.6)	37–78
	MND	ALS, PPS	8	200	86/39	47.5 (7.4)	22–70
	PND	HMSN	3	27	20/7	44.0 (8.5)	20–69
	NMJD	MG	2	16	8/8	54.5 (17.2)	_
	Mix*	HMSN, Dystrophies, Myopathies	2	17	15/2	29.0 (10.4)	16–49
RC	MND	SMA	1	14	11/3	27.0 (16.0)	10–48
SRC	IHM	LGMD, MD	1	6	4/2	34.0 (5.1)	_
	PND	HMSN	1	2	0/2	44.5	_
T	GSD	GSD II, V	3	17	12/5	45.2 (15.2)	16–72
	MitoD	_*	4	70	32/38	33.2 (11.7)	13–60
	IM	DM	1	45	17/28	29.0 (12.0)	10–51
	MND	ALS, PPS	2	76	44/32	54.0 (10.5)	54–76
	PND	HMSN	1	1	1/0	51.0	_
AC	MND	PPS	2	39	8/7	34.2 (4.5)	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; T: treadmill; AC: arm-crank ergometer; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; PND: peripheral nerve disorders; NMJD: neuromuscular junction disorders; CM: cardiomyopathy; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PEO: progressive external ophthalmoplegia; RRFD: ragged red fiber disease; CPTD: carnitine palmityl transferase deficiency; MD: myotonic dystrophy; FSHD: facioscapulohumeral muscular dystrophy; LGMD: limb-girdle muscular Dystrophy; CMyo: congenital myopathy; CCD: central core disease; NM: nemaline myophathy; HMM: hereditary myosin myopathy; MS: multiple sclerosis; DM: dermatomyositis; PM: polymyositis; ALS: amyotrophic lateral sclerosis; PPS: post-polio syndrome; SMA: spinal muscular atrophy; MG: myasthenia gravis; HMSN: hereditary motor and sensory neuropathy; n: number; m: male; f: female; SD: standard deviation; -: not reported; * not specified.

Table 2. Study population characteristics – Pediatric.

Exercise Modality	NMD sub classification	Disease	Studies (n)	Patients (n)	Sex (M/F)	Age (Mean-SD)	Range
UPC	GSD	GSD Ia, III, VII	1	3	2/1	12.2 (1.0)	12–13
	MitoD	MCAD, SCAD,MADD	3	13	9/4	11.0 (6.0)	8–20
	IHM	DMD, BMD	3	23	23/0	9.4 (2.7)	5–20
	IM	JDM	7	114	43/55	11.0 (3.6)	6–27
SC	IM	JDM	1	4	3/1	15.7 (3.5)	_
T	GSD	GSD V	1	1	1/0	8.0	_
	IM	JDM	4	52	15/27	11.0 (2.6)	5–18

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; SC: supine cycle ergometer; T: treadmill; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; MCAD: medium-Chain Acyl CoA; SCAD: short-Chain AcylCoA dehydrogenase deficiency; MADD: Multiple AcylCoA dehydrogenase deficiency; DMD: duchenne muscular dystrophy; BMD: becker muscular dystrophy; JDM: juvenil dermatomyositis; n: number; m: male; f: female; SD: standard deviation; -: not reported.

We created an adapted list (Supplementary Material B) and scored all included articles on 18 different criteria. The required information was collected and double-checked by a reviewer (GD), and for each criterion met, an article was attributed one point score. Additionally, a sum score was calculated and the studies were classified as low quality (≤7 points), sufficient quality (>7 points), moderate quality (11 to 14 points) and high quality (≥14 points of the maximum score of 18).

2.5. Analysis and data synthesis

The information on CPET protocols and outcome parameters obtained from the included studies were qualitatively summarized in overview tables and text. To facilitate the interpretation, the data were grouped based on the subclassifications of the NMDs and the exercise modality. The NMDs were grouped as: (1) Glycogen storage disorders (GSD), (2) Mitochondrial disorders (MitoD), (3) Inherited myopathies (IHM), (4) Inflammatory myopathies (IM), (5) Motor neuron disorders (MND), (6) Peripheral nerve disorders (PND) and (7) Neuromuscular junction disorders (NMJD) [19]. The exercise modality was classified as upright (UPC), recumbent (RC), semi-recumbent (SRC), and supine (SC) cycle ergometer, arm-crank (AC), and treadmill (T).

The quality of the CPET performance was based on the minimum test duration recommended for age range, and the number of patients that achieved the criteria of maximal effort (Tables 5 and 6). The feasibility of CPET was determined based on the percentage of patients that completed the tests and the number of adverse events reported (Tables 5 and 6), and the number of patients who achieved at least 80% of the predicted VO_{2peak} considering age and exercise modality (Tables 7 and 8). The studies with sufficient quality scores on the ATS/ACCP adapted list (>7 points), and which met the quality and feasibility criteria that supported the recommendations on how to test patients with NMDs, were included (Tables 5, 6, 9, 10).

3. Results

A total of 3618 articles were identified from the databases search after removing the duplicates, and another 26 articles were identified from additional sources (Figure 1). After the initial screening, 227 articles were included and assessed for eligibility. Ninety-two studies were included in the quantitative analysis, of which 74 articles assessed adults, and 18 articles assessed children and adolescents.

3.1. Study design

Most studies in adults (59%, n = 44) [8,9,20–61] and pediatric populations (61%, n = 11) used a cross-sectional design [62–72] (Supplementary Material C). Forty-six percent of the adult studies (n = 34) used CPET outcomes to determine the metabolic and exercise response of patients with NMDs [8,20,21,23,24,26–31,33–35,37–44,46–49,51,57,59–61,73–75], and 38% of studies (n = 28) to prescribe exercise intensity and assess the efficacy of an intervention, medication or diet supplement [9,10,58,76–100]. In the pediatric population, most of the studies (61%, n = 11) used CPET outcomes to understand the metabolic and exercise response [63,67–72,101–104], and only 17% of the studies (n = 3) aimed to prescribe exercise intensity and assess the efficacy of an intervention or another therapy [105–107].

3.2. Characteristics of the population

A total of 1237 adults (m, 625; f, 513) and 210 children and adolescents (m, 96; f, 88) with NMD were assessed in the included studies (n = 92) (Tables 1 and 2). Three articles did not report the gender of patients [64,65,76]. An overview of the included studies is shown in the Supplementary Material C. In general, the adult patients were ambulatory (with or without assistive devices) or able to cycle [8,9,20–26,73,76–84,108]. They were inactive, with moderate exercise intolerance [9,25,27–31,74–88], and did not have symptomatic cardiac or pulmonary disease [23,26,31–36,73,75,77,89–92]. The pediatric patients were also ambulatory with or without using assistive devices [63,66,101] and sedentary [105,106]. Specifically, for patients with inflammatory myopathy, three studies assessed patients with active and inactive myositis [67,68,102], and two other studies only assessed patients with active [69] and inactive myositis [70].

3.3. Characteristics of the CPET

Information about the CPET protocol is presented in Tables 3 and 4. The upright cycle ergometer exercise modality for CPET was used in 84% (n = 62) of the adult studies [8,10,20–31,34,36,38–44,46–56,59,61,66,73–80,83,85–88,90–92,94–100,108], evaluating most adult patients with mitochondrial disease (n = 325) and 67% (n = 12) of pediatric studies [63,65–

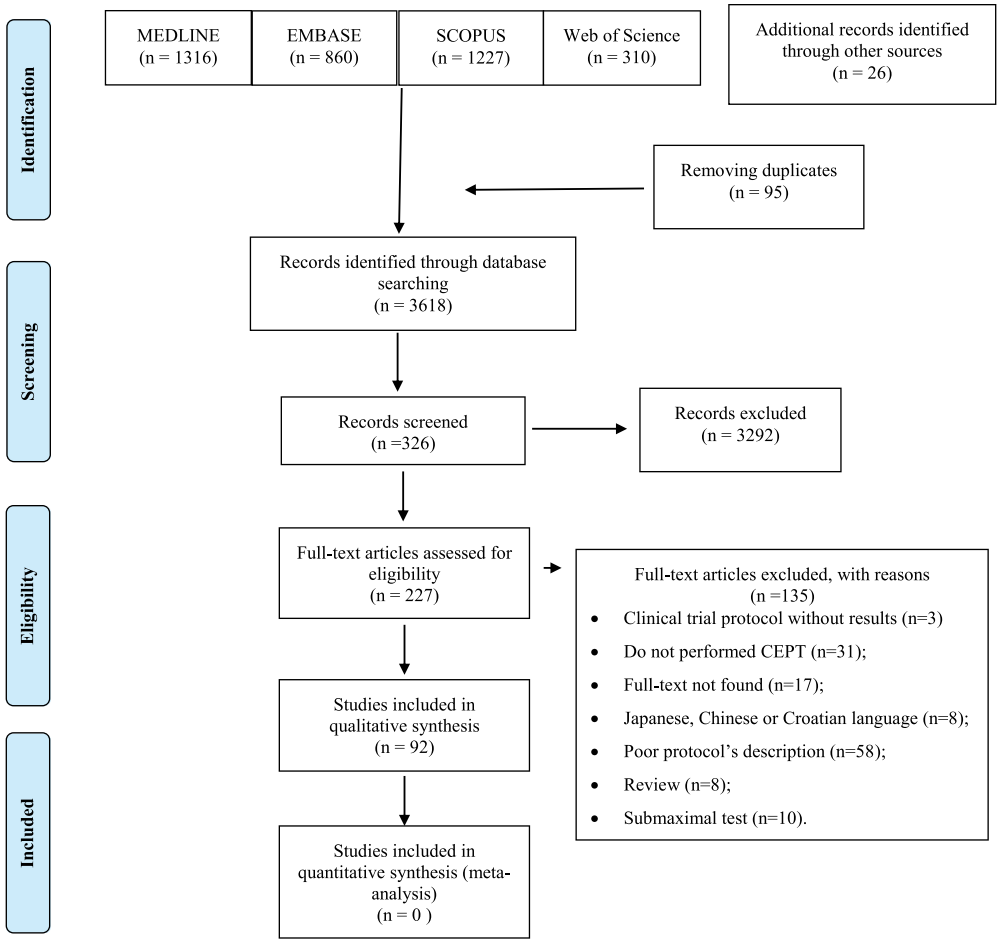

Figure 1. Flowchart of search and selection process.

69,72,101–103,106] and young patients with inflammatory myopathy (n = 114). Most upright cycle ergometers were electromagnetically braked (48%, n = 30/62 and 83%, n = 10/12, adults and children, respectively) [22,23,25–29,31,34,35,38,39,41,44,52–54,58,59,63,65–69,79,83,85,88,90,95–98,102,103,106,108]. The treadmill was only used in 13% (n = 10/74) of the adult [9,33,37,42,45,57,60,82,89,93] and 28% (n = 5/18) of pediatric studies [62,64,104,105,107], and most studies assessed adult patients with motor neuron disease (n = 76) and young patients with inflammatory myopathy (n = 52). In both adult and pediatric populations, few studies adopted other exercise modalities. The recumbent cycle ergometer (n = 1) [81], semi-recumbent cycle ergometer (n = 1) [46], and arm-crank ergometer (n = 2) were only reported in adults [32,74], and one study assessing children/adolescents used a supine recumbent cycle ergometer [70]. Moreover, two studies used more than one device: the upright cycle ergometer and treadmill, and the upright cycle ergometer and arm-crank [42,74].

In the adult population, 42% of studies with the upright cycle ergometer (n = 26) [8,22,23,28,34–36,40,43,44,56,68,73,75,76,79,80,86,90,91,94–97,99,100], three studies with the treadmill [37,89,93] and one with the recumbent cycle ergometer [81] and arm-crank [32] reported the warm-up as part of the CPET protocol. For the pediatric population, more than half of the studies using the upright cycle ergometer (67%, n = 8/12) [63,66,67,69,72,102,103,106], and one study using the treadmill [104] and supine cycle ergometer [70] reported the warm-up period (Tables 3 and 4). This initial phase of the protocol was most often performed by adults with motor neuron disease (n = 172) and by children with inflammatory myopathies (n = 76).

Concerning the exercise protocol and work increment for cycle ergometers, most studies in the adult population used step protocols (73%, n = 48/66) [10,20,22,24–26,29–31,34,38,39,41–44,46–53,55–59,61,74,75,77,78,80,83,84,86–88,90–92,94–96,98,99,108] and individualized workload increments (62%, n = 41/66) [8,19,22–25,27,28,30–32,36,40,42,44,46,47,49–52,54–56,58,59,61,74,76,80,81,84,85,88,92,96–98,100]. Some exceptions were the studies with inflammatory myopathies at the upright cycle ergometer that used set workload increments (83%, n = 5) (Table 3) [10,21,43,48,87]. This protocol selection for the upright cycle ergometer differs from the one observed in the studies that assessed children and adolescents, where most upright cycle ergometer studies use a ramp protocol, which is characterized by the continuous increase of work rate, and individualized increments of workload (75%, n = 9/12) [66,67,69,71,72,101–103,106]. Only for the supine cycle ergometer was a step protocol used (Table 4) [67]. For treadmills, the protocol that was used varied between the studies. The Naughton (speed increment: 0.8 km/hr and grade: 3.5% each 3 minutes) and the Bruce protocols (speed increment: 1.3–1.5 km/hr and grade: 2% each 3 minutes) were selected for the adult population with glycogen storage disorders (n = 2) [9,42,57], and a protocol developed by Ortega [109] (constant self-selected speed and grade increment in 5% each 3 minutes) was selected for patients with mitochondrial disorders (n = 2) [33,41]. In

Table 3. Characteristics of CPET – Adults.

Exercise Modality	NMD sub classification	Disease	Studies (n)	Warm-up (n)	Ergometer (n)		Exercise protocol (n)		Work increment (n)	
					M	E	R	S	Set	Ind.
UPC	GSD	GSD II, V, VII	19	5	1	9	2	17	5	14
	MitoD	MELAS, PEO, RRFD, CPTD	29	8	2	21	7	22	9	20
	GSD, MitoD	_*	1	1	_	_	1	1	_	1
	IHM	MD, FSHD, LGMD, CMyo, CCD, NM, HMM Dystrophies, Myopathies	8	4	1	2	2	7	1	7
	IM	DM, PM	6	1	_	2	1	5	5	1
	MND	ALS, PPS	8	5	1	2	3	5	3	5
	PND	HMSN	3	3	1	2	2	2	1	2
	NMJD	MG	2	2	1	1	_	2	_	2
	Mix*	HMSN, Dystrophies, Myopathies	2	1	2	1	_	2	1	1
RC	MND	SMA	1	1	_	1	1	_	_	1
SRC	IHM	LGMD, MD	1	_	_	_	_	1	_	1
	PND	HMSN	1	_	_	_	_	1	_	1
AC	MND	PPS	2	1	_	_	1	_	1	1

Exercise Modality	NMD sub classification	Disease	Studies (n)	Warm-up (n)	Exercise protocol				
					Naughton [16]	Bruce [17]	Balke [18]	Ortega [109]	Other [89]
T	GSD	GSD II, VPompe, McArdle	3	_	2[&]	2	_	_	_
	MitoD	_*	4	_	1	1	_	2	_
	IM	DM	1	1	_	_	1	_	_
	MND	ALS, PPS	2	1	1	_	_	_	1
	PND	HMSN	1	1	_	_	1	_	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; T: treadmill; AC: arm-crank ergometer; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; DAMC: disorders of activation of muscle contraction; IM: inflammatory Myopathies; PND: peripheral nerve disorders; NMJD: neuromuscular junction disorders; CM: cardiomyopathy; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PEO: progressive external ophthalmoplegia; RRFD: ragged red fiber disease; CPTD: carnitine palmityl transferase deficiency; MD: myotonic dystrophy; FSHD: facioscapulohumeral muscular dystrophy; LGMD: limb-girdle muscular Dystrophy; CMyo: congenital myopathy; CCD: central core disease; NM: nemaline myophathy; HMM: hereditary myosin myopathy; DM: dermatomyositis; PM: polymyositis; ALS: amyotrophic lateral sclerosis; PPS: post-polio syndrome; SMA: spinal muscular atrophy;; MG: myasthenia gravis; CM: cardiomyopathy; FA: friedreich's ataxia; BTHS: barth syndrome; HMSN: hereditary motor and sensory neuropathy; n: number of studies; m: mechanically; E: electrically; R: ramp; S: step; Ind.: individualized; min: minute. SD: standard deviation; -: not reported; * not specified; [&] One study used two different protocols.

Table 4. Characteristics of CPET – Pediatric.

Exercise Modality	NMD sub classification	Disease	Studies (n)	Warm-up (n)	Ergometer (n)		Exercise protocol (n)		Work increment (n)	
					M	E	R	S	Set	Ind.
UPC	GSD	GSDIa, III, VII	1	_	_	_	1	_	_	1
	MitoD	MCAD, SCAD,MADD	3	1	_	1	3	_	1	2
	IHM	DMD, BMD	3	1	_	2	2	1	1	2
	IM	JDM	7	5	_	7	5	2	1	6
SC	IM	JDM	1	1	1	_	_	1	_	1

Exercise Modality	NMD sub classification	Disease	Studies (n)	Warm-up (n)	Exercise protocol			
					Dubowy [15]	Bruce [17]	Balke [18]	Pérez [104]
T	GSD	GDS V	1	1	_	_		1
	IM	JDM	4	_	1	_ 3	_	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; SC: supine cycle ergometer; T: treadmill; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; CM: cardiomyopathy; MCAD: medium-Chain Acyl CoA; SCAD: short-Chain AcylCoA dehydrogenase deficiency; MADD: Multiple AcylCoA dehydrogenase deficiency;DMD: duchenne muscular dystrophy; BMD: becker muscular dystrophy; JDM: juvenil dermatomyositis; BTHS: barth syndrome; FA: friedreich's ataxia; n: number of studies; m: mechanically; E: electrically; R: ramp; S: step; Ind.: individualized; min: minute; -: not reported; * not specified .

children and adolescents, the Bruce protocol was used to assess patients with inflammatory myopathy in 75% (n = 3) of articles [62,64,107] (Table 4).

3.4. Quality of test performance

3.4.1. Test duration

Seventeen studies (23%) in adults and eight (44%) studies in children reported the duration of the CPET. From those, four studies assessing adult patients with inflammatory myopathies (n = 1 study, 11 patients), mitochondrial disorders (n = 2 studies, 16 patients) and glycogen storage disorders (n = 1 study, 1 patient) in the upright cycle ergometer presented a mean duration below eight minutes [20,21,86,108] (Table 5). All pediatric studies reported a mean duration of the CPET above eight minutes [62–64,66,68,70,105,107].

3.4.2. Criteria of maximal effort

Concerning maximal effort during the CPET, 22 studies with adult NMDs [8,9,25,29,31,32,37,43,44,47,58,59,61,76,81,88,89,92,94,98,100,108] and seven studies with pediatric NMDs presented criteria for maximal effort [37,62,64,66,68,101,103] (Table 3a and b). From these studies, adult patients with glycogen storage disorders and motor neuron disease most often performed a maximal CPET in the upright cycle ergometer (98%, n = 42, and n = 94 patients) [23,24,36,41,76,96,100]. More than 60% of the adults with mitochondrial disorders (n = 24), inherited myopathies (n = 11), inflammatory myopathies (n = 13), and peripheral nerve disorders (n = 12) met the criteria of maximal CPET in the upright cycle ergometer [8,23,28,41,43,44,48], and 64% of patients with motor neuron disease (n = 9) and 75% of patients with inflammatory myopathies (n = 6) achieved the criteria in the recumbent cycle ergometer and treadmill [9,81].

In the pediatric studies, more than 90% of patients with mitochondrial myopathy (n = 2) and inflammatory myopathy (n = 10 and n = 4) met the maximal criteria in the upright cycle ergometer and supine cycle ergometer [67,70,101] (Table 6). This percentage was lower in inflammatory myopathies (67%, n = 10) on the treadmill [62] and in inherited myopathies (11%, n = 1) on the upright cycle ergometer [66] (Table 6).

3.5. Feasibility of CPET

3.5.1. Measurement completion

From most of the included studies, it was possible to extract the number of patients who completed the CPET (Tables 5 and 6). In a few articles that used the upright cycle ergometer to assess adult patients with glycogen storage disorders (26%, n = 5) [22,30,35,42,53], mitochondrial disorders (27%, n = 8) [22,23,42,50,51,85,90,95], inherited myopathies (37%, n = 3) [22,50,99], motor neuron disease (75%, n = 6) [23,24,26,73–75], peripheral nerve disorders (67%, n = 2) [20,77], myasthenia gravis (n = 2) [22,79] and a mix of diseases (n = 2) [22,91], the information on feasibility was missing (Table 5). In contrast, studies assessing children/adolescents clearly present this information (Table 6).

Considering only the studies that reported the completion rate, three adults with mitochondrial disorders were unable to finish the CPET in the upright cycle ergometer, one due to syncope [20,34] and the other two because of an inability to cycle. Difficulties in cycling were also reported in another six patients with motor neuron disease [48]. In treadmill tests, only one adult with glycogen storage disorders discontinued the CPET, because of dizziness [57] (Table 5). Moreover, in the test performed at the upright cycle ergometer, three pediatric patients (with glycogen storage disorder, mitochondrial disorder, and inherited myopathy) did not complete the CPET. For the patient with glycogen storage disorder, the reason was an intense myalgia episode; for the other two patients, no explanation was given [72] (Table 6).

Table 5. Quality and feasibility of CPET – Adults.

Exercise Modality	NMD sub classification	Disease	Studies (n)	Quality of test performance					Feasibility						Safety	
				Duration		Criteria of maximal effort			Completion rate		Adverse events		Perception exertion			
				Studies (n)	Time	Studies (n)	Criteria	Patients (%)	Studies (n)	Patients (%)	Studies (n)	Event (n)	Studies (n)	Scale/ grade	Studies (n)	Parameters
UPC	GSD	GSD II, V, VII	19	4	11.0	4	HR_{peak} ≥85% of predicted* RER_{peak}>1.1 Borg≥7	98	14	100	4	0	3	Borg 0–20/ 19.0	_	_
	MitoD	MELAS, PEO, RRFD, CPTD	29	4	9.4 (2.7)	6	HR_{peak} = [&] or >80% of predicted[&]; RER_{peak} ≥1.1–1.2 Borg≥7	63	21	99	2	0/1 (Syncope)	5	Borg 0–10/ 8.0 (1.3)	_	_
	GSD, MitoD	_*	1	1	10.8	1	HR_{peak}>85% of predicted[#], RER_{peak} >1.1, Borg≥7	44	1	100	_	_	_	_	_	_
	IHM	MD, FSHD, LGMD, CMyo, CCD, NM, HMM Dystrophies, Myopathies	8	3	13.0	3	HR_{peak}>85% of predicted[& or #]; RER_{peak} >1.0–1.1, Borg≥7 or 17–19.	65	5	100	1	1 (CPK>1000) [FSHD]	2	Borg 0–20/ 19.0 (1.0) Borg 0–10/10.0	1	CPK
	IM	DM, PM	6	1	5.8 (2.4)	2	HR_{peak}>90% of predicted[&]; RER_{peak} ≥1.2; BL>6.0 mmol; Δph>0.04; VR<20%; EqO2 > 40	62	6	100	3	0	2	Borg 0–20/ 19.0 (0.4)	_	_
	MND	ALS, PPS	8	2	15.3 (-)	1	RER_{peak} >1.1	98	2	100	2	0	2	Borg 0–20/ 18.0 Borg 0–10/7.0 (4.0)	_	_
	PND	HMSN	3	1	10.8	1	HR_{peak}>85% of predicted[#], RER_{peak} >1.1, Borg≥7	67	1	100	_	_	1	Borg 0–10/ 10.0	1	CPK<170 IU·L
	NMJD	MG	2	_	_	1	HR_{peak}≥ predicted**, RER_{peak} ≥1.2, BL>8.0 mmol/L, Borg≥17	_	_	_	_	_	_	_	_	_
	Mix*	HMSN, Dystrophies, Myopathies	2	_	_	_	_	_	_	_	_	_	_	_	_	_
RC	MND	SMA	1	_	_	1	OMNI Scale≥8 RER_{peak} >1.0	64	1	100	1	0	_	_	_	_
SRC	IHM	LGMD, MD	1	_	_	_	_	_	1	100	_	_	1	Borg0-20/ 16.0 (1.0)	_	_
	PND	HMSN	1	_	_	_	_	_	1	100	_	_	1	Borg0-20/ 16.0 (1.0)	_	_
T	GSD	GSD II, V	3	3	9.4 (5.5)	1	HR_{peak} ≥85% of predicted[&] RER_{peak}≥1.1	_	3	94	1	1 (Dizziness)	2	Borg 0–10/ 8.5 (1.1)	_	_
	MitoD	_*	4	3	12.1 (3.4)	1		_	4	100	_	_	2	Borg 0–10/ 8.4 (2.1)	_	_
	IM	DM	1	_	_	1	HR_{peak}>80% of predicted[&]	75	1	100	_	_	1	Borg 0–20/ 18.0 (17.0–19.0)	_	_
	MND	ALS, PPS	2	_	_	1	HR_{peak}>75% of predicted[&], 55–65% of predicted VO_2	_	2	100	_	_	_	_	_	_
	PND	HMSN	1	1	25.0	1	_	_	1	100	_	_	_	_	_	_

(*Continued*)

Table 5. (Continued).

Exercise Modality	NMD sub classification	Disease	Studies (n)	Quality of test performance					Feasibility				Perception exertion		Safety	
				Duration		Criteria of maximal effort			Completion rate		Adverse events					
				Studies (n)	Time	Studies (n)	Criteria	Patients (%)	Studies (n)	Patients (%)	Studies (n)	Event (n)	Studies (n)	Scale/ grade	Studies (n)	Parameters
AC	MND	PPS	2	1	9.6 (1.9)	1	BL>8.0 mmol	_	2	100	_	_	2	Borg 0–20/ 18.2 (0.21)	_	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; T: treadmill; AC: arm-crank ergometer; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; DAMC: disorders of activation of muscle contraction; IM: inflammatory Myopathies; PND: peripheral nerve disorders; NMJD: neuromuscular junction disorders; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PEO: progressive external ophthalmoplegia; RRFD: ragged red fiber disease; CPTD: carnitine palmityl transferase deficiency; MD: myotonic dystrophy; FSHD: facioscapulohumeral muscular dystrophy; LGMD: limb-girdle muscular dystrophy; CMyo: congenital myopathy; CCD: central core disease; NM: nemaline myophathy; HMM: hereditary myosin myopathy; MS: multiple sclerosis; DM: dermatomyositis; PM: polymyositis; ALS: amyotrophic lateral sclerosis; PPS: post-polio syndrome; SMA: spinal muscular atrophy;; MG: myasthenia gravis; HMSN: hereditary motor and sensory neuropathy; n: number of studies; %: percentage of patients; HR_{peak}: heart rate peak; RER_{peak}: respiratory exchange ratio; OMNI/Borg: scale of perception exertion; PE: perception exertion BL: blood lactate level; Δph: delta of blood ph; VR: ventilatory reserve; EqO_2: ventilatory equivalent for oxygen; SD: standard deviation; CPK: creatine phosphokinase; mmol: millimol; U.L: units per liter -: not reported; * not specified.*210-0.65 x age; &220-age; #(210–0.65 x age); **(208–0.7xage)-10.

Table 6. Quality and feasibility of CPET – Pediatric.

Exercise Modality	NMD sub classification	Disease	Studies (n)	Quality of test performance					Feasibility				Perception exertion		Safety	
				Duration		Criteria of maximal effort			Completion rate		Adverse events					
				Studies (n)	Time	Studies (n)	Criteria	Patients (%)	Studies (n)	Patients (%)	Studies (n)	Event (n)	Studies (n)	Scale/ grade	Studies (n)	parameters
UPC	GSD	GSD Ia, III, VII	1	_	_	_	_	_	1	67	1	1 Myalgia	_	_	_	_
	MitoD	MCAD, SCAD, MADD	3	_	_	1	HR_{peak}>180 bpm; RER_{peak} ≥1.0	100	3	92	_	_	_	_	_	_
	IHM	DMD, BMD	3	2	8.1 (1.4)	1	HR_{peak}>180 bpm; RER_{peak} ≥1.0	11	3	96	2	1 Elevated CPK [BMD]	1	Borg 0–10/ 7.0 (1.8)	2	RMH >6 RPE 2–5 days after visit CPK
	IM	JDM	7	1	8.1	2	HR_{peak} >95% of predicted; RER_{peak}>1.0–1.1	91	7	100	4	0	_	_	1	_
SC	IM	JDM	1	1	10.0 (2.0)	1	HR_{peak}>180 bpm; RER_{peak} ≥1.0	100	1	100	_	_	_	_	_	_
T	GSD	GSD V	1	_	_	_	_	_	1	100	_	_	_	_	_	_
	IM	JDM	4	4	9.0 (2.1)	2	HR_{peak}>180bpm; RER_{peak} ≥1.0	67	4	100	3	0	_	_	_	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; SC: supine cycle ergometer; T: treadmill; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; MCAD: medium-Chain Acyl CoA; SCAD: short-Chain AcylCoA dehydrogenase deficiency; MADD: Multiple AcylCoA dehydrogenase deficiency;; DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; JDM: juvenile dermatomyositis; n: numbers of studies; %: percentage of patients; HR_{peak}: heart rate peak; bpm: beats per minute; RER_{peak}: respiratory exchange ratio; Borg: rating of perceived exertion; PE: perception exertion; RMH: the rating of muscle hurt; SD: standard deviation; CPK: creatine phosphokinase; mmol: millimol; U.L: units per liter -: not reported; * not specified, &220-age.

3.5.2. Adverse events

In general, few studies reported on the occurrence of complications or adverse events during the CPET in the adult group (upright cycle ergometer = 13, recumbent cycle ergometer = 1, treadmill = 1) [10,23,25,30,34,54,57,76,77,81,87,96,100] and in the pediatric group (upright cycle ergometer = 6, treadmill = 3) [62,64,66,67,69,72,102,103,107]. Adverse events occurred in three of the adult studies (upright cycle ergometer = 2, treadmill = 1) [34,57,77]. Each was an isolated event (one patient in each study), and most of the time connected to an interruption of the test (Table 5). One pediatric study reported an isolated adverse event with a patient with glycogen storage disorder, and one complication with a patient with an inherited myopathy (Table 6) [72].

Specific parameters for measuring the safety of CPET were only reported by two studies assessing adult patients [77,79], and by another two comprised of pediatric patients [66,72]. Most of the studies used the comparison of creatine phosphokinase (CPK) levels before and after the test, and values >150 U/L were considered elevated [79]. One study also used the rating of muscle hurt (RMH), where a score >6 indicates severe muscle pain [66].

3.6. Aerobic fitness of NMD patients

All NMD subgroups presented a reduced aerobic fitness (<80% of the predicted VO_{2peak}), except adults with inflammatory myopathies using the treadmill, and pediatric patients with glycogen storage disorders using the upright cycle ergometer (81% and 82% of the predicted $VO_{2peak,}$ respectively). The lowest aerobic fitness levels were observed in adult patients with motor neuron disease (32% of the predicted VO_{2peak}) on the recumbent cycle ergometer (Table 7), and in pediatric patients with glycogen storage disorders (38% of the pre-

Table 7. Aerobic fitness of patients – Adults.

Exercise Modality	NMD sub classification	Disease	Studies (n)	VO_{2peak} (ml/kg/min)	VO_{2peak} (% of predicted)	Studies (n)	HR_{peak} (bpm)	HR_{peak} (%)	Studies (n)	RER_{peak}	Studies (n)	W_{peak} (watts)
UPC	GSD	GSD II, V, VII	18	20.1	44	16	165	88	11	1.0	11	79.4
	MitoD	MELAS, PEO, RRFD, CPTD	26	20.8	47	20	146	80	15	1.2	22	86.0
	GSD, MitoD	_*	_	_	_	1	134	_	_	_	1	67.0
	IHM	MD, FSHD, LGMD, CMyo, CCD, NM, HMM Dystrophies, Myopathies	6	26.0	58	6	161	88	3	1.2	8	122.2
	IM	DM, PM	5	19.0	40	3	146	85	2	1.1	2	107.6
	MND	ALS, PPS	6	21.2	54	5	156	89	4	1.1	7	75.2
	PND	HMSN	2	34.0	74	1	149	84	_	_	2	128.2
	NMJD	MG	2	25.0	64	_	_	_	_	_	1	163.6
	Mix*	HMSN, Dystrophies, Myopathies	2	24.0	50	1	174	93	_	_	1	88.0
RC	MND	SMA	1	15.2	32	_	_	_	1	1.0	_	_
SRC	IHM	LGMD, MD	1	18.2	43	1	164	93	_	_	1	94.0
	PND	HMSN	1	17.1	50	1	152	82	_	_	1	102.0
T	GSD	GSD II, V	3	20.2	48	3	158	90	3	0.9	_	_
	MitoD	_*	4	24.0	52	2	170	91	2	1.2	2	143.0
	IM	DM	1	40.4	81	1	190	101	1	1.1	_	_
	MND	ALS, PPS	1	28.0	61	1	92	56	_	_	_	_
	PND	CMT	1	30.0	71	_	_	_	_	_	_	_
AC	MND	PPS	1	21.5	47	1	160	87	1	1.0	1	74.5

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; T: treadmill; AC: arm-crank ergometer; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; DAMC: disorders of activation of muscle contraction; IM: inflammatory Myopathies; PND: peripheral nerve disorders; NMJD: neuromuscular junction disorders; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PEO: progressive external ophthalmoplegia; RRFD: ragged red fiber disease; CPTD: carnitine palmityl transferase deficiency; MD: myotonic dystrophy; FSHD: facioscapulohumeral muscular dystrophy; LGMD: limb-girdle muscular Dystrophy; CMyo: congenital myopathy; CCD: central core disease; NM: nemaline myophathy; HMM: hereditary myosin myopathy; MS: multiple sclerosis; DM: dermatomyositis; PM: polymyositis; ALS: amyotrophic lateral sclerosis; PPS: post-polio syndrome; SMA: spinal muscular atrophy; MG: myasthenia gravis; HMSN: hereditary motor and sensory neuropathy; n: number; m: male; f: female; SD: standard deviation; VO_{2peak}: oxygen uptake at peak of CPET; ml: milliliter; Kg: kilogram; min: minute;%: percentage; HR_{peak}: peak heart rate during CPET; bpm: beats per minute; W_{peak}: peak workload during CPET; RER_{peak}: peak respiratory exchange ratio; -: not reported; * not specified.

Table 8. Aerobic fitness of patients – Pediatric.

Exercise Modality	NMD sub classification	Disease	Studies (n)	VO_2peak (ml/kg/min)	VO_{2peak} (% of predicted)	Studies (n)	HR_{peak} (bpm)	HR_{peak} (%)	Studies (n)	RER_{peak}	Studies (n)	Wpeak (watts)
UPC	GSD	GSD Ia, III, VII	1	40.5	82	1	190	97	1	1.0	_	_
	MitoD	MCAD, SCAD, MADD	2	36.2	79	3	182	93	3	1.2	2	134.1
	IHM	DMD, BMD	3	21.0	44	3	147	75	2	1.1	1	55.6
	IM	JDM	4	24.0	48	6	175	89	5	1.2	4	81.0
SC	IM	JDM	1	36.0	71	1	182	93	1	1.1	1	30.0
T	GSD	GSD V	1	19.0	38	1	166	83	1	0.8	_	_
	IM	JDM	4	34.0	67	2	174	87	2	1.0	_	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; SC: supine cycle ergometer; T: treadmill; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; MCAD: medium-Chain Acyl CoA; SCAD: short-Chain AcylCoA dehydrogenase deficiency; MADD: Multiple AcylCoA dehydrogenase deficiency;; DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; JDM: juvenil dermatomyositis; n: number; m: male; f: female; SD: standard deviation; VO_{2peak}: oxygen uptake at peak of CPET; ml: milliliter; Kg: kilogram; min: minute;%: percentage; HR_{peak} : heart rate at peak of CPET; bpm: beats per minute; W_{peak}: peak workload during CPET; RER_{peak}: peak respiratory exchange ratio; -: not reported.

Table 9. Characteristic of the studies with sufficient score in the ATS/ACCP adapted quality list – Adults.

								Quality of test				Feasibility of test		Aerobic fitness		
Exercise Modality	NMD sub classification	Disease	Studies (n)	Patients (n) [M/F]	Age (Mean-SD)	Protocol	Studies (n)	Duration (min)	Studies (n)	Criteria of maximal effort Patients (%)	Studies (n)	Completion rate Patients (%)	Adverse events (n)	Studies (n)	VO_{2peak} (%pred)	HR_{peak} (% pred)	RER_{peak}
UPC	GSD	GSD V, VII	5	18 [10/8]	35.7 (4.8)	Start: 10–40 W Effort: 5–10 W/min (Step) or 20–30 W/2 min or 40 W/3 min Start: 20–50 W (6 min) Effort: 10–25 W/min (Ramp) Cadence: 60–80-rpm	2	11.5	1	HR_{peak} ≥85% of predicted _	3	100%	_	5	19.0 (42%)	172 (94%)	0.87
	MitoD	MitoD, RRFD	9	86 [24/34]	35.5 (9.0)	Warm-up: submaximal W/3-4 min or 20 W/1 min Effort: 5–20 W/min or 20–30 W/2 min (Step) Cadence: 50 rpm Warm-up: 0 W/4 min Effort: 5–25 W/min (Ramp) Cadence: 60–80 rpm	2	10.7	1	HR_{peak}>180 bpm or 85% of predicted; RER_{peak}>1.00 100%	8	86%	(n = 1) Syncope	9	23.0 (51%)	140.0 (77%)	1.30
	GSD, MitoD	_*	1	9 [6/3]	49.0	Warm-up: 0 W/1-3 min Effort: 5–10 W/min (Ramp) Cadence: >50rpm	1	10.8	1	HR_{peak}>85% of predicted* RER_{peak}>1.10, Borg≥7 44%	1	100%	_	1	_	134 (77%)	_
	IHM	MD, FSHD, LGMD, CMyo, CCD, NM, HMM Dystrophies, Myopathies	2	42 [25/17]	33.2 (2.3)	Warm-up: 0 W/1-3 min Start:20–50 W/6 min Effort: 5–25 W/min (Ramp), Cadence: 60–80 rpm	2	13.9	1	HR_{peak}>180 bpm or 85% of predicted; RER_{peak}>1.00 65%	2	100%	_	1	31.1 (68%)	158 (85%)	1.10
	IM	DM, PM	1	9 [2/7]	42.0 (3.0)	Effort: 5–15 W/min (Step) Cadence: 60 rpm		_	_	_	1	100%	_	1	14.2 (33%)	127 (71%)	1.10
	MND	ALS, PPS	4	66 [42/24]	51.1 (8.3)	Warm-up: 0 W/2 min Effort: 3–20 W/min (Step) Cadence: 50–80 rpm Warm-up: 0 W/2 min Effort: 3–20 W/min (Ramp)	1	8.0	_	_	2	100%	_	4	19.6 (49%)	138 (79%)	1.10
	PND	HMSN	1	18 [12/6]	49.0	Warm-up: 0 W/1-3 min Effort: 5–10 W/min (Ramp), Cadence: >50rpm	1	10.8	1	HR_{peak}>85% of predicted* RER_{peak}>1.10, Borg≥7 67%	1	100%	_	1	_	133 (76%)	_
SRC	IHM	LGMD, MD	1	6 [4/2]	34.0 (5.0)	Start: 25 W/2 min Effort:12.5–25 W/2 min (Step) Cadence: 50–60 rpm	_	_	_	_	1	100%	_	1	17.1 (50%)	152 (82%)	_
	PND	HMSN	1	2 [0/2]	44.5	Start: 25 W/2 min Effort: 12.5–25 W/2 min (step) Cadence: 50–60 rpm	_	_	_	_	1	100%	_	1	18.2 (43%)	164 (93%)	_
T	GSD	GSD II, V	2	10 [7/3]	51.7 (10.1)	Naughton protocol (speed increment: 0.8 Km/h/3 min grade increment: 3.5%/3 min) Bruce protocol (speed increment: 2.7 Km/h, grade increment: 2%/3 min)	2	9.2	1	HR_{peak} ≥85% of predicted; RER_{peak}≥1.11 75%	2	100%	_	2	19.6 (49%)	142 (82%)	0.97
	MitoD	_*	2	27 [13/14]	30.8 (11.3)	Ortega protocol (constant self selected speed, grade increment: 0–5%/3 min) Bruce protocol (speed increment: 2.7 Km/h, grade increment: 2%/3 min)	1	10.0	_	_	2	100%	_	2	23.6 (50%)	167 (88%)	1.40
	PND	HMSN	1	1 [1/0]	51.0	Modified Balke protocol (constant speed: 4.8 Km/h, grade increase: 1%/min)	1	25.0	_	_	1	100%	_	1	30.0 (71%)	_	_

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; T: treadmill; AC: arm-crank ergometer; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; PND: peripheral nerve disorders; NMJD: neuromuscular junction disorders; CM: cardiomyopathy; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PEO: progressive external ophthalmoplegia; RRFD: ragged red fiber disease; CPTD: carnitine palmityl transferase deficiency; MD: myotonic dystrophy; FSHD: facioscapulohumeral muscular dystrophy; LGMD: limb-girdle muscular Dystrophy; CMyo: congenital myopathy; CCD: central core disease; NM: nemaline myophathy; HMM: hereditary myosin myopathy; MS: multiple sclerosis; DM: dermatomyositis; PM: polymyositis; ALS: amyotrophic lateral sclerosis; PPS: post-polio syndrome; SMA: spinal muscular atrophy;; MG: myasthenia gravis; HMSN: hereditary motor and sensory neuropathy; n: number; m: male; f: female; SD: standard deviation; -: not reported; * not specified.

Table 10. Characteristic of the studies with sufficient score in the ATS/ACCP adapted quality list – Pediatric.

Exercise Modality	NMD sub classifcation	Disease	Studies (n)	Patients (n)	Age (Mean-SD)	Protocol	Quality				Feasibility			Aerobic fitness			
							Studies (n)	Duration (min)	Studies (n)	Criteria of maximal effort	Studies (n)	Completion rate	Adverse event	Studies (n)	VO_{2pico} (% pred)	HR_{pico} (%pred)	RER_{pico}
UPC	MitoD	MCAD, SCAD, MADD	1	4 [2/2]	15 (5.1)	Warm-up: 0 W/2 min Effort: 5–20 W/min (Ramp)	–	–	–	–	1	100%	–	1	–	185 (94%)	1.16
	IHM	DMD, BMD	1	9 [9/0]	10.3 (4.7)	Warm-up: 0 W/1-2 min Effort: 5–10 W/min (Ramp)	1	8.3	1	HR_{peak}>180 bpm RER_{peak}≥1.00 1%	1	100%	–	1	25.2 (51%)	156 (79%)	1.10
	IM	JDM	5	66 [24/26]	12.3 (3.7)	Warm-up: 0 W/1-3 min Effort: 10–20 W/min (Ramp) Cadence:>60-80rpm	1	8.1	1	RER_{peak}>1.10 91%	5	100%	–	3	25.3 (51%)	176 (90%)	1.14
T	IM	JDM	2	41 [15/26]	11.2 (1.0)	Modified Dubowy (speed increment: 0.5 Km/h, grade increment: 3%/1.5 min) Bruce protocol (speed incremente: 1.3–1.5 Km/h, grade increment: 2%/3 min)	2	9.3	1	HR_{peak}>180 bpmRER_{peak}≥1.00 67%	–	–	–	2	34.1 (68%)	184 (92%)	1.05

Legend: UPC: upright cycle ergometer; RC: recumbent cycle ergometer; SRC: semi-recumbent cycle ergometer; SC: supine cycle ergometer; T: treadmill; GSD: glycogen storage disorders; MitoD: mitochondrial disorders; IHM: inherited myopathies; IM: inflammatory Myopathies; MCAD: medium-Chain Acyl CoA; SCAD: short-Chain AcylCoA dehydrogenase deficiency; MADD: Multiple AcylCoA dehydrogenase deficiency; DMD: duchenne muscular dystrophy; BMD: becker muscular dystrophy; JDM: juvenil dermatomyositis; n: number; m: male; f: female; SD: standard deviation; -: not reported; n: number of articles; m: male; f: female; SD: standard deviation; -: not reported.

dicted VO_{2peak}) on the treadmill (Table 8). Moreover, adult patients with glycogen storage disorders, mitochondrial disorders and inflammatory myopathies, and pediatric patients with inherited myopathies and inflammatory myopathies showed a VO_{2peak} below 50% of the predicted value in the upright cycle ergometer (Tables 7 and 8).

The highest percentages of the HR_{peak} (≥90% of the predicted value) for the adult population were found using the treadmill for patients with glycogen storage disorders, mitochondrial disorders and inflammatory myopathies. For cycle ergometry, normal values of the HR_{peak} were observed in patients with inherited myopathies on the semi-recumbent cycle ergometer, and in patients with a mix of diseases on the upright cycle ergometer (93% of the predicted value). In children/adolescents, only patients with glycogen storage disorders on the upright cycle ergometer showed an HR_{peak} ≥95% of the predicted value. As expected, low values of the respiratory exchange ratio (RER_{peak} <1.1 in adults and <1.0 in children/adolescents) were observed in patients with glycogen storage disorders using the upright cycle ergometer (RER_{peak} = 1.0) and treadmill (RER_{peak} = 0.9–0.8) (Tables 7 and 8). Adult patients with motor neuron disease using the recumbent cycle ergometer and the arm-crank also showed low RER_{peak} values (Table 7).

3.7. Methodological quality

The methodological quality of the included studies varied. In the adult population, 17 studies (28%) that used the upright cycle ergometer and four studies (40%) that used the treadmill demonstrated respectively sufficient (upright cycle ergometer = 16; treadmill = 3) [8,26,28,30,34,42,44,45,52,"_58,59,73,75,80,83,93,97,98] and moderate (upright cycle ergometer = 1; treadmill = 1) [9,25] methodological quality. One study using the semi-recumbent cycle ergometer had moderate methodological quality [46]. However, no studies achieved a high methodological quality. In children and adolescents, seven studies (50%) using the upright cycle ergometer [66–69,101,102,106] and two studies (40%) using the treadmill [62,105] demonstrated sufficient methodological quality (Supplementary Material D).

3.8. Data syntheses

Tables 9 and 10 summarize the protocol, quality of test performance, feasibility, and aerobic fitness from the 30 studies (one study used two exercise modalities) with sufficient-to-moderate methodological quality. From these studies, 10 presented information about the quality of the test performance, including test duration [8,9,34,42,62,66,68,75,93,105] and the number of patients reaching maximal effort [8,9,25,44,58,59,62,66,68,98]; over 25 studies reported feasibility or aerobic fitness details (n = 27 and 26 studies, respectively) [8,9,25,26,28,30,34,42,44,45,52,58,59,62,65–69,73,75,80,83,84,93,97,98,102,105,106].

Excellent feasibility with a completion rate of 100% and low aerobic fitness (<80% of the predicted VO_{2peak}) were found in those studies. However, a high quality of test performance, mainly for maximal effort, was only observed in six studies

[8,9,44,62,66,68]. The best evidence of CPET protocols was based on these studies with a higher quality of test performance and feasibility. In this regard, the upright cycle ergometer is recommended to assess most subtypes of ambulatory adults with NMDs and some ambulatory pediatric patients. The ramp protocol and individualized work increments are advisable for both populations, but different workloads are suggested for adults and pediatric patients. The level of functional capacity [8] or physical fitness of the adult patients [44] can guide the rater to select the best workload from 5 to 25 W/min. For pediatric patients, the distance covered during the six-minute walking test (6MWT) might help to select workloads from 5 to 15 W/min [66]. The treadmill can be used to assess ambulatory adults using the Naughton protocol [9], and children and adolescents with the Bruce protocol [62].

4. Discussion

Ninety-two studies (A, 74; P, 18) using CPET to assess patients with NMDs were included in this systematic review and evaluated on the quality of test performance, feasibility and methodological quality. Only 30 studies (A, 21; P, 9) met sufficient-to-moderate methodological quality according to the ATS/ACCP recommendations. However, from those, only six studies (A, 3; P, 3) were included in the best evidence synthesis of CPET protocols for patients with NMDs regarding excellent feasibility and quality of test performance.

4.1. Methodological quality

The main reasons for the low scores of the studies in the methodological quality checklist regard failure in reporting methodological information, such as calibration, monitoring measurements, for example, blood pressure and oxygen saturation, and performing pretest procedures such as pulmonary function tests. Not following the ATS/ACCP recommendations [6] in performing and reporting CPET may compromise the study's reproducibility and creditability, as well as the patients' safety and performance during the test. Problems in calibration may generate unreliable CPET outcomes, while abnormalities in blood pressure and saturation are primary relative and absolute indications for terminating the test [24,29]. Moreover, since some patients with NMDs present with respiratory muscle weakness, a pulmonary function test can help to identify a pulmonary limitation during exercise [8,110]. Therefore, to increase the body of evidence for the applicability of CPET in NMD, future studies should apply the methodological quality checklist of the ATS/ACCP in the design and report of CPET in NMDs.

4.2. Characteristics of the CPET

The upright cycle ergometer was the most frequently used device for assessing various adult and pediatric patients with NMD. Our findings agree with those of other systematic reviews of CPET for healthy, oncologic, and neurologic patients [111–113]. For clinical situations, the upright cycle ergometers are recommended over treadmills, due to their safety, less need for coordination and balance, easy measurement, and better quality of monitoring physiological variables [5,6]. A step protocol with individualized increments was the most frequently used for assessing adults patients with NMDs in the studies with sufficient methodological quality. However, a ramp protocol was selected in the included studies that presented the best evidence synthesis for the adult population, regarding excellent feasibility and quality of test performance [8,44]. A ramp protocol is advisable for use in patients with NMDs, because it has a linear increase of workload allowing slight metabolic changes and neuromuscular recruitment through the CPET [114]. In agreement with this, most studies assessing pediatric patients used a ramp protocol.

For this type of protocol, workload increments from 5 to 25 W/min were prevalent in the studies, with sufficient-to-moderate methodological quality and the best evidence synthesis assessing adult patients. In the pediatric population, the workload steps varied from 5 to 20 W/min. Earlier fatigue will occur in more intense workload steps. Therefore, the workload steps should be selected carefully, using the level of functional capacity [8] or aerobic fitness of the patients [44]. The six-minute walking test (6MWT) for example, might be a good option for screening the functional capacity of the patient before the CPET [66].

When an upright cycle ergometer is not available, a treadmill might be an alternative option for assessing aerobic fitness in some subtypes of NMDs. It was the second most frequently used device in the included studies and in those included in the best evidence synthesis [9,62]. The Naughton and the Bruce protocols offered the best evidence for respectively assessing adults and pediatric patients [9,62]. The Bruce protocol is a frequently used protocol [115]; however, it has some disadvantages when assessing children and adolescents with reduced functional capacity. The primary disadvantage is posed by the large and unequal increments that impact the obtained exercise response [115], and a secondary disadvantage is the high metabolic demand in the first stages, requiring an oxygen cost of 17.5 ml/kg/min (5 METS), which represents more than 60% of the mean VO_{2peak} achieved by the young NMD patients on the treadmill. Therefore, the Dubowy protocol, with small and even increments (speed increment: 0.5 km/hr and grade: 3% each 1.5 minute), is more advisable for assessing aerobic fitness in children and adolescents with NMDs.

4.3. Quality of test performance

The recommended test duration was met in the CPET protocols used in all studies with sufficient methodological quality, suggesting that the work rate selected might be appropriated for terminating the CPET in 8–12 minutes, without early termination due to localized muscular fatigue, and low stress of the cardiopulmonary system [5]. However, even in the studies with high methodological quality, few patients performed a maximal CPET regarding the objective criteria (HR_{peak} and RER_{peak}), applied when a plateau in the VO_{2peak} is not observed [116].

In general, we found a reduced HR_{peak} and RER_{peak} within the minimum established limits (1.0 and 1.1) for most

subtypes of NMDs. When muscle metabolism is the primary limiting factor of the CPET, a low HR_{peak} is expected, because exercise ends before maximally stressing the cardiovascular system [7,116]. Involvement of the components of the motor unit (one or more) and some structures related to energy production cause changes in the muscle structure and metabolism of patients with NMDs [15,117]. This impacts the oxygen conduction and use by the active muscles [7,44], and helps to explain the observed low HR_{peak}. Moreover, this suggests that the HR_{peak} may not be a good quality criterion by which to assess maximal performance in patients with NMDs.

4.4. Feasibility of CPET

A high completion rate and few adverse events and complications were found in the studies with sufficient methodological quality, indicating excellent feasibility of the CPET protocols for ambulatory patients with NMDs. The feasibility of CPET was also evaluated for other clinical groups, such as adults with multiple sclerosis, advanced cancer [113,118], and children with pulmonary hypertension [119]. In these studies, as observed in the present review, the feasibility of CPET was limited to patients with high physical abilities. Therefore, in order to make CPET part of the daily clinical evaluation of patients with NMDs, the clinician must consider the functional level of patients when selecting the exercise modality. Moreover, less commonly used devices, such as arm-crank ergometers and treadmills with body weight support, can be alternatives by which to assess patients with reduced physical abilities [120–122]. Another relevant aspect of the feasibility of CPET is the patient's ability to follow the rater instructions because. Some patients with NMD may exhibit cognitive impairments. A reduced understanding of commands during the CPET may compromise the patient's motivation and, consequently, his or her performance.

4.5. Aerobic fitness in NMD patients

In general, patients with NMDs assessed in the included studies presented with reduced aerobic fitness. The low VO_{2peak} may result from anything that changes the pathway of oxygen uptake, extraction or use by the active muscle. Although cardiac or pulmonary diseases cannot be ruled out, the low VO_{2peak} can be primarily explained by the limited capacity of the muscles to extract and use oxygen during exercise (muscle metabolism limitation), associated with a mitochondrial defect and the effect of deconditioning due to a sedentary lifestyle [8,44].

Additionally, heterogenous percentages of the predicted VO_{2peak} were observed in patients with the same subtypes of NMDs who performed the CPET in diverse exercise modalities. Most adults, for example, had a higher predicted VO_{2peak} on the treadmill as compared to the upright cycle ergometer; with the exception of patients with motor neuron diseases. This finding agrees with the observation in healthy subjects that shows a 5–10% higher VO_{2peak} on the treadmill [6]. Indeed, walking on a treadmill activates a higher muscle mass and requires a higher metabolic cost to support the body weight against gravity than does the cycling ergometer [6]. The opposite finding for patients with motor neuron diseases in these devices can be justified by the functional level of the assessed patients who are able to walk on the treadmill with or without hand support [82]. Holding the treadmill handrail while walking affects the metabolic demand of the task, reducing the VO_{2peak} [6].

Pediatric patients also showed a different predicted VO_{2peak} between the diverse devices. In glycogen storage disorders, for example, a higher VO_{2peak} was found using the upright cycle ergometer as compared to the treadmill. However, it is important to notice that the CPET results in the upright cycle ergometer were only based on one patient [104]. Surprisingly, young patients with inflammatory myopathies had a higher predicted VO_{2peak} in the CPET using a supine cycle ergometer as compared to the treadmill. Nevertheless, only patients in disease remission composed the study using the supine cycle ergometer, while younger patients and patients with both active disease and disease remission composed the studies using the treadmill [62,104,105,107]. Submaximal CPET outcomes were shown for younger inflammatory myopathy patients with active disease [62].

5. General recommendations for CPET in NMDs

Wwe advise clinicians to use the upright cycle ergometer as the primary exercise modality to assess ambulatory patients with NMDs. The ramp-wise protocol with workload selection based on the patient's functional capacity and aerobic fitness (5 to 25 W/min for adults and 5 to 20 W/min for young patients with NMDs) is also suggested for this device. Prior to the assessment of a CPET, we recommend that the patient receives a thorough cardiovascular screening. During the CPET, the use of additional measurements in addition to the gas exchange, for example, baseline pulmonary function test, 12-lead electrocardiogram, saturation, and blood pressure monitoring. Most NMDs might have asymptomatic cardiac diseases, and these measures help to guarantee the patient's safety during the performance of a CPET. Moreover when assessing the quality of CPET performed, we suggest to consider the RER_{peak} as the principal physiological variable to classify the patient's delivered effort.

6. Conclusion

The knowledge about exercise limiting factors and aerobic fitness in NMDs is increasing and brings the need to understand the applicability and safety of the gold-standard method, CPET, in assessing these variables for this specific group. Our results indicate that CPET is feasible for adult and young patients with NMDs when the patient's functional level and the exercise modality of CPET are taken into account. However, to safely implement CPET in the routine assessment of patients with NMDs, clinicians are urged to follow the ATS/ACCP recommendations for performing and reporting CPET. Furthermore, there is a vast potential for standardization and design of disease-specific CPET protocols for patients with NMDs.

7. Expert opinion

From the results of this systematic review, we provide information about the best-evidence synthesis of CPET protocols and their feasibility for ambulatory patients with NMDs. Understanding the best-evidence for incremental protocol design and work rate increment is fundamental for clinicians to test the metabolic and exercise responses without generating early-localized peripheral fatigue. Nevertheless, future studies should assess the applicability of timed tests, such as the six-minute walking test, in screening the functional capacity of the patients and in the guidance for workload selection.

Even though our results suggest that CPET is feasible for ambulatory patients, the low adherence of the included studies to the ATS/ACCP recommendations and the wide variety of available protocols indicate a need for standardization in performing and reporting CPET for this group. However, it is important to highlight that the reports of the included studies limited our assumptions. Perhaps more patients did not complete the CPET and thereby were excluded from the final sample and not reported in the studies, or perhaps more authors followed the recommended procedures from the ATS/ACCP guidelines but did not report this in the publications. Moreover, there is no information available regarding the feasibility of CPET for non-ambulatory patients. Future studies are urged to fill this gap. Novel devices, such as the lower body positive support treadmills, might offer an alternative and should be explored in the design of specific CPET protocols for less functional patients.

For many years, exercise has been a stigma for patients with NMDs, due to the theoretical concept that weak muscles work near their maximal limitLeading health professionals did therefore not recommend exercise for this group. Despite this uncertainty, safety was an under-investigated aspect for CPET in this group. The analysis of safety (bio)markers, such as the CPK level and the rating of perceived muscle hurt before and after CPETs, would encourage CPET use for some progressive NMDs and NMDs associated with cardiomyopathy.

The reduced aerobic fitness of patients with NMDs is another alarming observation from this systematic review. For the healthy and chronically impaired populations, a low aerobic fitness indicates a high risk of morbidity and mortality. Exercise training programmes have great potential in dealing with the harmful effects of reduced physical activity and low aerobic fitness. Most clinical trials included in this review used CPET to prescribe training intensity and to assess its efficacy. Therefore, improvements in CPET protocols for ambulatory and non-ambulatory patients might favor the implementation of CPET in the routine assessment of patients with NMDs, for prescribing individual exercise training intensity and assessing the efficacy of an intervention, thereby boosting the development of the first exercise training guidelines for this group.

Finally, our results also suggest that the existing objective criteria of maximal effort should be revised for patients with NMDs, because their muscle metabolism limits the achievement of $HR_{peak.}$ Other CPET variables, such as anaerobic threshold (AT), oxygen uptake efficiency slope (OUES), and the relation between oxygen uptake and work rate (ΔVO2/ΔWR), should be better explored in futures studies.

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