Cardiopulmonary exercise performance and factors associated with aerobic capacity in neuromuscular diseases

Gita M. Ramdharry PhD1,2 | Amanda Wallace PhD1 | Philip Hennis PhD3 | Elizabeth Dewar MSc2 | Magdalena Dudziec BSc1,3 | Katherine Jones PhD2 | Aleksandra Pietrusz BSc1 | Mary M. Reilly MD1 | Michael G. Hanna BMBCh1

1Department of Neuromuscular Diseases, Institute of Neurology, University College London, London, UK
2Queen Square Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, University College Hospitals, NHS Foundation Trust, London, UK
3Institute of Sport, Exercise and Health, UCL, London, UK

Correspondence
Gita M. Ramdharry, Queen Square MRC Centre for Neuromuscular Diseases, Box 102, 8-11 Queen Square, London WC1N 3BG, UK. Email: g.ramdharry@ucl.ac.uk

Funding information
Medical Research Council, Grant/Award Number: MR/K000608/1; National Institute for Health Research, Grant/Award Number: PB-PG-0711-25151

Abstract

Introduction/Aims: Aerobic deconditioning, due to lower levels of physical activity, could impact independence for people with neuromuscular conditions. We report the maximal cardiopulmonary response in a cohort of people with Charcot Marie Tooth disease type 1A (CMT 1A) and inclusion body myositis (IBM). We also explored potential predictors of aerobic capacity with measures of physical impairment and functional performance.

Methods: Participants underwent maximal cardiopulmonary exercise testing (CPET) using a semi-recumbent cycle ergometer. Data were analyzed to determine the peak O2 consumption (VO2 peak), anaerobic threshold (AT), maximum heart rate (MHR), ventilatory equivalent for CO2 slope (VE/VCO2), and respiratory exchange ratio (RER). Impairment, functional and patient reported measures were also recorded. Predicted CPET variables were calculated based on published normative data for age, gender, and weight.

Results: Twenty-two people with CMT and 17 people with IBM were recruited. Both groups showed significantly lower VO2 peak, MHR, AT, and VE/VCO2. The CMT group overall performed better than the IBM group, with significantly higher VO2 peak, MHR, and AT, but lower VE/VCO2. Linear regression analysis demonstrated that VO2 peak was related to body fat percentage and 6-min walk distance for both groups, and steps per day for the IBM group.

Discussion: Lower than predicted CPET variables were observed that were not explained by cardiopulmonary limitations or reduced effort, implicating peripheral factors in limiting the cycling task. Regression analysis implied prediction of VO2 peak by body fat percentage and 6-min walk distance. Six-minute walk distance could be a potential proxy measure of cardiopulmonary fitness.

Abbreviations: 10MTW, 10 meter timed walk; AT, anaerobic threshold; BMI, body mass index; BP, blood pressure; CMT, Charcot Marie Tooth disease; CMT 1A, Charcot Marie Tooth disease type 1A; CMTESv2, CMT Examination Score version 2; CPET, cardiopulmonary exercise testing; FVC, forced vital capacity; IBM, inclusion body myositis; IBMFRS, Inclusion Body Myositis Functional Rating Scale; IPAQ, International Physical Activity Scale; MHR, maximum heart rate; NMD, neuromuscular disease; P-P plots, normally probability plots; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAS, Visual Analogue Scale; VE/VCO2, ventilatory equivalent for CO2 slope; VO2 peak, peak O2 consumption.
People with neuromuscular diseases (NMDs) may be at increased risk of morbidities such as obesity, cardiovascular, and metabolic conditions, because of lower levels of physical activity. Insufficient physical activity is a major risk factor for the development of non-communicable diseases, with an associated 20%–30% increased risk of all-cause mortality. Low aerobic capacity can negatively impact on independent community living. Aerobic de-conditioning and secondary disuse muscle atrophy are common in people with NMD and are a likely consequence of reduced general activity levels. Investigations of people with Charcot Marie Tooth disease (CMT) found they are less active than the general population and are “de-conditioned,” as measured by oxygen uptake during exercise. Similar reductions in aerobic capacity have been reported in people with idiopathic inflammatory myopathy, but this has not been explored in inclusion body myositis (IBM).

The objective of this study was to undertake detailed measurement of the cardiopulmonary response during maximal cycling exercise in large cohorts of adult patients with two neuromuscular diseases: CMT type 1A (CMT 1A) and sporadic IBM. We anticipated that both disease groups would have lower than predicted aerobic capacity when compared to normative data; however, we also aimed to explore body structure, impairment and functional factors that relate to aerobic capacity. This would allow us to understand if there are factors that can be targeted with rehabilitation, and whether there are proxy measures that may indicate aerobic capacity without complex, laboratory measurement procedures.

2 | METHODS

Potential participants were recruited as a convenience sample from clinics and research databases of the National Hospital for Neurology and Neurosurgery, plus national clinics of colleagues from the British Myology Society over a 26-mo period. All participants were recruited on an aerobic exercise training intervention trial, and here we present an analysis of the baseline data This study achieved NHS NRES ethical approval (ref: 11/LO/0760) and consent for participation was obtained. The main trial was registered on the ISRCTN clinical trials registry (ID: 99826269).

Participants were included in the study if they met the following criteria: clinical and genetic diagnosis of CMT1A, or a clinical diagnosis of IBM, supported by histological confirmation as per the established Griggs criteria (only Griggs definite IBM cases were included); aged 18–80; able to walk for 30 m with or without a walking aid or orthotic devices; able to safely mount/dismount an exercise bike with minimal assistance.

Exclusion criteria were: presence of other significant neurological disorders or major co-morbidities; limb surgery during the 6 mo prior to screening (or planned before final assessment); failure to pass the screening assessment for exercise testing; concurrent involvement in another intervention trial; people already participating in moderate aerobic exercise more than three times per week; women of child-bearing age if they were pregnant.

In total, 282 people with CMT 1A were invited to participate in the main intervention trial and 254 were excluded, refused or did not respond. The most common reasons for active exclusion were co-existing illness or recent limb surgery; already exercising over 3 days per week; unable to meet time commitments; did not meet the more detailed screening criteria. In total, 122 people with IBM were invited to participate and 102 were unable to commit to the trial or did not meet the study criteria on initial screening. The most common reasons were too old for the age criteria; did not want to participate; co-existing illness.

Study subjects with CMT 1A and IBM underwent cardiopulmonary exercise testing (CPET) in accordance with American Thoracic Society/American College of Chest Physicians. A screening algorithm was used, prior to maximal exercise testing, that included details of medical history, physical examination and electrocardiogram (ECG) findings. Participants performed a single symptom-limited, incremental ramp protocol to volitional exhaustion using a semi-recumbent electromagnetically braked cycle ergometer (Lode Corival, Groningen, Netherlands). During the test on-line gas exchange analysis, ECG monitoring, and arterial blood pressure were measured with a Cortex MetaLyzer® (Biophysik, Leipzig, Germany). ECG and blood pressure (BP) were monitored before, during, and after the test. Tests were considered suitable for inclusion if it was judged that the participant gave a maximal effort and reached their physiological limitation as per the American Thoracic Society/American College of Chest Physicians statement on Cardiopulmonary Exercise Testing. Other tests were excluded if technical or practical difficulties stopped the test early (e.g., unable to get a clear BP or ECG reading, or the participant was unable to keep their foot on the bike pedal due to straps having loosened). This ensured that all data included in this analysis were true maximal test data.

CPET data only were analyzed by an experienced exercise physiologist (co-author P.H.) to determine the peak O2 consumption (VO2 peak) normalized to body weight, anaerobic threshold (AT) using the modified v-slope method, maximum heart rate and ventilatory equivalent for CO2 slope (VE/VC02). AT is the physiological point during exercise at which lactic acid starts to accumulate in the muscles, which occurs around the point during increasing intensity exercise that anaerobic processes become more dominant. The VE/VC02 slope reflects the increase in ventilation in response to CO2 production, and thus shows increased ventilatory drive. The peak respiratory exchange ratio (RER) is an indicator of exercise exertion level. It is defined as carbon dioxide production divided by oxygen consumption, and a peak RER equal to or more than 1.10 indicates maximal exercise effort. The exercise physiologist only had access to the CPET data and not additional demographic and clinical data.

Other variables recorded were age, sex, and disease severity; version 2 of the CMT Examination Score (CMTESv2) was recorded by a neurologist for CMT participants and Inclusion Body Myositis Functional Rating Scale (IBMFRS) for IBM participants. Body structure and impairment measures were recorded: body mass index, body fat percentage using skinfold callipers, waist circumference, forced vital capacity (FVC), resting heart rate, blood pressure, isokinetic peak
torque of the knee flexors and extensors at 60°/s (Cybex HUMAC dynamometer). After a minimum of 1 h of rest, measures of functional activity included: 10 m timed walk (10MTW), 6-min walk; and 7 days of physical activity monitoring using a multi-sensor wearable device (Sensewear Activity Monitor). The 6-min walk was the final functional measure to maximize the time following the exercise testing. Participant reported outcome measures captured some of the non-motoric symptoms and perceptions: Fatigue Severity Scale, Visual Analogue Scale (VAS) for pain, International Physical Activity Scale (IPAQ), barriers to activity and exercise.

3 | ANALYSIS

Predicted CPET variables were calculated based on published normative data for age, gender and weight. Comparing the actual with predicted values between the groups accounted for potential confounds of age, gender, and weight.

| TABLE 1 Demographic, disease severity, body structure and impairment measures, and functional activity outcomes |
|---------------------------------------------------------------|
| **Group** | **CMT** | **IBM** | **P-Value** |
| Demographics | | | |
| N | 22 | 17 |  |
| Age (y) | 43.8 ± 14.5 | 61.5 ± 10.08 | <.0001 |
| Sex (male/female) | 9 female, 13 male | 4 female, 13 male |  |
| Disease severity scales | | | |
| CMTES | 10 (8–12) |  |
| IBMFRS | 28 (24–31) |  |
| Body structure and impairments | | | |
| Body mass index (kg/m$^2$) | 27.70 ± 3.49 | 26.08 ± 3.77 | .154 |
| Waist/hip ratio | 0.89 ± 0.09 | 0.95 ± 0.11 | .099 |
| Body fat % | 25.45 ± 5.69 | 24.27 ± 4.78 | .503 |
| Forced vital capacity in sitting (L) | 3.28 ± 0.85 | 2.88 ± 0.91 | .172 |
| Resting heart rate (beats/min) | 67.64 ± 7.89 | 68.13 ± 8.91 | .503 |
| SBP (mmHg) | 121.68 ± 15.70 | 131.13 ± 13.22 | .037 |
| Diastolic blood pressure (mmHg) | 77.73 ± 6.21 | 78.69 ± 5.49 | .069 |
| Peak isokinetic knee extensor torque (nm) | 85.25 ± 41.93 | 23 ± 23.74 | >.0001 |
| Peak isokinetic knee flexor torque (nm) | 46.16 ± 19.18 | 24.18 ± 19.16 | .0011 |
| Fatigue severity scale | 32 (20–40) | 29 (22–46) | .681 |
| Visual analogue scale for pain | 2 (0.9–4.5) | 1 (0–2) | .117 |
| Functional activities | | | |
| 10 meter timed walk (s) | 17.09 ± 3.19 | 22.58 ± 7.10 | .0026 |
| 6-min walk (m) | 378.81 ± 79.12 | 292.03 ± 87.85 | .0025 |
| Total daily energy expenditure (calories) | 2613.28 ± 463.40 | 2356.18 ± 487.15 | .101 |
| Average steps per day | 8214 ± 3965 | 4732 ± 2840 | .0041 |
| Average METs per day | 1.432 ± 0.189 | 1.306 ± 1.187 | .067 |
| Physical activity duration per day (min) | 120.14 ± 64.36 | 85.65 ± 71.20 | .122 |
| Sedentary time (min) | 1151.14 ± 242.03 | 1281.18 ± 146.58 | .059 |
| Walk-12 | 34.5 (31–41) | 42 (36–49) | .055 |
| IPAQ sitting time (min/day) | 378 ± 183.58 | 388 ± 177.63 | .871 |
| Falls self-efficacy scale | 41 (33.3–50.0) | 42 (36–49) | .379 |

Note: Continuous data are expressed as the group mean ± standard deviation and categorical data as the group median and interquartile range. Continuous P values are shown following inferential testing. Abbreviation: METs, metabolic equivalent.
RESULTS

Twenty-two people with CMT and 17 people with IBM were recruited to the study. The IBM group was older with a smaller proportion of females and slightly higher systolic blood pressure (SBP), but there were no other differences between disease groups in demographics and general health measures (Table 1).

4.1 | CPET performance

Comparisons with normative data demonstrated that the CMT participants had significantly lower CPET performance for all variables except for VE/VCO2 slope. There was a highly significant difference in percentage predicted AT and percentage predicted VO2 peak (Table 2), with the IBM group performing worse (Figure 1).

Participants with CMT performed significantly better than the IBM group when comparing the actual values, with the exception of maximum ventilation and RER (Table 2). No differences between the groups were observed for maximum heart rate and ventilatory efficiency (VE/VCO2) slope. RER was 1.10 and above for both groups indicating patients in both groups were working at high intensities at exercise cessation (Table 2).

4.2 | Differences in body structure and impairment, activity, and patient reported outcomes

Body structure and impairment measures were comparable between groups, with the exception of higher SBP for the IBM group (Table 1).


### Summary of univariate regression analysis with VO2 peak

**Table 3**

| Disease severity scales | IBMFRS | CMTFRS |
|-------------------------|--------|--------|
| **R coefficient**       | **P-Value** | **Lower CI** | **Upper CI** | **R coefficient** | **P-Value** | **Lower CI** | **Upper CI** |
| IBM                     | −0.302 | 0.239  | 0.467 | 0.911 | −0.242 | 0.279 | −0.610 | 0.266 |
| CMTEFS                  | 0.520  | 0.573  | 0.467 | 0.911 | 0.282 | 0.284 | 0.188 | 0.377 |

**Abbreviation:** CI, confidence interval.

Exploratory correlation analysis between VO2 peak with body structure and impairment variables for the CMT group revealed significant, moderate relationships with three measures: body fat percentage, FVC and peak isokinetic knee extensor torque (Table 3). Multiple regression modelling showed no significant associations with the three variables. FVC, then isokinetic knee extensor torque was removed using a stepwise method. The final model showed body fat percentage had low association with VO2 peak (Table 4).

For the IBM group, initial correlation analysis showed significant relationships with the same three variables. FVC and peak knee extensor torque were removed stepwise from the model due to weak correlations leaving body fat percentage had a low association with VO2 peak (Table 4).

**4.3 Associations with aerobic capacity (VO2 peak)**

The disease severity measures for both conditions performed differently in the correlation analysis. In the group of participants with IBM, the IBMFRS scale showed a moderate to strong correlation with VO2 peak but the same was not observed for the CMTEFS scale in the CMT cohort (Table 3). However, there was a difference in muscle function, with significantly higher peak knee extensor and flexor isokinetic torque observed in the CMT group (Table 1). The CMT group also walked significantly faster over 10 m and covered a greater distance in 6 min (Table 1). Physical activity monitoring revealed that the CMT group took significantly more steps per day, but interestingly there were no differences in total daily energy expenditure. There were no differences in time spent in sedentary, moderate, or vigorous physical activity. Patient reported outcome measures were comparable with no differences between the groups.

| Body structure and impairments | IBM | CMT |
|-------------------------------|-----|-----|
| **R coefficient** | **P-Value** | **Lower CI** | **Upper CI** | **R coefficient** | **P-Value** | **Lower CI** | **Upper CI** |
| BMI | −0.568 | 0.222 | −0.841 | −0.086 | −0.606 | 0.003 | −0.795 | 0.377 |
| Waist/hip ratio | −0.568 | 0.086 | −0.841 | −0.086 | −0.606 | 0.003 | −0.795 | 0.377 |
| Body fat % | 0.486 | 0.048 | −0.060 | 0.867 | 0.532 | 0.011 | 0.223 | 0.758 |
| FVC in sitting | 0.084 | 0.749 | −0.420 | 0.539 | 0.077 | 0.732 | −0.285 | 0.412 |
| Resting heart rate | −0.460 | 0.623 | −0.843 | 0.227 | 0.247 | 0.268 | −0.172 | 0.719 |
| Resting SBP | 0.646 | 0.005 | 0.266 | 0.732 | 0.501 | 0.017 | 0.128 | 0.721 |
| Isokinetic knee extensor torque | 0.302 | 0.032 | 0.266 | 0.732 | 0.501 | 0.017 | 0.128 | 0.721 |
| Isokinetic knee flexor torque | 0.302 | 0.032 | 0.266 | 0.732 | 0.501 | 0.017 | 0.128 | 0.721 |
| Fatigue severity scale | −0.289 | 0.210 | −0.717 | 0.188 | −0.187 | 0.404 | −0.617 | 0.317 |
| VAS for pain | −0.249 | 0.335 | −0.710 | 0.331 | −0.439 | 0.041 | −0.759 | 0.042 |

**Functional activities**

| | IBM | CMT |
|----------------------------|-----|-----|
| **R coefficient** | **P-Value** | **Lower CI** | **Upper CI** | **R coefficient** | **P-Value** | **Lower CI** | **Upper CI** |
| 10-meter walk time | −0.611 | 0.009 | −0.554 | −0.004 | −0.290 | 0.190 | −0.568 | 0.008 |
| 6-min-walk distance | 0.776 | 0.001 | 0.344 | 0.777 | 0.581 | 0.005 | 0.331 | 0.782 |
| Total energy expenditure per day | 0.372 | 0.142 | −0.140 | 0.545 | 0.201 | 0.369 | −0.162 | 0.553 |
| Steps per day | 0.657 | 0.004 | −0.186 | 0.367 | 0.092 | 0.684 | −0.200 | 0.382 |
| Average METs per day | 0.641 | 0.006 | −0.099 | 0.652 | 0.312 | 0.158 | −0.097 | 0.660 |
| Physical activity duration per day | 0.623 | 0.008 | −0.279 | 0.448 | 0.070 | 0.758 | −0.292 | 0.428 |
| Sedentary time | −0.264 | 0.306 | −0.644 | 0.128 | −0.181 | 0.421 | −0.666 | 0.124 |
| Walk-12 scale | −0.607 | 0.010 | −0.862 | −0.269 | −0.573 | 0.005 | −0.779 | 0.189 |
| IPAQ sitting time (min/day) | −0.174 | 0.505 | −0.643 | 0.381 | 0.051 | 0.827 | −0.361 | 0.467 |
| Falls self-efficacy scale | −0.014 | 0.957 | −0.496 | 0.472 | 0.372 | 0.088 | −0.115 | 0.780 |

*Significant correlations following modified Bonferroni adjustment. Pearson correlations were undertaken for continuous data and Spearman correlation tests were undertaken for ordinal data.

However, there was a difference in muscle function, with significantly higher peak knee extensor and flexor isokinetic torque observed in the CMT group (Table 1). The CMT group also walked significantly faster over 10 m and covered a greater distance in 6 min (Table 1). Physical activity monitoring revealed that the CMT group took significantly more steps per day, but interestingly there were no differences in total daily energy expenditure. There were no differences in time spent in sedentary, moderate, or vigorous physical activity. Patient reported outcome measures were comparable with no differences between the groups.
TABLE 4  Summary of multivariate regression models

| Condition | R² | Variable            | Coefficient | Standard Error | P-Value | Lower CI | Upper CI |
|-----------|----|---------------------|-------------|----------------|---------|----------|----------|
| IBM       | 0.323 | Body fat percentage | −0.358 | 0.138 | .022 | −0.645 | −0.061 |
| IBM       | 0.323 | Constant            | 23.249 | 3.42  | .0001 | 15.913 | 30.584 |
| CMT       | 0.367 | Body fat percentage | −0.491 | 0.144 | .003  | −0.791 | −0.19  |
| CMT       | 0.367 | Constant            | 34.075 | 3.75  | .0001 | 26.252 | 41.897 |
| IBM       | 0.717 | 6-min walk distance | 0.021 | 0.006 | .002  | 0.009  | 0.033  |
| IBM       | 0.717 | Steps per day       | 0.0004 | 0.00017 | .031 | 0.0004 | 0.0007 |
| IBM       | 0.717 | Constant            | 0.079  | 1.534 | .001  | 2.787  | 9.369  |
| CMT       | 0.338 | 6-min walk distance | 0.0338 | 0.011 | .005  | 0.012  | 0.056  |
| CMT       | 0.338 | Constant            | 8.773  | 4.094 | .045  | 0.233  | 17.313 |

Note: Model 1: associations between body structure and impairment variables and VO2 peak. Model 2: associations between functional measures and VO2 peak.

Abbreviation: CI, confidence interval.

For the IBM group, a larger number of functional variables were identified in the initial correlation analysis: IBMFMR, 10 MTW time, 6-min walk distance, Walk-12, IPAQ, and average steps per day. The following variables were removed stepwise from the model: Walk-12, IPAQ, IBMFMR, 10 MTW time. The resulting model included 6-min walk distance and average steps per day showing a strong association with VO2 peak (Table 4):

5 | DISCUSSION

There are some similarities in performance between the two cohorts but also some key differences that may help us understand the impact of the presenting impairments on cardiorespiratory fitness.

When comparing the two conditions, both disease groups demonstrated lower maximum heart rate, lower anaerobic threshold and reduced VO2 peak variables compared to predicted norms. Participants with IBM showed even greater limitations than the CMT group with the very low VO2 peak value of 14.3 ml/kg/min; this is particularly notable when one considers that, a VO2 peak of 18 ml/min/kg is deemed the minimum required for independent community living.24 The CMT group were younger, with less proximal muscle wasting, which could have influenced the cycling task used for testing.

In healthy individuals, VO2 peak is considered to be limited by central O2 delivery mechanisms, in particular due to the achievement of maximal cardiac output.25 In this study, participants with CMT and IBM terminated exercise with a reserve in heart rate (CMT, 76.1%; IBM, 76.6%) and ventilation (CMT, 50.5%; IBM, 48.2%), indicating central O2 delivery did not limit exercise. The low maximum values for HR and ventilatory effort are unlikely due to early exercise cessation as patients exhibited high RER values, indicating high effort levels.26 These two conditions do not have cardiac dysfunction as a presenting symptom so chronotropic incompetence is unlikely, therefore, the attainment of VO2 peak in our cohorts appears largely due to peripheral limiting factors.

The exercise test protocol in this study used a bicycle ergometer that requires activity of the knee extensors and flexors in the most part. It is reported in MRI studies that knee extensor function is altered in both CMT and IBM.27 In people with IBM this is due to primary atrophy and fat infiltration. Weakness of the quadriceps is a primary presentation so if individuals are weaker to start with, they may reach thresholds of function earlier, even if they are fatiguing at a normal rate. No previous work has been published exploring peripheral fatiguability of muscle in people with IBM.

The same MRI study showed more general loss of thigh muscle volume in the cohort of people with CMT that was thought to represent secondary disuse atrophy.27 Previous studies using stimulation to explore fatigue in people with CMT demonstrate increased central activation failure.28 Another study found normal fatigue rate, but people with CMT demonstrated lower activation initially, possibly due to central activation failure.29 More recently, increased compensatory central activation in the prefrontal cortex has been observed during a fatiguing task.30 The same group also observed impaired neuromuscular recovery from fatigue in CMT1A. These studies are in small cohorts, but there is an implication that central activation influences task fatigue in people with CMT. This may explain the early cessation during CPET testing observed.

The regression analysis demonstrated that body fat percentage in both conditions was associated with aerobic capacity. A negative relationship between VO2 max and body fat percentage has been observed in younger, healthy populations,31 so this may also be an influence in this study but the direction of causality is not clear. Body weight also forms part of the calculation for VO2 peak so could increase the likelihood of association, but weight does not automatically imply adiposity and is further complicated in muscle wasting diseases. In addition, body mass index (BMI) was not associated with VO2 peak in this cohort. The R² values were relatively low, however, implying that other factors that were not measured in this study could have greater associations with aerobic capacity.

Functional predictors of aerobic capacity are useful to ascertain as they may be potential surrogate measures where CPET testing is
not available or indicated in an individual. Six-minute timed walk was predictive of VO₂ peak in both exercise groups and is a simple clinical test to administer. The IBM participants also demonstrated that steps per day were associated. Steps per day give an indication of physical activity levels in this ambulant group and may represent the impact of deconditioning through sedentary behavior. The same relationship was not seen in the CMT participants, but there was greater variability in steps per day as evidenced by the very high standard deviation.

It is important to acknowledge the limitations of this study. We made comparisons with normative data from upright bicycle ergometry and participants in this study were in a semi-recumbent position. The literature in non-neurological cohorts indicates no significant difference in VO₂ peak between upright and semi-recumbent cycling position of 65°, comparable to the cycling position in this study.³² This has not been tested in people with neuromuscular diseases.

Participants were able to ambulate, so we did not have an opportunity to explore cardiorespiratory fitness in more severe disease and/or at later stages due to the inclusion criteria for the main intervention study, that may have also introduced recruitment bias. This will be impacted by the small sample size. Recruitment of people with rare diseases is difficult, and small samples are common in trials, but the bias to more able individuals will influence how representative the participants were of the population.

6 CONCLUSIONS

This study explores performance of CPET testing in two neuromuscular diseases and factors that may relate to performance. Maximum heart rate was not reached by the participant groups at peak oxygen uptake indicating that peripheral factors, such as muscle atrophy, may have limited performance. Peak oxygen uptake was predicted by body fat percentage in both groups. Performance of the 6-min walk test was also associated and could be recommended as a surrogate measure in the clinic.

ACKNOWLEDGMENTS

This work was funded by an NIHR Research for Patient Benefit Award PB-PG-0711-25151 [Chief Investigator: G.M.R]. This is a summary of independent research funded by the National Institute for Health Research (NIHR)’s Research for Patient Benefit Program. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The Queen Square MRC Centre for Neuromuscular Diseases is supported by a Medical Research Council grant (MR/K000608/1) [M.G.H., M.M.R., G.M.R.]. M.M.R. is grateful to the Medical Research Council (MRC), MRC Centre grant (G0601943), and the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712) for their support. This research was also supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre [GMR].

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Gita M. Ramdharry https://orcid.org/0000-0001-9344-0301
Amanda Wallace https://orcid.org/0000-0001-8743-8897
Alessandra Pietrusz https://orcid.org/0000-0002-2615-9613

REFERENCES

1. Aitkens S, Kilmer DD, Wright NC, McCrory MA. Metabolic syndrome in neuromuscular disease. Arch Phys Med Rehabil. 2005;86:1030-1036.
2. Anens E, Emtner M, Hellström K. Exploratory study of physical activity in persons with Charcot-Marie-tooth disease. Arch Phys Med Rehabil. 2015;96:260-268.
3. Ramdharry GM, Pollard AJ, Grant R, et al. A study of physical activity comparing people with Charcot-Marie-tooth disease to normal control subjects. Disabil Rehabil. 2016;39:1753-1758.
4. World Health Organisation WHO. Physical Inactivity: A Global Public Health Problem. (2014). Accessed December 29, 2020. https://www.who.int/health-topics/physical-activity#tab=tab_2.
5. Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. J Psychosom Res. 2007;62:571-579.
6. Carter GT, Abresch RT, Fowler WM Jr, Johnson ER, Kilmer DD, McDonald CM. Profiles of neuromuscular diseases. Hereditary motor and sensory neuropathy, types I and II. Am J Phys Med Rehabil. 1995;74:S140-S149.
7. Wiesinger GF, Quittan M, Nuhr M, et al. Aerobic capacity in adult dermatomyositis/polymyositis patients and healthy controls. Arch Phys Med Rehabil. 2000;81:1-5.
8. Wallace A, Pietrusz A, Dewar E, et al. Community exercise is feasible for neuromuscular diseases and can improve aerobic capacity. Neurology. 2019;92:e1773-e1785.
9. Griggs RC, Askanas V, DiMauro S, et al. Inclusion body myositis and myopathies. Ann Neurol. 1995;38:705-713.
10. World Health Organisation. WHO | Global recommendations on physical activity for health. https://www.who.int/publications-detail-redirect/9789241599979. Accessed September 14, 2021.
11. American Thoracic Society & American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167:211-277.
12. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986;60:2020-2027.
13. Pinkstaff S, Peberdy MA, Kontos MC, Finucane S, Arena R. Quantifying exertion level during exercise stress testing using percentage of age-predicted maximal heart rate, rate pressure product, and perceived exertion. Mayo Clin Proc. 2010;85:1095-1100.
14. Murphy SM, Herrmann DN, McDermott MP, et al. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-tooth disease. J Peripher Nerv Syst. 2011;16:191-198.
15. Jackson CE, Barohn RJ, Gronseth G, Pandya S, Herbelin L, The Muscle Study Group (MSG). Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve. 2008;37:473-476.

16. Krupp LB. Measurement of fatigue. Fatigue. Philadelphia, PA: Butterworth Heineman; 2003.

17. Graham RC, Hughes RAC. Clinimetric properties of a walking scale in peripheral neuropathy. J Neurol Neurosurg Psychiatry. 2006;77:977-979.

18. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381-1395.

19. Mulligan HF, Hale LA, Whitehead L, Baxter GD. Barriers to physical activity for people with long-term neurological conditions: a review study. Adapt Phys Activ Q. 2012;29:243-265.

20. Blackie S, Fairbarn MS, McElvaney NG, Morrison NJ, Pardy RL. Normal values and ranges for ventilation and breathing pattern at maximal exercise. Chest. 1991;100:136-142.

21. Sun X-G, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med. 2002;166:1443-1448.

22. Wasserman K. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

23. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika. 1986;73:751-754.

24. Paterson DH, Govindasamy D, Vidmar M, Cunningham DA, Koval JJ. Longitudinal study of determinants of dependence in an elderly population. J Am Geriatr Soc. 2004;52:1632-1638.

25. Bassett DR, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc. 2000;32:70-84.

26. Howley E, Bassett D, Welch H. Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc. 1995;27:1292-1301.

27. Morrow JM, Sinclair CDJ, Fischmann A, et al. MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study. Lancet Neurol. 2015;15:65-77. https://doi.org/10.1016/S1474-4422(15)00242-2

28. Schillings ML, Kalkman JS, Janssen HMHA, Van Engelen BGM, Bleijenberg G, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders. Clin Neurophysiol. 2007;118:292-300.

29. Lindeman E, Spaans F, Reulen JP, Leffers P, Drukker J. Surface EMG of proximal leg muscles in neuromuscular patients and in healthy controls. Relations to force and fatigue. J Electromyogr Kinesiol. 1999;9:299-307.

30. Menotti F, Laudani L, Damiani A, Macaluso A. Amount and intensity of daily living activities in Charcot-Marie-Tooth 1A patients. Brain Behav. 2014;4:14-20.

31. Mondal H, Mishra SP. Effect of BMI, body fat percentage and fat free mass on maximal oxygen consumption in healthy young adults. J Clin Diagn Res. 2017;11:CC17-CC20.

32. Egaña M, O’Riordan D, Warmington SA. Exercise performance and VO2 kinetics during upright and recumbent high-intensity cycling exercise. Eur J Appl Physiol. 2010;110:39-47.

How to cite this article: Ramdharry GM, Wallace A, Hennis P, et al. Cardiopulmonary exercise performance and factors associated with aerobic capacity in neuromuscular diseases. Muscle & Nerve. 2021;64(6):683-690. doi:10.1002/mus.27423