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Evaluation of a control paradigm allowing heart rate guided rehabilitative exercise for boys with Duchenne muscular dystrophy

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Abstract

Background Aerobic cycle-training counters deconditioning and induces muscle and cardiorespiratory benefits in various neuromuscular disorders. However, its application to Duchenne muscular dystrophy (DMD) is limited due to lack of exercise prescription guidelines, particularly for intensity. A balance between beneficial versus harmful effects of muscle activity must be established given the weakness and concerns of contraction-induced damage inherent to DMD. Previous studies in DMD used motor-assisted cycling applying subjective ratings of perceived exertion to guide exercise intensity, whereas objective parameters such as heart rate (HR) or work performed were not reported. In efforts to develop exercise guidelines for DMD, we designed a motor-assisted cycle-exercise paradigm using closed-loop control of motor effort and individualization of intensity based on HR. Feasibility of this paradigm in DMD was tested in the home setting with remote clinical supervision.

Methods A closed-loop controller was developed with user-defined saturation points for cadence and baseline motor inputs to ensure safety of cycling and adjustments in level of muscle overload (assistive current). The controller allowed remote, interactive adjustment of current based on HR biofeedback, providing cycling assistance when velocity approached a lower-bound and resistance when the upper-bound was approached. A target intensity of 40–50% HR reserve was individualized for each participant and motor effort was adjusted accordingly by the clinician. Force-sensors were embedded in the pedals for quantification of passive and active power.

Results Six ambulatory boys with DMD (aged 7.7 ± 0.9 years) completed at least two bouts of cycling exercise (3-10 min per bout) with an average 0.53 ± 0.15 amps assistive current (range 0.3–0.8 amps). HR increased from rest during passive and active cycling (mean 109.2 ± 6.1; 119.2 ± 8.5; 149.7 ± 4.6 bpm respectively), where boys were actively exercising at 45% of HR reserve at an average cycling power of 5.7 ± 1.3 watts (ranging 3-8 watts depending on disease severity).

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Conclusion These results show for the first time that boys with DMD can cycle actively to generate power and raise HR to a prescribed intensity, supporting feasibility of this home-based, remotely-supervised control paradigm. They warrant future study to establish clinical exercise prescription parameters and the potential of aerobic cycling as a rehabilitative strategy in DMD.

Keywords Closed-loop control, Custom-engineered device, Aerobic exercise prescription, Active cycling power, Individualized training, Heart rate biofeedback, Home-based rehabilitation

Introduction

Duchenne muscular dystrophy (DMD) is a severe, rapidly progressive neuromuscular disorder affecting approximately 1 in 5000 live male births [1]. It is caused by a gene mutation in the sarcolemmal protein dystrophin, rendering muscle susceptible to contraction-induced damage. DMD is characterized by established patterns of muscle degeneration and fibrofatty replacement leading to significant weakness and fatigue, mobility impairment and loss of ambulation typically by 12 years of age. Disease progression prior to wheelchair dependence is associated with reduced daily physical activity [2]. The role of rehabilitative exercise to delay loss of function and improve quality of life is a key consideration in management and care of DMD.

Current DMD care considerations recommend avoidance of high intensity, eccentric muscle contractions and promote participation in regular submaximal, low-impact aerobic activities (swimming and cycling) with assistance as needed [3, 4]. However, due to longstanding concerns of contraction induced injury, apprehension and avoidance of exercise still persist in the majority of DMD patients. This relates largely to the lack of exercise prescription parameters for the DMD population, particularly regarding the optimal dose (intensity and time) where a balance between beneficial versus harmful effects of muscle activity must be established [4]. For aerobic exercise, the dose recommended by the American College of Sports Medicine (ACSM) for deconditioned populations is 40–60% of heart rate reserve (HRR) for 20–30 min continuously or intermittent bouts [5]. Regular cycling exercise using these exercise prescription parameters is known to counter secondary muscle disuse and benefit musculoskeletal and cardiorespiratory health in a wide spectrum of clinical populations, including other neuromuscular diseases [6, 7]. However, whether boys with DMD are capable of cycling at this intensity for even one exercise bout is unknown. The prevailing notion in DMD (and the neuromuscular diseases community in general) is that muscle weakness restrains the cardiopulmonary system and prevents HR increases into the ACSM prescribed training zone [8, 9]. Supporting this notion, every study assessing aerobic training in boys with DMD used motor-assisted cycling that promoted predominantly passive cycling movements [10–13]. The intensity of exercise was guided by subjective ratings of perceived exertion (RPE), and objective measures (i.e. HR or work performed) were not reported. Therefore, whether the motor-assisted exercise imposed sufficient load to trigger adaptive mechanisms associated with aerobic-training benefits is unknown. We recently demonstrated the ability of boys with DMD to safely reach peak heart rates indicative of maximal effort exercise (85% age predicted maximum) [14], suggesting they may tolerate the sub-maximal cardiorespiratory demands associated with aerobic-training.

To understand the potential of aerobic exercise in DMD, we developed a motor-assisted cycling paradigm using a closed-loop controller for motor input. Integrating computer aided design and feedback sensors in the pedals, this paradigm allowed the clinical research team (physical therapists and exercise physiologists) to monitor cadence and power generated during passive and active cycling, with the ability to remotely adjust the degree of assistive or resistive cycling based on real-time HR. Our objective was to establish proof of concept that boys with DMD can cycle actively with their legs and exercise safely within a HR zone recommended for physiological adaptation. To evaluate our proposed paradigm, we: (1) quantified cycling power generated by the participant above that of the motor; (2) examined participant HR response to cycling at varying levels of assistance on our customized device; and 3) evaluated the feasibility of remote clinical supervision and control of motor input during an exercise session. These data are essential for development of exercise prescription guidelines and integration of aerobic training into rehabilitation for those with DMD.

Methods

Experimental device

Our choice of exercise modality is cycling which is considered low-impact and avoids high-intensity, eccentric actions that are known to be damaging to dystrophic muscle. The motor-assisted cycling paradigm is intended for long-term, home-based use by ambulatory boys with DMD, and includes the following: exercise chair, custom-built cycle ergometer, a laptop computer (Dell Latitude, Dell Technologies, Round Rock, Texas, USA) to provide feedback to the participant on real-time cycling cadence, as well as a chest strap and watch (Polar H9 sensor and Polar Unite, Polar Electro Oy, Kempele Finland) to

monitor participant HR. Design and development of the mechanical system and control scheme took place within the Mechanical and Aerospace Engineering lab at the University of Florida (UF).

The mechanical components of the ergometer are shown in Fig. 1. A commercially available leg extension device (Valor Fitness CC4) was available from a previous study [15], and modified to serve as the ergometer chair. To accommodate the spectrum of heights within the target age range, a child's car seat (Mifold Hifold) was affixed to the seat of the exercise chair to prevent excess movement during exercise. The base of the cycle was designed to act as the housing for all electronic components. The frame of the base was made of aluminum plating, 80/20, ABS plastic siding, and a removable plexiglass top. Aluminum upright supports fix the crank shaft assembly to the base of the cycle. Crank arms with adjustable lengths help account for variation in sizes between participants, and velcro straps securely fix the rider's feet to the pedals. A plastic chain guard was fastened over the crank assembly to ensure participant safety. A bike chain mechanically couples the crank shaft to an electric motor for motor assistance and to an encoder assembly for crank angle measurements. Motor control is implemented using an Advanced Motion Controls motor driver and power supply (see Fig. 1). The ergometer is equipped with torque sensors in the pedals allowing measurement of active forces produced during cycling versus passive forces provided by the motor. Torque measurements about the crank shaft are recorded using a torque sensor (Science Road, SRM, USA). Position and cadence about the crank shaft are measured using US Digital H1 encoders. An onboard data acquisition board (Q2-USB, Quanser, Canada) is installed to measure the encoder signal. Although the system does not contain an onboard computer, controllers are implementable via MATLAB/Simulink and QUARC software on an external computer. ANTware software was used to convert the blue tooth signal from the torque sensor to power data. An emergency cut-off switch is fastened to the side of the cycle base to ensure participant safety.

The motor controller for the cycle ergometer is designed as a closed-loop system with user-defined saturation points and a constant motor effort. The controller is fully automated within the system, intended is to provide multiple exercise modalities by allowing the participant to cycle at a given level of baseline assistance, or receive additional motorized assistance or resistance as needed to meet the exercise goals (Fig. 2A). The inputs include human-powered torque to the system and motor effort (u_{motor}) with the output defined as revolutions per minute (RPM). A constant baseline current is set and then altered as needed using a hyperbolic tangent (tanh) function. The baseline current is experimentally derived with the stated goal of maintaining a desired cadence and range. Resistive or assistive current (i.e., the result of the tanh function) is provided when the participant approaches the outer bounds of the safe range of desired velocity. The mid-point of the safe range of desired velocity is denoted by $\dot{q}_{mid}$, and the outer edges of the safe set are denoted by $\pm\alpha$. The range across which assistive or resistive effort should be applied is denoted by β. The difference between the outer bound of the safe set and the assist/resist range is defined as $\delta : \delta = \alpha - \beta$. The calculated motor control input current (Amps) can be represented by Eq. 1:

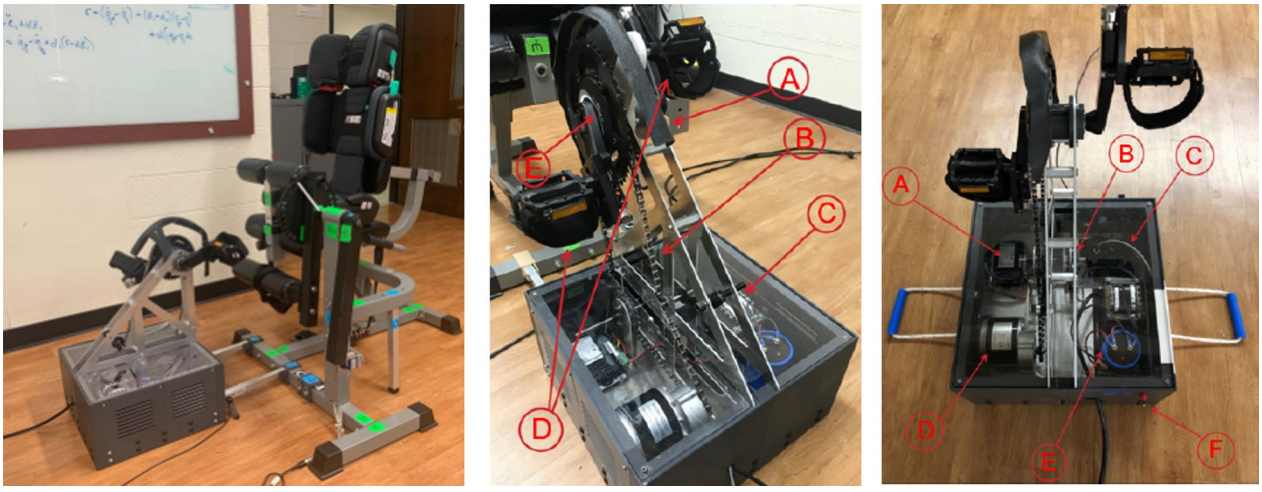

Fig. 1 An overview of the mechanical system developed for motor-assisted cycling. It consisted of a modified exercise chair, child car seat, recumbent cycle ergometer (left). Close up (middle) of the motor-assisted ergometer, depicting chain guard (**A**), bike chain (**B**), aluminum supports (**C**), pedals (**D**) and torque sensor (**E**). Top-down view (right) of the motor driver (**A**), encoder (**B**), data acquisition device (**C**), electric motor (**D**), power supply (**E**), and emergency cut-off switch (**F**)

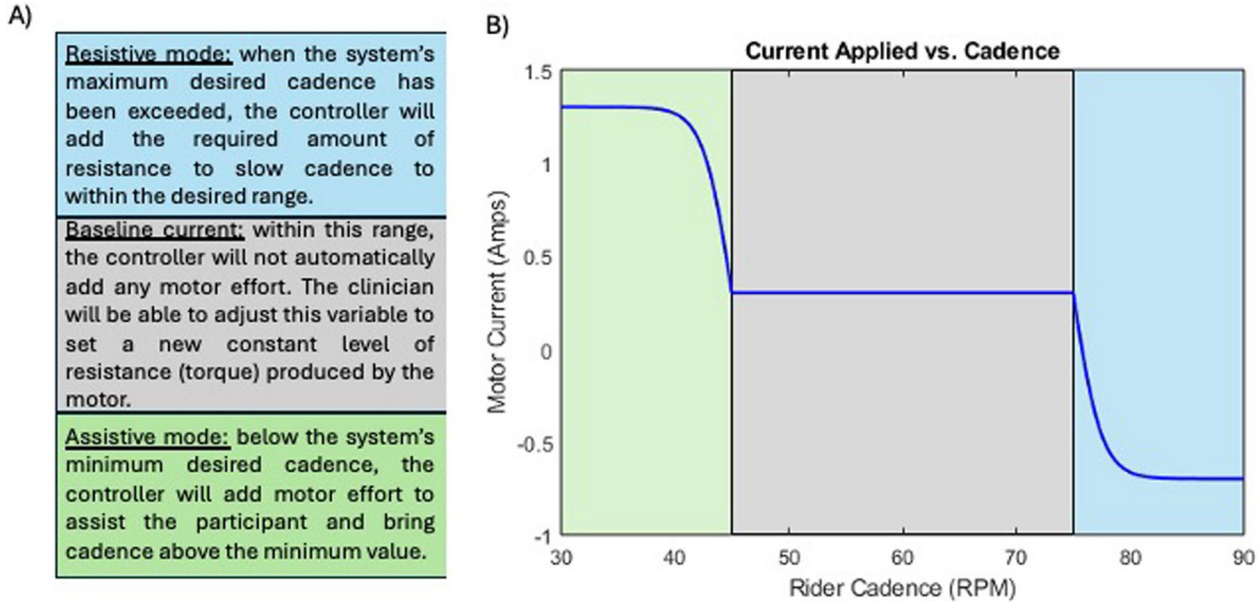

Fig. 2 Controller design. Left: The intended modalities for motor-assisted cycling using the closed-loop controller. Right: A plot of the resulting motor current in relation to the rider's pedaling cadence. When the participant is pedaling within ± 15 RPM of the midpoint of the target pedaling range (60 RPM), the motor current remains constant at a predetermined set point of (0.3 Amps). When pedaling slows below 45 RPM, the resulting motor current gradually increases for greater assistance. Conversely, when pedaling increases above 75 RPM, motor current gradually decreases to resist the participant's efforts. Note that the change in motor current saturates at ± 1 Amp above the predetermined set point. Details regarding the control variables can be found in Eq. 1 (Methods)

$$u_{motor}\left(\dot{q}\right) \triangleq \begin{cases} \zeta + k\tanh\left(\frac{\dot{q}_{mid}+\delta-\dot{q}}{\beta/2}\right) & if\, \dot{q} > \dot{q}_{mid} + \delta, \\ \zeta + k\tanh\left(\frac{\dot{q}_{mid}-\delta-\dot{q}}{\beta/2}\right) & if\, \dot{q} < \dot{q}_{mid} - \delta, \\ \zeta & otherwise, \end{cases}$$

where $\dot{q} \in \mathbb{R}_{>0}$ represents the angular velocity of the cycle, $\zeta \in \mathbb{R}$ represents the user selected constant baseline current (Amps), and $k \in \mathbb{R}_{>0}$ represents a user selected positive constant which sets the maximum value of resistive/assistive current. Note: to ensure participant safety, the total motor effort is upper-bounded when $\dot{q} \geq \dot{q}_{mid} + \alpha$ and lower-bounded when $\dot{q} \leq \dot{q}_{mid} - \alpha$. A secondary safety limit was placed on the system where μ would not exceed ± 3 A.

We selected values for these variables to be $\dot{q}_{mid} = 60, \alpha = 20,$ and $\beta = 5,$ with the rationale that 50–60 rpm is typically used as a pedaling cadence during cardiopulmonary exercise testing in children and adults [16–18]. A plot of the resulting motor current using these values is shown in Fig. 2B, noting that if the cadence is within a desired range, there is no change in the baseline current. The controller only assists or resists momentarily when the desired cadence falls out of range. A reduction in motor current represents resistance (i.e. a reduction in torque applied by the motor) and an increase in motor current represents assistance.

In addition to the automated controller maintaining motor current, an input window was added to the graphic user interface within the Matlab software allowing the supervising study member to manually alter any of the variables (target RPM, outer bounds of safe cadence range, baseline current, assist/resist) as shown in Fig. 3A. This pertained primarily to the baseline current, which could be modified as needed to ensure that the desired exercise intensity (reflected as heart rate) was maintained.

Participants

This research protocol was approved by the Institutional Review Board 1 (Project number 201901339) at UF, and all participants provided informed consent to participate in this study. Ambulatory boys aged 6–9 years with a genetically confirmed DMD diagnosis and on a stable glucocorticoid regimen were recruited from the Center for Neuromuscular and Rare Diseases at UF and ongoing investigations at UF. Boys were considered ambulatory if they were able to independently walk at least 100 m without an external assistive device. Exclusion criteria included presence of unstable or concomitant medical problems, including severe cardiomyopathy or cardiac conduction abnormalities, presence of a secondary condition that impacts muscle function or muscle metabolism, history of rhabdomyolysis, inability to comply with instructions and/or current or prior participation in investigational studies. As part of standard pre-exercise health screening [19], the study neuromuscular physician and cardiologist reviewed inclusion/exclusion

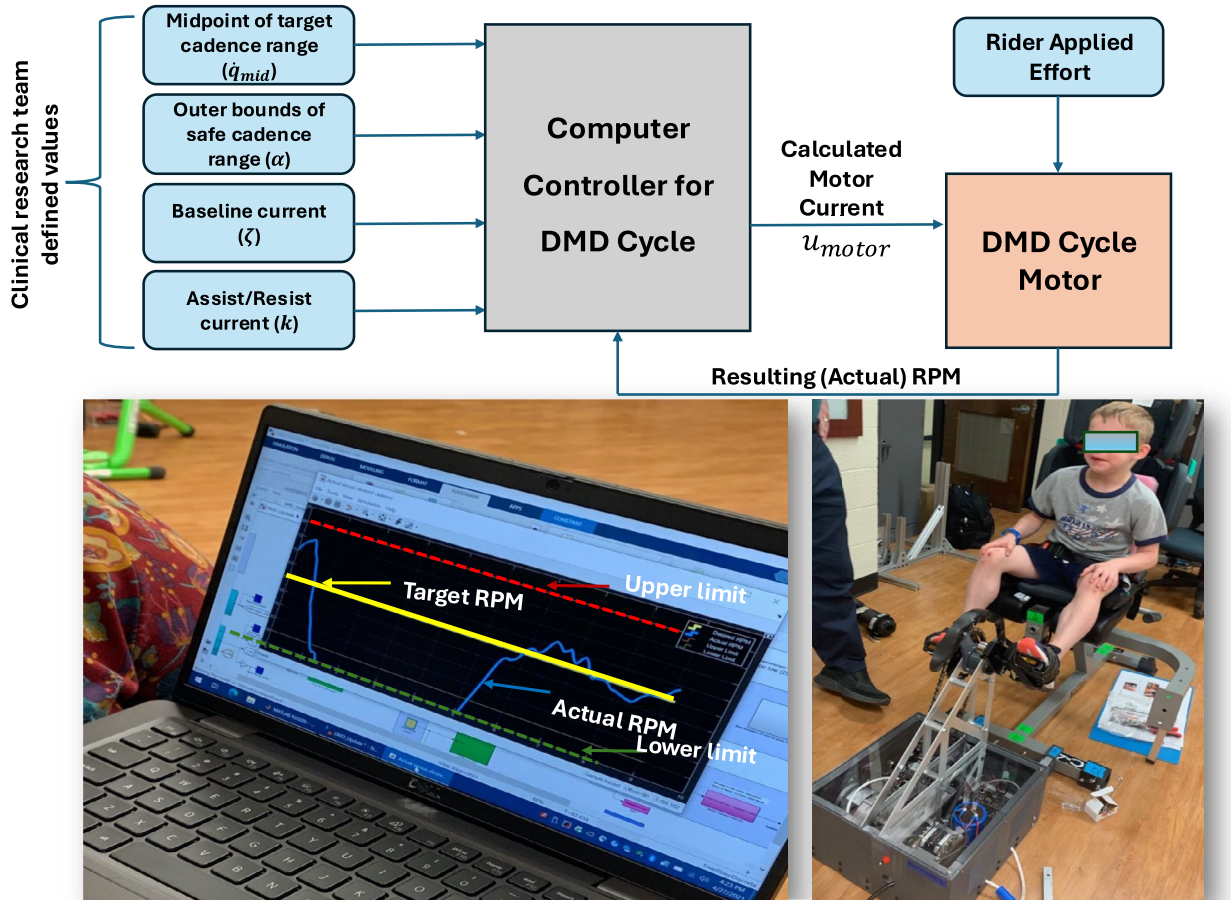

Fig. 3 Overview of the closed loop controller and cycle-exercise paradigm designed for DMD. Top: A graphical representation of the controller and cycle motor inputs and outputs. The blue rectangles represent inputs specific to the computer by the clinical research team (desired cadence range, safety bounds, baseline current, and assistive/resistive current values) and to the cycling system by the user (rider applied effort). The calculated motor current is the output of the computer and pedaling cadence is the resulting output of the cycling system. Bottom left: Feedback provided to the individual from the laptop computer indicating actual cadence (blue line) relative to the target cadence (yellow line). If the actual cadence falls below the target, motor-assistance is automatically provided to minimize error. If actual cadence is higher than target, resistance will be provided. Note that it is not possible for the participant to operate the system outside of the desired cadence range (noted as upper and lower limits) due to the user-set saturation points on motor current. Bottom right: A study participant is seated on the customized ergometer and instructed to maintain cadence as close to the target as possible. Heart rate is continuously monitored using a chest strap (not visible) and watch (on right wrist)

criteria and medical history and cleared each participant to undergo submaximal cycling exercise. Informed consent and assent were obtained from parents and participants respectively as part of their study visit at UF. All procedures performed in our human participants were in accordance with the ethical standards of the 1975 Helsinki declaration.

Experimental tasks and protocol

Ambulatory ability and physical function: To characterize DMD disease severity in our participant cohort, standard physical functional tests commonly used in clinical trials were performed at the UF's Clinical Research Center. These included assessment of the 6-min walk distance (6MWD), the time to complete the 10 m walk/run (10 m w/r), and the North Star Ambulatory Assessment (NSAA). Briefly, the 6MWD was assessed on a 25-m course using standard guidelines for DMD [20]. The distance traversed in 6 min was recorded in meters and also presented as % predicted to compare to normative data taking differences in age and height into account [20]. The 10 m w/r test was performed with participants up to 3 times wearing shoes, with the fastest time used for analysis [21]. The NSAA, which comprises 17-items of physical function yielding a clinician-rated score between 0 and 34 was also conducted [22].

Familiarization to cycling paradigm: This session was held in the Mechanical and Aerospace lab to inform the participant and parent about use of the equipment. The study team instructed the parent on how to set up and use the cycling ergometer, as the intent was to use the same equipment at home. Parents were also instructed on how to set up the HR monitor and to allow the study team to remotely access the controller on the laptop

using video-calling (Zoom Communications Inc, Denver, USA). The participant tested the equipment by first having the study team ensure proper sizing of the seat distance to the ergometer. The crank arms were adjusted as needed to allow the participant to pedal comfortably without full extension of the knee joint. The controller software was opened, and the participant was asked to cycle for no more than 5 min and instructed to pedal at the mid-point (target) of the desired RPM values to the best of their abilities. The goals of this exercise session were to have the participant cycle and follow the individualized cadence trajectory displayed on the laptop computer as well as understand how to read HR on the watch. During this session, the study team determined what baseline current was most appropriate based on disease severity (as assessed by the physical function outcomes) and participant ability to follow the target cadence. The baseline current was recorded for each participant for later use in the home-based exercise session.

Home-based cycle exercise session: Within 3 weeks of the study visit, a similar equipment set-up (cycling ergometer, HR monitors and laptop computer) was shipped to the participants' home. The goal of this session was to assess whether the participant could perform exercise in their own home with remote supervision by the study team using exercise prescription parameters based on the 'FITT' principle (a framework for structuring exercise based on the factors of Frequency, Intensity, Time (duration) and Type of exercise) [23]. More specifically, 'Frequency' was set as one session of exercise (as opposed to three times per week as recommended for training purposes), 'Type' was active cycling exercise, and 'Intensity' and 'Time' factors were based on recommendations for deconditioned individuals (ACSM) where 'Intensity' = 40–50% HR reserve (moderate intensity) and 'Time' = a maximum of 20 min of continuous or intermittent bouts [5]. HRR was calculated as the difference between predicted peak HR ($HRpeak_{pred)} = 208—0.7 \times age$ [24] and HR at rest [5]. HRR was chosen as the optimal approach rather than a percentage of $HRpeak_{pred}$ to guide individualized exercise intensity for boys with DMD given their known resting tachycardia [14]. Therefore, for each participant, a heart rate zone was calculated as (HRtarget zone = [HR rest + 0.4 HRR] to [HR rest + 0.5HRR]). Ratings of perceived exertion (RPE) using the Borg scale (1 to 10) were also monitored as a secondary gauge of exercise intensity [25]. For the 'Time' factor, we chose intermittent bouts rather than continuous exercise given the lack of previous exercise and to avoid muscle pain or fatigue.

For the home-based exercise session, the study team used Zoom video (Zoom communications Inc, Denver, USA) to communicate with the participant's parent for connecting the laptop at the participants' home. Using the remote access feature, the research team member took control of the software and launched the necessary software for operating the exercise ergometer and collecting the data. This remote access enabled the study team member to oversee the exercise session and adjust the difficulty of cycling by adjusting the level of baseline current depending on live feedback from the participant's heart rate. The parent was present with the child for the duration of the exercise session, and helped place the HR chest strap and watch, and seat the participant comfortably on the chair next to the ergometer with the feet strapped into the pedals. When ready to begin the session, the study team instructed the parent or participant to start the HR watch allowing collection of data, and the participant rested for up to 3 min. Following this, the study team input the baseline current in the Matlab software and instructed the participant to cycle passively for the first minute, saying 'just let the motor move your legs'. After one minute, the participant was instructed to cycle actively ('push the pedals to follow the yellow line') at the target cadence (60 RPM) shown on the laptop computer. Feedback was continuously provided to the participant with the actual cadence shown in real-time as a blue line. The participant was encouraged to keep actual cadence on the target trajectory. The baseline current was adjusted (increased to add assistance or decreased to remove assistance to individualize the exercise workload) by the study team based on participant HR (with the aim of keeping HR within the predetermined zone) and participant RPE (with the aim of keeping it less than 7 out of 10). Our goal was to have each participant cycle within their individual HR zone for at least 3 min continuously, up to a maximum of 10 min. If the upper limit of HR was reached, baseline current would be increased by the study investigator offering additional motor assistance and making it easier for the participant to cycle (to lower HR), or the exercise was stopped. Up to 3 exercise bouts were performed as part of the cycling session for a given participant. The 1-min of passive cycling was only performed as part of the first exercise bout to assess the work of the motor. At the end of the exercise session, the study investigator asked the participant and parent about any symptoms (i.e. muscle pain or soreness, dyspnea and/or overall fatigue) and ensured that participant's HR had returned to the pre-exercise level before logging off.

Data analysis

Outcomes (HR, current, power) were collected onto the home-based laptop during each exercise session. Following the session, the files were transferred by the study team to a secure drive at UF for subsequent analysis. HR was averaged every minute (rest through exercise). Power measurements from the 1-min of passive cycling were averaged and subtracted from the total power of the

active cycling session to provide participant power per exercise bout.

All statistics were analyzed using Prism, Version 10.2.2 for macOS. Quantitative descriptive statistics are presented as mean ± SD. One-way ANOVA was used to compare HR between rest, passive and active exercise. The Tukey's multiple comparisons test was used to adjust for P values in multiple comparisons. Simple linear regression was used to determine strength of relationship between variables. The level of baseline current provided for each participant was compared to the 6MWD or performance in NSAA and 10 m w/r using Pearson correlation. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Results

Participant demographics and physical function

Six ambulatory boys with genetically confirmed DMD ranging in age from 6.5 to 9.0 years (mean 7.7 ± 0.9 years) participated in this study (Table 1). Participants were on a stable corticosteroid regimen, and only one boy was taking a cardiac medication (lisinopril) commonly prescribed for DMD in this age range. All boys were cleared by the study cardiologist to undergo cycling exercise at submaximal intensity based on review of medical history and a cardiac ejection fraction greater than 45%. There were no adverse events associated with any of the study procedures.

Disease severity was characterized by performance in physical function tests (Table 1). The 6MWD ranged from 177 to 509 m (mean 357.0 ± 113.7 m), equaling on average 61.8 ± 19.7% of predicted distance walked by healthy individuals [20]. The average time to complete the 10 m walk/run was 5.6 ± 3.0 s (ranging from 3.3 to 11.5 s) and the NSAA score was 22.7 ± 9.0 (range 6 to 30 noting 34 is a maximal score). Collectively these tests reflect reduced walking ability and physical function in the cohort on average, and highlight the known variability in physical function in individuals with DMD.

Familiarization session

All boys successfully tested the motor-assisted cycle-exercise paradigm at UF (Fig. 3). The study team set the controller gains in the Matlab graphic user interface. A baseline current of 0.3 amps was applied for most participants and, based on the equation for u_{motor}, the assist / resist value (i.e., the variable k) was set at 1 amp value. If participant effort appeared too difficult within the first minute, the baseline current was increased. The baseline current value was recorded for use in their home-based exercise session. Each participant cycled for 3 to 5 min within the upper and lower limits of the set cadence and experienced assistance and resistance from the motor during cycling. The actual amount of assistance or resistance was modulated by the $tanh\,(\bullet)$ term (Eq. 1) based on the proximity of the participant's output RPM to the boundaries of the desired cadence range. Each participant learned how to use the HR monitor, but data were not recorded.

Controller function and cycling power

Data on automated controller function and cycling power were collected as part of the home-based sessions for every participant's exercise bout. The motor controller was designed to apply the maximum assistive current value until the lower bound of the desired cadence range is reached. Once the participant is within the desired cadence range, the motor effort is adjusted from baseline only when the participant is pedaling the cycle at a cadence near the upper or lower bounds of the cadence range (as shown in Fig. 2). Figure 4A and B demonstrate the controller data in two representative participants, where cadence and applied motor current were tracked during 1-min of passive cycling followed by the active cycling phase of the exercise bout. As seen during the first minute when the participant is instructed to just let the motor move their legs, the applied motor current continuously increases (upward lines relative to baseline current) in response to the cadence being near the bottom of the desired range as set by $\dot{\boldsymbol{q}}_{\boldsymbol{mid}} \pm \boldsymbol{\alpha}$, (i.e., a lower bound of 40 RPM). Similarly, during the active phase when the participant (DMD-02) is following the

Table 1 Characteristics of the participants with DMD

Code	Age (years)	Dystrophin mutation	EF (%)	Medications	6MWD, meters (% predicted)	NSAA	10 m (sec)
DMD-01	7.5	c.5082delA	68	Prednisone	387 (66.8%)	30	4.1
DMD-02	7.0	Deletion 46–50	69	Prednisone	426 (77.0%)	29	3.3
DMD-03	8.0	Deletion 4–8	70	Prednisone	509 (84.4%)	27	4.4
DMD-04	6.5	Deletion 31–43	67	Prednisone	343 (62.2%)	25	5.0
DMD-05	8.0	c.7075C > T	50	Prednisone, lisinopril	300 (50.7%)	19	5.0
DMD-06	9.0	Deletion 49–52	66	Deflazacort, exon-skipping	177 (29.4%)	6	11.5
AVG ± STDEV	7.7 ± 0.9		65 ± 7.5		357 ± 113 (61.8 ± 19.7%)	22.7 ± 9.1	5.6 ± 3.0

Demographics of six ambulatory boys with DMD are provided. All individuals were on a regular dosing regimen of corticosteroids. Only one individual was taking a cardiac medication at the recommended dose; and one other individual was on a stable treatment regimen of FDA-approved exon skipping. *EF* ejection fraction, *6MWD* six-minute walk distance, *%* percent predicted based on normative data [16], *NSAA* North star ambulatory assessment

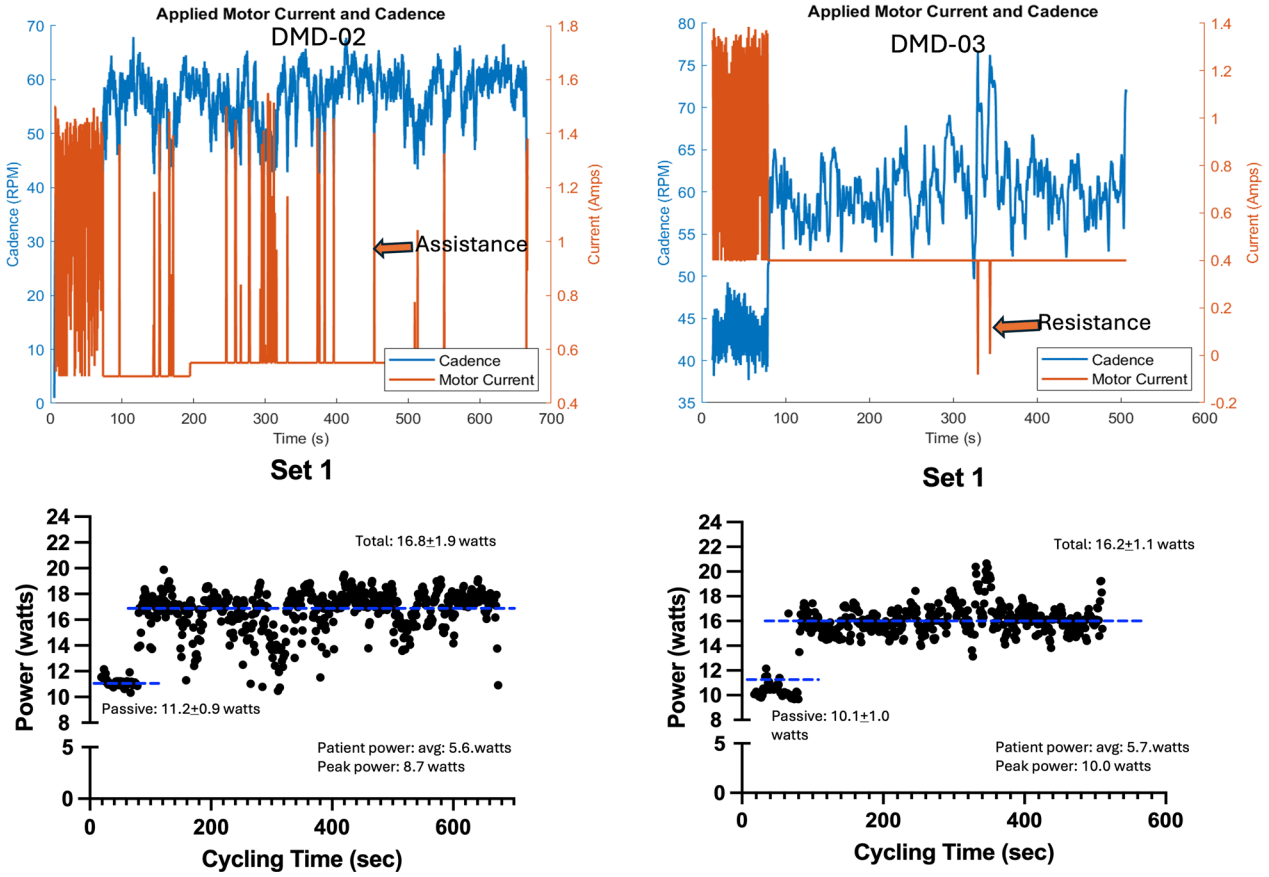

Fig. 4 Representation of data captured during motor assisted cycling in two different boys with DMD. **A** and **B**: Cadence and applied motor current are shown during the passive (first minute) and active cycling phase, along with the level of baseline current (horizontal line indicating motor current). When cadence falls below the target (60 rpm), the controller increases the current applying assistance to cycling (**A**). When cadence increases above the target, the degree of motor current assistance decreases (downward orange lines) applying resistance to cycling (**B**). Force sensors in the ergometer pedals allow quantification of power during the passive and active cycling phase of each exercise session. Periods of assistance during active cycling result in lower power (**C**) or greater power output (**D**) relative to baseline current (as indicated by the orange circles). The difference between total and passive power is the power generated by participant

target cadence, applied motor current increased each time cadence fell below 45 RPM and assistance was added (Fig. 4A). In addition, Fig. 4A demonstrates a manual increase in baseline current (from 0.50 amps to 0.55 amps) by the supervising clinician after approximately 1 min of active cycling. In contrast, when the participant (DMD-03, Fig. 4B) pedaled at a cadence higher than 75 RPM, motor current decreased reflecting the application of resistance. Furthermore, it is also shown that u_{motor} never exceeds the selected motor current saturation points, supporting our intent to enforce a boundary on desired cadence values for participant safety. Overall, the closed-loop controller performed as expected.

Simultaneous to motor current and cadence, data on power generated during passive and active cycling were collected through the force sensors in the pedals for every exercise bout. As shown in Fig. 4C and D, when the participant was instructed to let the motor move their legs, power was relatively constant and lower compared to the active cycling phase. The variability in power during active cycling reflects differences in applied motor current, where the watts generated during the assistive and resistive phases are lower (Fig. 4C) or higher (Fig. 4D) respectively, compared to cycling at the set baseline current. The difference between total power (during active cycling) minus passive power reflects the watts generated by the participant compared to the motor. On average, boys with DMD cycled at 5.7 ± 1.3 watts (ranging from 3.4 to 8.0 watts).

Cycle exercise duration and intensity

For the home-based session, each participant completed 2–3 bouts of cycling exercise ranging from 3 to 12 min per bout. Whether a third bout was performed was determined based on individual tolerability and clinician judgement to achieve approximately 20 min of total exercise. The duration of each exercise bout was based on individual HR and reported RPE with the goal

Table 2 Data collected during the home-based cycle exercise sessions in six boys with DMD

Code	HR rest (bpm)	HR peak predicted (bpm)	Prescribed exercise HR zone (bpm)	# of exercise bouts	Duration per bout (min)	Passive HR (bpm)	Active HR (bpm)	Assistive current (amps)	Power (watts)	RPE
DMD-01	111	203.8	148–157	3	6,6,6	127	142.3	0.45, 0.45, 0.40	6.5, 6.8, 8.0	5.0
DMD-02	105	203.1	144–154	2	10,12	128	153.1	0.55, 0.50	5.0, 5.6	1.0
DMD-03	118	202.4	143–154	3	7,6,8	110	151.4	0.40, 0.35, 0.30	5.7, 6.2, 6.3	5.7
DMD-04	120	203.5	153–162	2	6,10	125	156.8	0.65, 0.60	6.0, 6.3	na
DMD-05	102	202.4	142–153	2	5,5,4	111	153.7	0.55,0.55, 0.50	6.1, 6.3, 6.6	1.0
DMD-06	110	201.7	147–156	3	3,3,3	120	148.2	0.75, 0.75, 0.75	3.4, 3.5, 2.9	na
AVG ± SD	111 ± 7.0	202.6 ± 0.6		2.5 ± 0.55	6.3 ± 2.6	120.2 ± 8.0	150.9 ± 5.1	0.54 ± 0.14	5.7 ± 1.3	3.2 ± 2.5

Bpm beats per minute, *#* number, *min* minute, *RPE* rating of perceived exertion, *SD* standard deviation

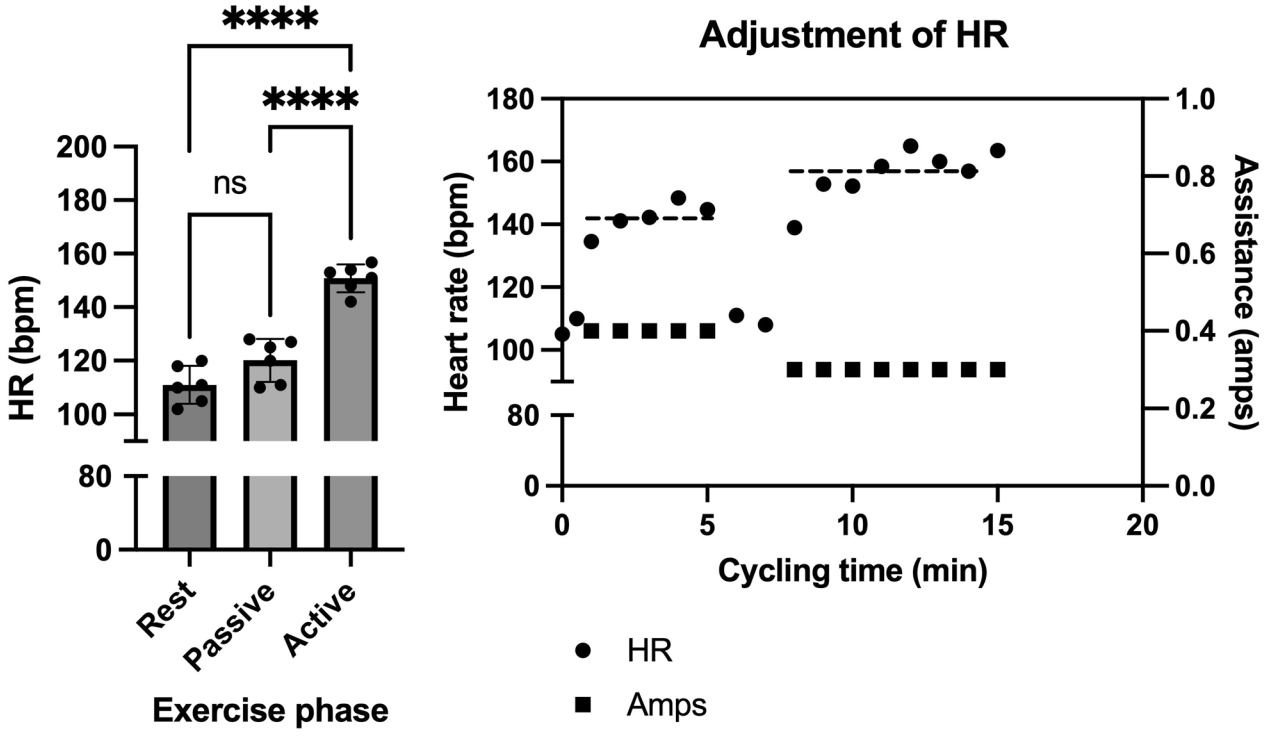

Fig. 5 Changes in heart rate during motor-assisted cycling in boys with DMD. **A** The increase in HR from rest to passive cycling is not significant (ns) whereas active cycling induced a 40 bpm increase in the group of boys. **B** Heart rate response during cycling exercise bout with varying degrees of motor assistance. After one minute of passive cycling, motor-assisted cycling with 0.4 amps leads to an average heart rate of 142.2 ± 5.1 bmp over 5 min of cycling. After two minutes of passive cycling, a second 8-min bout of exercise performed at a lower degree of motor assistance (0.3 amps) leads to a higher average heart rate (156 ± 8.0 bpm)

of achieving moderate-intensity effort. The prescribed HR zone (40 to 50% of HRR) for each participant is shown in Table 2. The average HR at rest of this cohort was 111.0 ± 7.0 bpm reflecting tachycardia consistent with DMD, and peak predicted HR was 202.6 ± 0.6 bpm. Thus, the calculated target HR zone for cycling exercise reflected an approximate 10 bpm window (i.e. 143–154 bpm) for each participant.

The first exercise bout consisted of passive cycling for one minute. During this phase, the increase in HR relative to rest (mean change 9.2 ± 10.5 bpm) was not significant (Fig. 5A) and reflected predominantly motor-assisted effort. However, when individuals were instructed to follow the target cadence at their established level of motor-assistance, HR increased by 40.0 ± 9.1 bpm to 150.9 ± 5.1 bpm ($p < 0.001$). This reflected 44.5 ± 6.1% of HRR and fell within the prescribed intensity zone for active cycling.

Attainment of the prescribed HR zone was possible due the design of the controller allowing the supervising clinical research team member to remotely adjust the level of motor assistance from the baseline current when needed. For example, when HR was at the lower limit of the prescribed zone during the first exercise bout, the clinician decreased the level of assistive current from 0.4 amps to 0.3 amps which resulted in a corresponding increase

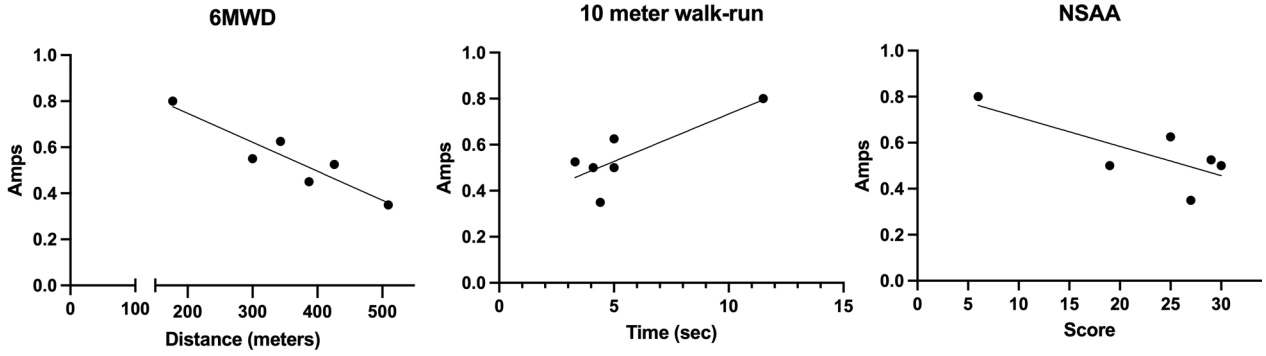

Fig. 6 Correlations between physical function tests and baseline level of motor-assistance during the home-based cycling session for the DMD cohort. *6MWD* six-minute walk distance; *NSAA* North Star Ambulatory Assessment

of HR to reach the prescribed zone in the second bout (Fig. 5B). Alternatively, when HR approached the upper limit, current was increased to provide more assistance and lower HR. The adjustments in assistive current for each participant's exercise bout are shown in Table 2.

Exercise intensity was also assessed subjectively at the end of each cycling bout using the Borg RPE. Four out of six participants provided RPE scores and two participants did not due to their focus on maintaining cycling cadence at the target RPM. Borg RPE values ranged from 1 (corresponding to 'very light activity') to 6 (corresponding to the upper limit of moderate intensity activity), with an average of 3.2 ± 2.5.

Correlation between level of motor-assistance and function

A linear correlation was detected between ambulatory ability based on the 6MWD and level of motorized-assistance amongst the cohort (6MWD and amps: $R^2 = 0.86$, $p < 0.01$, Fig. 6). The individual with the lowest 6MWD required an assistive current of 0.80 amps whereas 0.30 amps was used for the individual with the highest 6MWD. Similarly, the time to complete the 10 m walk run correlated with amps ($R^2 = 0.66$, $p < 0.05$) and a trend was detected between physical function (NSAA) and baseline current ($R^2 = 0.58$, $p = 0.07$). Thus, participants with greater ambulatory and functional ability needed less assistance compared to participants with more severe mobility limitations.

Feasibility of remotely supervised exercise sessions

For each participant, the investigator at UF was able to successfully log on and control the laptop computer at the individuals' home. The parent ensured the participant was securely strapped into the chair and ergometer pedals, and started the HR monitor when instructed to by the clinician. Thereafter, the session resembled a telehealth appointment where the study team and boy with DMD interacted. Each participant completed at least two sessions of cycling exercise, and complied with the exercise instructions of cycling at the target cadence. All data were collected with the exception of Borg RPE in two individuals. There were no adverse events relating to the cycling exercise.

Discussion

This study evaluated an assisted cycling paradigm using closed-loop control of motor effort and individualization of exercise intensity based on HR in boys with DMD. No adverse events related to exercise using this paradigm were observed, and all boys were able to cycle within a HR zone considered safe and reflective of moderate cardiorespiratory intensity, and while doing so, actively perform work above that of the motor. Moreover, we designed this paradigm for use in the home setting with remote supervision and demonstrated its feasibility. The ability to remotely and interactively adjust the degree of motorized assistance during cycling exercise based on participant HR as demonstrated offers a potential new approach to personalize exercise and ensure the appropriate dose. Findings from this study are expected to inform development of exercise prescription parameters for this patient population and drive future studies assessing the impact of cycle exercise training as rehabilitation for DMD.

Prior barriers to aerobic exercise in DMD

Benefits of aerobic exercise training are well recognized for clinical populations, however there is a paucity of information regarding its role in DMD. A recent survey of healthcare professionals treating adults with neuromuscular disorders indicated that a large majority (81%) believed that aerobic exercise should be incorporated into rehabilitation [26]. However, they cited lack of knowledge in prescribing exercise (FITT factors), and specifically the dose of exercise, as a major perceived barrier to recommending aerobic training, hindering the application of exercise programs in the management of individuals with neuromuscular disorders. This is particularly true for DMD, the most debilitating of these

disorders due to the complete absence of the dystrophin protein, where the exercise dose factor for contraction-induced damage is not known.

In addition to a lack of guidelines on the optimal exercise dose, other barriers to implementation of aerobic exercise exist. Travel to a rehabilitation facility to undergo supervised and specialized exercise sessions three times per week is challenging for individuals with limited mobility (particularly for pediatric populations requiring parental support to travel). Another obstacle is access to appropriate equipment to suit the limitations of the disease. For example, the minimum load to overcome inertia during unassisted cycling on commercialized recumbent devices is approximately 5–7 watts. When attempting to exercise on a commercially available mobility trainer, three boys with DMD were unable to cycle at the lowest resistance (7.7 watts) due to exhaustion, necessitating use of fixed motor assistance to complete six minutes of cycling [27]. Finally, lack of expertise and supervision to ensure appropriate exercise parameters (once developed) are followed raise concerns of exercise in this patient population.

For these reasons, we developed a comprehensive home-based clinical rehabilitation approach to exercise in DMD which includes remote, online video supervision of exercise. For this study, our physician approved the exercise prescription for each patient and a member of our clinical research team with expertise in physical therapy or exercise physiology supervised the sessions. This remote rehabilitation approach is increasingly being used [28], including by our team in a recent study assessing isometric strength training in boys with DMD [15]. Such supervision is necessary particularly at the onset of a rehabilitation program to ensure patient safety and appropriate intensity is being followed. Our clinical research team assessed the participant's HR, RPE and any symptoms, and remotely accessed the controller to adjust the level of motor assistance as needed for the duration of the exercise session. Thus, the safety of each patient was ensured, evidenced by lack of adverse events during the study. In addition, the patient and family experience of using the cycling paradigm was positive. The clinical research team prioritized building a strong rapport at the in-person familiarization session that translated to the in-home video-supervised sessions thereafter. Boys appeared motivated to use the equipment (ergometer and heart rate monitor) and parents expressed enthusiasm towards their child participating in physical activity. Although these are subjective accounts, they are supported by the fact that each boy from this study enrolled to participate in the subsequent (ongoing) 6-month trial of regular structured cycle training. Practical challenges, as in any pediatric population, were occasionally encountered with brief deficits in attention span and focus on maintaining cadence and heart rate within appropriate zone. When necessary, we would use motivational tools including video game rewards during the exercise sessions to ensure completion of the exercise.

Novel findings on cycling power in DMD

Based on the concepts of physiological adaptation to aerobic exercise, sufficient demand/overload on skeletal muscle and cardiorespiratory capacity is required to induce adaptations and gain benefits of training (i.e. increased endurance) over time. Passive cycling alone is not expected to impose sufficient demand and therefore any adaptations associated with aerobic training are expected to be minimal. Prior studies using cycle exercise in boys with DMD did not provide information on the degree of muscle overload or cycling power [10–13]. To address this gap, our study was designed to quantify power output during motor-assisted cycling, and differentiate the work performed by the motor (during the passive phase) from that of the participant (during the active cycling phase). Our results show that boys with DMD can generate power with their legs during cycling. Compared to the passive phase, they produced on average 5 watts above that of the motor when actively cycling within the prescribed HR intensity. Although participants with more limited ambulatory ability and physical function required greater motor-assistance, they were still capable of cycling at 3 watts (which is better than complete motor-assistance). Those with greater ability required less motor assistance and cycled close to 8 watts. Collectively, our data describing the range of watts produced by boys with DMD are novel and our analysis demonstrating correlations between standard functional tests and level of motor-assistance required during cycling provide insight for exercise rehabilitation recommendations. For example, commercially-available bicycles may not be appropriate for a large majority of the DMD population as they require a level too great to overcome inertia and cycle in an appropriate HR zone. The 6MWD could be used to stratify boys with DMD who can use such bicycles. It remains to be determined whether skeletal muscle of boys with more limited function may adapt with continued use (i.e. aerobic training), thus permitting eventual use of commercially-available bicycles.

Novel findings on cycling HR in DMD

Increases in HR are typically used to reflect exercise intensity and inform exercise prescription. However, information on use of HR as an intensity measure in DMD is limited. Morse et al. [29] reported negligible increases in heart rate or blood lactate (metabolic exercise by-product) with six-minutes of motor-assisted cycling in adult males with DMD compared to other dystrophinopathies (who showed increases more similar

to that of healthy controls). These results were taken to reflect the inability of adults with DMD to respond to an exercise demand due to muscle weakness and impaired lung function. However, if the cycling exercise was predominantly passive, there would be insufficient cardiorespiratory demand to raise HR.

Our study was designed to evaluate use of individualized HR as an intensity outcome during active cycling exercise in boys with DMD. We used a HR zone established for deconditioned clinical populations reflecting moderate intensity (40–50% HRR) and based the calculation on age and resting HR. Our results reveal that DMD participants were able to increase HR from rest to reach the prescribed zone without muscle pain or cardiorespiratory limitation. The prescribed zone given the age of boys was approximately 140–150 bpm. Notably, the increase in HR from rest during passive cycling was negligible (~ 10 bpm), reflecting the work performed primarily by the motor and possibly accounting for the lack of HR response in the above-mentioned study [29]. However, when our participants were instructed to follow the target and actively cycle, HR increased significantly (by 40 ± 9.1 bpm) relative to the resting condition and was within the prescribed intensity (44.4 ± 7.5% HRR). In patients who were able to provide subjective ratings of perceived exertion, scores did not exceed the 'moderate-intensity' level of the exercise bout. However not every patient provided a score during exercise, consistent with reports in other pediatric populations [18, 30] emphasizing the use of HR as a preferred outcome. These results are significant because they demonstrate the potential to prescribe exercise intensity for training purposes based on a HR zone (using age-predicted maximum and resting HR) in boys with DMD. Additionally, these findings will inform future dosing trials of exercise frequency and progression as they suggest that the use of ACSM clinical exercise parameters (with Volume and Progression included in the FITT-VP framework) [23] are appropriate for this patient population.

Study limitations

This pilot study was limited to 6 ambulatory boys with DMD and whether these findings translate to a larger cohort is not known. Our participants spanned an age range from 6.5 to 9 years, limiting generalization of these findings to boys younger or older. We chose a minimum age of 6 years based on our experience and knowledge that younger children may not understand the instructions to cycle at a target cadence. As DMD is a rapidly progressive disease, the potential of older and/or non-ambulatory individuals to cycle in a HR zone and generate active power is unknown. We were careful to include a spectrum of disease severity as shown by the range of 6MWD and NSAA scores. Our findings demonstrating feasibility of the cycling paradigm in one participant who was at the low end of ambulatory ability support feasibility in older and non-ambulatory individuals with DMD.

This study demonstrated the ability of individuals with DMD to undergo one session of exercise using the home-based, motor-assisted cycling paradigm, thus mimicking a training session that would be performed regularly and remotely supervised by a clinical rehabilitation team as part of disease management. However, the feasibility of multiple sessions was not assessed and the cumulative effect of such exercise in a patient population susceptible to contraction-induced injury is currently not known. Data from animals studies indicate that repeated high-intensity and eccentric actions cause micro-tears and cellular damage to a greater extent in dystrophic compared to healthy muscle [31, 32], underscoring recommendations to avoid such activity in patients with DMD. In contrast, we previously showed that moderate intensity, repeated isometric strengthening exercise did not induce damage in boys with DMD as evidenced by lack of increase in serum creatine kinase or muscle inflammation using magnetic resonance imaging [15]. Other groups have reported safety of cycling exercise in various neuromuscular diseases [33, 34]. Although information on the training impact at the tissue level is limited in these studies, Sveen et al. reported no significant changes in muscle morphology obtained from biopsies in men with Becker muscular dystrophy after cycle training at moderate heart rate intensity for a duration of 12 weeks [35].

Translational potential, scope of applicability and future work

This study provides proof of concept for personalized, heart rate-guided cycling exercise using equipment engineered specifically for boys with DMD. These findings may be applicable to a broader group of children and adults with muscular dystrophies (i.e. limb-girdle, facioscapulohumeral, Becker muscular dystrophy) for whom exercise guidelines are also lacking due to similar concerns of muscle weakness and contraction-induced damage. Therefore, ongoing and future work is needed to elucidate translation of these findings towards clinical and home-based implemention of exercise. This includes further consideration of equipment requirements. For example, in regards to the engineered ergometer, we propose development of a similar closed-loop controller and mechanical system whereby adjustments of the baseline motor effort occur automatically based on feedback from the HR sensor (i.e. closed-loop control as a function of HR and $\dot{q}$ rather than just $\dot{q}$). We also emphasize use of similar controller gains and saturation points where the clinical rehabilitation team sets a range of acceptable cadence values and the controller enforces a boundary

on those values to ensure motor effort does not get too high. This type of automated ergometer would ensure safety and simplify remote supervision of exercise intensity during every session, thus promoting feasibility of tele-rehabilitation.

A practical consideration for future implementation of this work is use of commercially-available devices that allow for adaptive cycling. For example, the Rifton adaptive tricycle (Rifton Equipment, New York, USA) was developed for children with limited mobility and neurodevelopmental disabilities [36]. It combines optimized gearing and positioning to make therapeutic cycling accessible for individuals with limited lower extremity strength. Based on our findings that boys with DMD can generate power actively, future research assessing adaptive (unassisted) cycling is warranted as it may offer an alternate, real-world approach for home-based rehabilitation, including the option for outdoor exercise.

In addition to equipment considerations, implementation of this training paradigm will require coordination between the clinical care team and the patient/family. For example, clinical visits should include cardiac assessment and clearance for the patient to safely undergo the personalized exercise prescription in the home setting, whereas tele-rehabiliation appointments are needed to remotely supervise exercise sessions and assess patient symptoms, questions or concerns. Given current technological advances and wearables, telerehabilitation is increasingly being implemented in clinical research trials, including in pediatric heart transplant [37] and DMD [38]. A similar tele-rehabilitation approach by health care professionals (i.e. physical therapists, exercise physiologists, physician assistants, nurse practioners) can be envisioned to integrate aerobic exercise into neuromuscular disease care. Proper training for families regarding exercise guidelines, use of a HR monitor and criteria to alert the rehabilitation team and/or physicians will also be required. Technical skills required for parents at home are minimal and largely involve access to video-streaming (i.e. on a cell-phone or computer).

Finally, future research is needed to evaluate the longer-term outcomes (safety and efficacy) of this cycling paradigm in DMD and other dystrophinopathies. Regularly cycling within the heart rate intensity used in this study at least 3 times per week for 20–30 min is known to counter secondary muscle disuse and benefit musculoskeletal and cardiorespiratory health in a wide spectrum of clinical populations, including other neuromuscular diseases [6, 7]. Given the prevalence of physical inactivity, systemic comorbidities and chronic corticosteroid use amongst individuals with DMD, regular exercise is expected to have a clinically meaningful impact on health and quality of life. Building upon these current results, we designed a longitudinal trial investigating the longer-term outcomes of our proposed cycling paradigm in boys with DMD (ongoing trial: NCT04322357), using the same intensity (40–50% HRR) and exercise duration (intervals up to 20 min) as in this study over a 6-month intervention (3 times per week) with the goal of defining an exercise load threshold that is safe for muscle, promotes adaptation and is feasible for patients and families to incorporate into daily life.

Conclusions

This paper presented the design and testing of a remotely supervised exercise paradigm using a closed-loop controller enabling active cycling in boys with DMD. Our study also provides a dose (intensity parameter based on HR) of aerobic exercise to be tested in future studies assessing potential benefits of cycle training in DMD and other neuromuscular diseases. Establishing intensity is a critical factor in development of exercise prescription guidelines and the integration of exercise into rehabilitation for patients who experience significant muscle weakness and fatiguability. Our study also provided novel information on the amount of work (muscle overload) done by boys with varying levels of DMD disease severity which may help guide clinical management and rehabilitation recommendations. For example, recommendations for exercising with a combination of assistive and active power or unassisted (i.e. adaptive cycling) can be considered based on ambulatory ability and physical function. Although our data support feasibility rather than efficacy of this exercise paradigm, future studies based on these findings have potential to reshape/revolutionize rehabilitation for DMD and other neuromuscular diseases.

Abbreviations

ACSM	American college of sports medicine
Bpm	Beats per minute
DMD	Duchenne muscular dystrophy
HR	Heart rate
HRR	Heart rate reserve
UF	University of Florida

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Author contributions

T.T. obtained funding for the study and together with K.S., W.D., D.L. and H.L.S. developed the concepts for the ergometer. K.S. and W.D. designed the motor-controller and K.S. was the lead developer in building the components of the ergometer with assistance from E.G., H.S., W.M. T.T. and D.L. developed the exercise prescription factors specific to DMD. E.G., H.S., W.M., M.B. and D.L. helped collect data as part of the familiarization study visit. J.C. and R.S. were the study clinicians and oversaw participant safety and cardiac function. M.B. and T.T. oversaw and collected data from the home-based training sessions. K.S, M.B and T.T. analyzed the data and prepared the Figures. K.S., M.B. and T.T. wrote the main manuscript and all authors reviewed the manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants and their legal guardians provided informed assent and consent respectively to participate in this study which was approved by the Institutional Review Board 1 at the University of Florida (IRB201901339).

Consent for publication
Consent to publish was obtained from the participant.

Competing interests
The authors declare no competing interests.

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