1. Title Page

(a) Alterations in the metabolic and cardiorespiratory response to exercise in Huntington's Disease

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2. Abstract

Background

Limited data suggests that an altered metabolic and cardiorespiratory exercise response may affect exercise performance in individuals with Huntington's disease (HD). There is no clear exploration of the response in individuals at different stages of the disease or in relation to genetic markers. This study aimed to examine the exercise response and recovery of HD participants, and the relationship to genetic and clinical markers.

Method

HD gene-positive participants (n=31; 9 pre-manifest; 22 manifest HD) and a healthy control group (n=29) performed an incremental exercise test until exhaustion. Performance, cardiorespiratory, metabolic and perceptual responses to exercise were determined from a maximal cycle ergometer test throughout the exercise test and during a recovery period.

Results

During sub-maximal exercise, metabolic (lactate levels, oxygen uptake) and cardiorespiratory markers (heart rate) were elevated in HD participants compared to controls. Lactate elevation was specific to pre-manifest HD participants. Work capacity was reduced in both pre-manifest and manifest HD participants with tests terminated with no difference in metabolic, perceptual or cardiorespiratory markers. Submaximal oxygen uptake was correlated with motor score, whilst peak measures were unrelated to genetic or clinical markers. Heart rate recovery was attenuated in pre-manifest and manifest HD participants.

Conclusions

Our findings confirm metabolic and cardiorespiratory deficits reduce exercise performance and affect recovery from an early stage in HD, with submaximal deficits related to phenotypic expression. Exercise capacity appears to be limited by an altered movement economy, thus clinicians should consider an altered exercise response and recovery may affect prescription in HD.

3. Introduction

Huntington's disease (HD) is a neurodegenerative disorder caused by the expansion of a polyglutamine stretch within the Huntingtin gene[1]. Neuropathology causes progressive motor disturbances, cognitive dysfunction and psychiatric symptoms[2]. However, as the mutant Huntingtin gene is ubiquitously expressed, people with HD also experience an array of peripheral organ dysfunctions, including a severe metabolic phenotype, weight loss, abnormal fat and glucose homeostasis, cardiomyopathy, skeletal muscle wasting and reduced muscle strength[3–6].

In healthy people, exercise interventions reduce all-cause mortality and are beneficial for cardiorespiratory fitness, muscle strength, mental health and cognition[7–10]. Exercise prescription has also been shown to be safe, feasible and in some cases, beneficial for motor symptoms in HD[11–13]. However, results have been variable and detrimental effects of exercise training have also been reported[4,14]. These conflicting and variable findings may reflect an altered physiological and perceptual response to exercise in HD[15] which may consequentially affect exercise prescription outcomes. Importantly, the variability in the response to exercise suggests that targeted exercise prescription may be required for people with HD.

In order to develop targeted approaches, it is necessary to understand what factors affect the pathophysiological response to exercise. The current study was designed to improve knowledge on who may benefit from exercise prescription by understanding individual exercise responses. Previous work has found manifest HD participants experience an early increase in blood lactate and a reduced work capacity and peak oxygen consumption, with no abnormalities in peak cardiac and ventilatory performance[16]. Cardiac alterations and differences in perceived exertion were also found at lower exercise intensities in HD participants prior to commencing an exercise intervention[15], and an increased oxygen cost of exercise has been demonstrated[11].

Previous studies in HD showing an altered exercise response were measured at a distinct exercise stage, most commonly the response to maximal exercise intensity[11,17], whilst cardiorespiratory and metabolic recovery after exercise has not been previously studied in HD. Here, we measured the incremental response to exercise across the entirety of a cardiopulmonary test and recovery period. We hypothesised that the physiological responses to the submaximal, maximal and recovery phases may differ between controls and HD participants, which may relate to clinical and genetic disease markers.

4. Methods

Participants

Thirty-one HD participants (22 manifest, 9 pre-manifest) were recruited from specialist HD clinics in Cardiff, UK and Oxford, UK. Twenty-nine gene-negative controls were matched for age, gender and self-reported physical activity levels. Demographic and clinical data are shown in Table 1. Data was collected with ethical approval and participants gave informed consent.

Exercise protocol

Participants completed an incremental cycle ergometer exercise test[18] (Excalibur Sport, Lode, Netherlands) involving two minutes of rest, two minutes of unloaded cycling, followed by 25-watt increments every two minutes, starting at 50-watts (Supplementary Figure 1). The exercise test was symptom limited; individuals pedalled at 50 revolutions/minute until discomfort or fatigue due to effort prevented them from maintaining the work rate. A 10-point Borg Scale measured perceived exertion, fatigue in the legs and dyspnea. At 2 minute intervals, Borg ratings were collected along with whole blood capillary lactate concentration (Lactate pro, UK).

Pulmonary gas exchange was measured on a breath-by-breath basis (MetaMax 3B, Cortex Biophysik GmbH, Leipzig, Germany) and averaged every 30-seconds. Direct measurements of oxygen consumption (O_2), carbon dioxide production (CO_2), minute ventilation (VE), and derived variables including the respiratory exchange ratio (RER, i.e., O_2/CO_2), oxygen pulse (O_2/HR) and the ventilatory equivalents for oxygen (VE/O_2) and carbon dioxide (VE/CO_2) were obtained. Heart rate was continuously recorded using short-range telemetry (Polar S810, Finland).

After reaching exhaustion, participants cycled at an unrestrained speed at 25-watts for 2 minutes. Participants then transferred to a seated position and heart rate, blood pressure, lactate and Borg ratings were recorded every 2-minutes for 10-minutes. Additional protocol details can be found in the supplementary information.

Clinical and genetic measures

The motor component (TMS) of the UHDRS and the Total Functional Capacity (TFC)[19] score were recorded. Self-reported physical activity levels were recorded using the International Physical Activity Questionnaire [IPAQ][20]. CAG repeat length data was available for 19 HD participants. To assess

baseline cognition, participants completed the Trail Making Test (part B) and The Symbol Digit Modalities Test (SDMT).

Statistical analyses

HD participants were stratified according to disease stage (see Table 1; manifest HD participants = TFC score < 13 and TMS >18, Supplementary Figure 2 shows TFC range in manifest group).

As sample size differed across test stages due to different termination points, multiple univariate analyses of variance (ANOVA's) assessed group differences at each test stage (rest, submaximal stages [50-, 75-, 100- and 125-watts], and peak performance), using SPSS software [IBM, version 23]. Multiple comparisons were corrected for using the false discovery rate (FDR) at $p < 0.05$. Where results survived the FDR correction, Bonferroni-adjusted post-hoc pairwise analyses examined group differences. Multivariate ANOVA's were conducted for the recovery measures with post-hoc Bonferroni-adjusted analyses.

Where group differences were found, the relationship with clinical and genetic data was tested using a Pearson's correlation analysis.

A slope analysis assessed the relationship between physiology measures and work rate, from rest to peak. The oxygen uptake efficiency slope (OUES)[21], was determined from rest to peak using the following equation:

$$V\dot{O}_2 = a \, \log \dot{V}E + b;$$

Where a represents the OUES, the rate of increase in V0$_2$ in response to VE.

[Table 1 here]

5. Results

Despite no significant difference in age, BMI, and IPAQ score between control and HD participants overall (all $p > 0.05$), manifest HD participants were significantly older than pre-manifest HD and controls participants, thus age was included as a covariate in all analyses.

Exercise protocol compliance

Four HD participants were excluded from the analysis as they were unable to achieve the required speed of 50 revolutions/min (see Supplementary Table 1). One HD participant experienced syncope following maximal exertion.

Resting measures

Resting VO_2, heart rate, RER, mean arterial blood pressure (MAP) and lactate levels did not different between HD participants and controls (p > 0.05, Figure 1). Perceptually, there was no difference in resting ratings of fatigue (p > 0.05).

Submaximal exercise function

Exercise parameters across test stages are shown in Figure 1.

Physiology. VO_2 was elevated in manifest HD participants compared to controls at 50 watts (33% increase, $F_{2,50} = 5.42$, p = 0.006) and 75 watts (24.3% increase, $F_{2,50} = 3.45$, p = 0.035) with no differences between pre-manifest and control participants (p > 0.05). Similarly, heart rate was elevated in manifest HD participants compared to controls at 50 and 75 watts ($F_{2,49} = 5.54$ and 6.47 respectively, p < 0.05). In pre-manifest participants, heart rate was elevated compared to controls at 75 watts only (p = 0.024).

There was a main effect of group (HD vs. controls) on lactate levels at 50 watts ($F_{1,37} = 5.36$, p = 0.035), 75 watts ($F_{1,35} = 8.21$, p = 0.028) and 100 watts ($F_{1,34} = 5.90$, p = 0.034). Lactate was higher in pre-manifest HD participants compare to controls, surviving Bonferroni correction at 75 and 100 watts (p = 0.014 and 0.039) but not 50 watts (controls vs. manifest HD, p = 0.053). The difference between controls and manifest HD participants was significant at 50 and 75 watts (p = 0.027 and 0.049 respectively) before age was accounted for, however with age as a covariate, this difference was not significant.

Results from the slope analysis are shown in Supplementary Table 2. There was no difference in the OUES nor the relationship between work rate and VO_2, heart rate and lactate between control and HD participants (all p > 0.05).

Perceptual responses. There were no group difference in perceived exertion ratings at any workload between 50 and 125 watts (p > 0.05).

[Figure 1 here]

Peak exercise capacity

Figure 2 shows the individual and group data at exhaustion. Age-adjusted marginal means are shown in Supplementary Table 3.

Performance. Volitional exhaustion occurred at a lower working capacity (Wpeak) in HD participants ($F_{1,53}$ = 11.26, p = 0.001, Figure 2A). Pre-manifest and manifest participants had a lower Wpeak compared to controls (p = 0.049 and 0.026 respectively); there was no difference in Wpeak between pre-manifest and manifest HD participants (p > 0.05).

Physiology. There were no differences in $\dot{V}O_2$ peak, heart rate, oxygen pulse, RER, VE, VE/VCO$_2$ (controls = 28.9 ± 0.8; pre-manifest = 30.7 ± 1.4; manifest HD = 30.0 ± 1.0), VE/O$_2$ (controls = 35.5 ± 1.4; pre-manifest = 33.2 ± 2.1; manifest HD = 34.9 ± 1.6) at exhaustion between HD and control participants (p > 0.05).

Blood lactate production was 25.3% lower in HD participants at exhaustion compared to controls ($F_{1,40}$ = 9.37, p = 0.004, Figure 2E) and was lower in manifest HD participants compared to controls (p = 0.032). Pre-manifest HD participants did not differ from controls. To determine the effect of Wpeak on lactate production, peak lactate levels were normalised by Wpeak. There was no difference in normalised peak lactate between control and HD participants (controls = 0.057 ± 0.003; pre-manifest HD = 0.060 ± 0.004; manifest HD = 0.050 ± 0.003, p > 0.05).

Perceptual responses. There were no differences in perceived exertion ratings between HD participants and control participants at volitional exhaustion (p > 0.05).

[Figure 2 here]

Exercise recovery

Physiology. On a group level, heart rate did not differ between HD and control participants (Figure 3A). To examine individual variability in heart rate recovery (HRR), the change in heart rate from peak was calculated. HRR was slower in HD participants compared to controls ($F_{10,70}$ = 1.98, p < 0.05, Figure 3B). HRR was higher in controls compared to manifest HD participants at 2-minutes post exercise (p = 0.011), whereas after 4-minutes, HRR was higher in controls compared to pre-manifest and manifest participants (p = 0.038 and 0.007 respectively). At 6-, and 8-minutes post exercise, HRR remained higher in controls compared to pre-manifest participants (p = 0.016 and 0.021 respectively). There

were no differences in HRR between manifest and pre-manifest HD participants. Ten minutes following exercise, the difference between HRR in pre-manifest participants and controls was not significant (p = 0.07).

Lactate levels were reduced in manifest HD participants compared to controls at 2- and 4-minutes post exercise (p = 0.012 and 0.034 respectively, Figure 3C), with no differences between control and pre-manifest HD participants, and pre-manifest and manifest HD participants. To account for peak lactate levels, lactate change (from peak) was calculated. There were no differences between control and HD participants in lactate change during recovery (p>0.05, Figure 3D).

Perceptual response. Self-reported ratings of fatigue during the recovery phase did not differ between HD and control participants (Figure 3, p > 0.05).

[Figure 3 here]

Relationship between exercise measures and genetic and phenotypic HD expression

UHDRS TMS, where a higher score indicates greater movement disorder, was correlated with VO_2 at 50 watts (r= 0.49, p = 0.032), and 75 watts (r = 0.44, p = 0.041, Supplementary Figure 3). There was no correlation between submaximal VO_2 and UHDRS TFC or CAG repeat length (all p > 0.05). Heart rate at 50- and 75-watts, and lactate levels at 50-, 75- and 100-watts were not correlated with cUHDRS TMS and TFC or CAG repeat length, all p > 0.05.

No correlations were found between clinical data (UHDRS TMS and TFC), CAG repeat length and peak lactate or Wpeak, all p > 0.05.

The correlation between HRR at 4- and 6-minutes post exercise and the UHDRS TMS (r = -0.40 and -0.40, p = 0.039 and 0.041 uncorrected) and UHDRS TFC (r = 0.38 and 0.46, p = 0.053 and 0.017 uncorrected) was not significant after multiple comparison adjustments.

6. Discussion

This study shows an altered exercise response in people with HD during a graded exercise test. Despite normal resting physiology, upon initiation of low intensity exercise, heart rate, lactate, and oxygen uptake were elevated in HD participants compared to controls, suggestive of a movement economy

deficit and altered metabolism. The early elevation in lactate was observed in pre-manifest HD participants specifically, suggesting that abnormal oxidative metabolism in skeletal muscle may be an early feature of HD prior to functional decline. In contrast, elevated oxygen uptake at low intensities was related to greater motor dysfunction in HD participants. In agreement with previous work[16], volitional exhaustion occurred at a lower working capacity in HD participants and both pre-manifest and manifest HD participants produced less lactate at maximal effort. Almost one fifth of manifest HD participants were unable to maintain the required cycling speed, highlighting an altered exercise tolerance and physical ability in HD.

The altered cardiorespiratory and metabolic response to exercise may account for the variable responses to exercise prescription previously reported in HD[17]. The relationship between oxygen uptake during submaximal exercise and motor functioning suggest some of the variability can be accounted for by phenotypic disease expression, however metabolic differences were not accounted for by genetic load or phenotype, and were evident in pre-manifest HD participants, suggesting a complex physiological response to exercise in HD.

Notably, these novel findings provide support for individualised exercise prescription, and suggest that the effect of long-term exercise training may vary between individuals based on the prescribed exercise intensity and their subsequent physiological response. Further studies measuring the response to exercise are therefore recommended throughout the prescription period in order to understand if disturbances in exercise response interact with exercise prescription outcomes. In addition, it would be valuable to measure creatine kinase following exercise to explore muscle cell disturbance in HD and to further explore autonomic functioning.

Whereas previous work has shown a reduced $\dot{V}O_2$ peak in manifest HD[16], we failed to replicate this. The discrepancy is most likely explained by the inclusion of age as a covariate in this study; when VO_2 was measured as a percent of theoretical maximum capacity according to age, body type, and sex, differences due to HD were no longer observed[16]. In line with previous work[16], HD participants had a normal ventilatory response to maximal exercise and both clinical data and genetic data did not predict peak measures. CAG repeat length was also not predictive of the submaximal physiological response, suggesting that genetic markers are insensitive to exercise response in HD. The rate of $\dot{V}O_2$ may be affected by how effectively oxygen is delivered to the muscles (respiratory and cardiovascular systems), how it is utilised (metabolic systems) and how hard the muscles are working (neuromuscular systems). We propose that higher VO_2 at submaximal exercise and not at peak may be due to muscles working harder in people with HD due to chorea and/or poor co-ordination which requires greater

oxygen use. At peak exercise, aerobic metabolism is limited due to issues with bioenergetics and mitochondrial functioning in the HD group.

After reaching exhaustion, heart rate recovery was attenuated in HD participants. This is a novel finding; impaired heart rate recovery is an independent predictor of mortality in healthy populations[22]. The fall in heart rate immediately after exercise is a function of the reactivation of the parasympathetic nervous system, mediated by vagal reactivation in the first two minutes of recovery[23]. It is not clear whether vagal reactivation continues to mediate heart rate recovery for the eight minutes observed here, or whether other mechanisms drive the slowed response. Due to the cool-down protocol used, it is not possible to compare heart rate recovery with normative data attained immediately after exhaustive exercise cessation, however our findings complement work showing reduced cardiovagal modulation in middle-stage HD[24,25]. The elevated heart rate observed during submaximal exercise in HD participants replicates Dawes et al.[15] and increases the robustness of the observation that people with HD do not reach steady heart rates when initiating low-intensity exercise. This is informative for exercise prescription; applying objective submaximal markers as opposed to training intensities based on maximal measures (e.g. heart rate, VO_2), and measuring exercise recovery as an indicator of intervention effectiveness may be more appropriate.

The difference observed in peak lactate is most likely driven by differences in task performance. Working capacity was reduced in HD participants, and when peak lactate was normalised for maximal work rate, the lactate differences were no longer significant. This suggests that HD participants were unable to work as hard on the exercise test which contributed to the lower lactate levels and is supported by previous work showing a reduced work capacity in manifest participants[16]. The reduced working capacity in pre-manifest HD participants suggests an underlying energy deficit rather than reduced muscle bulk.

Altered metabolism was also evident during submaximal exercise. The failure of oxidative mechanisms can affect lactate production and clearance and previous work has shown elevated lactate production in symptomatic HD participants during a cardiopulmonary test at 50 watts and 75 watts[16]. We replicated this finding, however, lactate was also significantly higher in pre-manifest HD participants compare to controls at 75 and 100 watts, whereas the difference between controls and manifest HD participants was not significant after accounting for age. The discrepancy in the results may be partly explained by higher fitness levels in the current cohort and a broader symptomatic HD group.

A common limitation in clinical exercise research is the physiological effect of medication. Participants in this study were prescribed a diverse range of medications which alter metabolic

pathways[26]. It is not known if observed metabolic and cardiac deficits are a cause or consequence of HD toxicity, and/or mediated by medication. A comprehensive large-scale study is required to unpick medication effects, with the metabolic consequences of drugs in the same sub-class varying substantially due to differences in receptor pharmacology. Metabolic deficits observed in animal models and cell cultures of HD suggest that observed effects are not purely driven by medication[27,28], however they may account for some variability in exercise prescription responses.

Overall, we have demonstrated that metabolic and cardiorespiratory deficits contribute towards a reduced exercise performance and affects recovery in HD. Autonomic dysfunction has been reported in a variety of neurodegenerative dementias[29,30] and further work is required to elucidate whether deficits are a direct consequence of peripherally expressed mutant huntingtin protein, or secondary to a general decline in health or neurological dysfunction. This knowledge will be crucial for targeted exercise prescription in HD and for determining outcome measures.

Acknowledgments

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8. Figure Legends

*Figure 1 Response to submaximal exercise. Results are marginal means adjusted for age, error bars = standard errors of the mean. RER: Respiratory exchange rate. RPE: Ratings of perceived exertion. * p < 0.05 Bonferroni-adjusted. † unadjusted p < 0.05. preHD: pre-manifest, HD: manifest HD.*

Figure 2 Peak exercise response at test termination. Black line represents mean; grey box depicts 95% CI. RER: respiratory exchange ratio (VCO_2: VO_2); RPE: Rating of perceived exertion. PreHD: pre-manifest HD participants. HD: Manifest HD participants. P-values are Bonferroni- adjusted.

*Figure 3 Recovery response [B] & [D] show absolute change from peak. Results are marginal means adjusted for age. Error bars = standard errors of the mean. RPE: rating of perceived exertion. HR: heart rate (beats/minute). * p < 0.05, ** p < 0.01.*