Peak Jump Power Reflects the Degree of Ambulatory Ability in Patients with Mitochondrial and Other Rare Diseases

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Abstract Metabolic diseases that lead to neuromuscular, bone, and joint involvement can reduce ambulation and quality of life. Using jumping mechanography, we developed a novel assessment, peak jump power (PJP), and related this to ambulatory ability in patients either having a known or suspected underlying rare disease. From adults and children, we recruited 88 healthy controls and 115 patients (61 with mitochondrial disease and 54 with another diagnosis). Patients were categorized as having no complaints of weakness or ambulation (ambulatory competent; AC), weakness but able to ambulate without aids (ambulatory weakness; AW), or not able to ambulate without aids such as a walker, cane, or wheelchair (ambulatory assistance; AA). Subjects were asked to perform five successive

jumps from a squat position. Instantaneous power (W; watts) was calculated and the highest result was divided by the body mass (kg) to calculate PJP (W/kg). Between healthy controls and AC patients, there was no difference in mean PJP (20.5 ± 7.0 W/kg vs. 19.0 ± 7.4 W/kg, $p = 0.601$; mean $\pm$ SD). Progressively lower results were found in patients with AW with a mean PJP of 11.7 ± 5.1 W/kg ($p < 0.001$ versus AC) and further those with AA with a mean PJP of 5.8 ± 3.2 W/kg ($p < 0.001$ versus AW). A subgroup analysis of subjects showed that those who did not use ambulatory aids all had a PJP above 10 W/kg. Using this threshold, the receiver operating characteristic curve (ROC) analysis showed PJP to be highly sensitive evaluation of ambulatory ability (sensitivity 95.8%, specificity 52.1%).

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Abbreviations

6MWT	Six-minute walk test
ANOVA	Analysis of variance
AUROC	Area under the ROC curve
DCMA	Dilated cardiomyopathy with ataxia
DMD	Duchene muscular dystrophy
<i>F</i>	Force
FSHD	Facioscapulohumeral muscular dystrophy
GSD	Glycogen storage disorder type V or VII
MPS-I or II	Mucopolysaccharide storage disease
MRC	Medical Research Council
MS	Multiple sclerosis
<i>P</i>	Power
PJP	Peak jump power
ROC	Receiver operating characteristic curve
SD	Standard deviation
SSC	Stretch shortening cycle
<i>V</i>	Velocity
W	Watts

Introduction

In patients with inborn errors of metabolism, ambulation can be impaired from a combination of factors involving the nervous system, skeletal muscle, bones, and joints (Kling et al. 2014; Mathiowetz et al. 1985). The most commonly reported measure in ambulatory subjects in the literature is the six-minute walk test (6MWT). The 6MWT has been shown to relate to the degree of impairment in patients with chronic respiratory disease and heart failure (Solway et al. 2001). While the 6MWT can distinguish patients with impaired ambulatory ability from healthy controls (Bohannon 2006; Enright and Sherrill 1998; Roig et al. 2009; McQuiddy et al. 2015), and is used in clinical trials to measure ambulatory ability in patients who are able to walk, it has not been demonstrated to distinguish between levels of assistance required with walking in more severely affected patients of any type metabolic disease (McDonald 2002; Phillips et al. 2009). In many patients with metabolic diseases such as mitochondrial disease, Pompe disease, glycogen storage myopathies, or lysosomal storage diseases, the 6MWT cannot be performed due to the severity of underlying weakness. Furthermore, these patients do not have enough proximal strength to get up from a chair or perform an isometric force contraction for other measures of function such as the timed-up-and-go test (Bohannon 2006) or stair climbing. However, in trials using novel therapies that can take months to years to change ambulation, early assessment of efficacy in patients who start treatment when they have difficulty with ambulation is lacking. In pivotal trials using enzyme replacement therapy in lysosomal diseases, the distance walked by patients is far below that of the pulmonary disease population for which it was designed for (Redelmeier et al. 1997) and no clinically meaningful correlate has been established (Harmatz et al. 2005; Hendriksz et al. 2014; van der Ploeg 2010). It may be one thing to measure changes in walk distance in a population of adults who had no ambulatory disability prior to the onset of pulmonary disease and try to use that measure in a rare disease population with different physiology, due to muscle, bone, and joint problems, who at best may only be expected to walk a fraction of that distance. Yet it's clear that in drug therapy trials, some patients report benefits in quality of life from increased ambulatory ability that are not captured by their 6MWT (Brands et al. 2013). Being able to maintain ambulation, or improve it with therapy, occurs in a range of muscle performance that appears to be below the threshold of traditional measures of neuromuscular function and questionnaires are not able to capture smaller differences nor apply to both the pediatric and adult populations. This prompted us to look for a measure of ambulatory ability that could be easily performed in patients with severe

muscle weakness. In the literature, various terms are used to describe or measure the ability of a subject to move about to perform activities of daily living – terms such as ambulation, mobility, physical performance, and others. Since the clinical correlation in this study relates to whether subjects needed any aids, we will use the term ambulatory ability to reflect this function.

We adapted a method originally described by Giovanni Cavagna who used force plate ergometers to measure mechanical work by having subjects perform a vertical jump (Cavagna 1975). The ability of a muscle to perform work is determined by power (watts; W) (Josephson 1999). When an individual attempts a vertical jump, the combination of neuromuscular interactions and joint mechanics all contribute to the vertical height achieved which is the basis of peak jump power (PJP) (Bobbett and van Ingen Schenau 1988; Vanezis and Lees 2005). Studies in mobility-competent adults (Rittweger et al. 2004) and children (Taylor et al. 2010; Veilleux and Rauch 2010) have shown jump power to be highly reproducible and that declines in jump power are related to sarcopenia in aging adults (Buehring et al. 2010). Here we present the first application of jump mechanography in a clinical setting as a quantitative measure of ambulatory ability in patients with neuromuscular, bone, and joint diseases. We hypothesize that PJP has a number of advantages in measuring ambulatory ability in the clinical setting: (1) to plan which resources and treatments (such as ambulatory aids) are likely to help improve function, (2) to evaluate a response to treatment, (3) to measure disease progression, and (4) to facilitate future planning of resources for patients and their caregivers.

Methods

Patients (both children and adults) referred to the Metabolic Clinic at Alberta Children's Hospital, Calgary, Alberta for the investigation of an underlying metabolic disease were invited to participate in the study. Patients either had an existing diagnosis of mitochondrial disease or were sent for an evaluation to consider mitochondrial or other neuromuscular causes of their weakness. The muscle weakness was either apparent (e.g., subject was already using a walker) or perceived (subject may complain of muscle weakness but no weakness was apparent on physical exam). Subjects were screened in clinic regarding their ability to perform a jump maneuver from a standing position without falling but they did not necessarily have to be able to jump completely off the ground. Subjects who were not able to attempt a jumping maneuver or did not want to participate were not referred for a jumping power evaluation. The wheelchair-using patients could stand without support and push off the

ground. Healthy controls were recruited using a poster; their medical history was reviewed to exclude any medical condition in their history that or signs and symptoms related to muscle weakness, trauma, or injury, or the use of walking aids or wheelchairs. All healthy controls reported no perceived muscle weakness and no reduce function in activities of daily living. All subjects were examined by the principal investigator (AK) to collaborate their use of any walking aids with their self-report. Written informed consent was obtained by all participants prior to participation in the study with children requiring consent from a guardian. The majority of patients were referred for or had an existing diagnosis of mitochondrial disease. Patients also had other diagnoses of genetic or metabolic myopathy or nonspecific features of a muscle disease. Some patients had a disease primarily affecting ambulatory ability through bone, joint, or neurologic function. Patients recruited were globally classified as having a neuromuscular disease phenotype. All neuromuscular patients were separately characterized into the following categories based on their self-reported (and/or witnessed) ambulatory ability:

1. Ambulatory competent (AC) – no perceived physical impairment of daily activities
2. Ambulatory weakness (AW) – perceived impairment in physical ability
3. Ambulatory assistance (AA) – impairment in physical ability with use of walking aids or a wheelchair to ambulate

Inclusion criteria required participants to be able to perform the jump maneuver and have no preexisting condition that would impede ambulation. Inability to participate acted as the exclusion criteria. None of the volunteer subjects reported any degree of ambulatory disability or complaints of muscle weakness and were not observed to use any ambulatory aids. Each healthy subject was characterized into a single category: healthy control (HC).

All jump measurements were performed in the C.H. Riddell Movement Assessment Centre at Alberta Children's Hospital, Calgary, Alberta. Following recruitment, each subject was asked to stand on a force plate (Advanced Medical Technologies Inc., Watertown, MA, USA) for the measurement of body mass (kg). The subject was then asked to perform a jump without countermovement. This modification is necessary because patients with muscle weakness are not always able to do a countermovement and are not always able to squat to the same level before a jump. Traditional jumping protocols require a flight phase to calculate jump height and forces; however, this was not possible in some of our patients due to severity of muscle weakness and their fear of falling. Therefore, we asked the patients to squat into a

position that was comfortable for them and to then rapidly push to a standing position to reduce the variability caused by countermovement between patients. Through this modification, we were able to compute lower extremity power from the instantaneous force that exceeds the force due to body mass. That is, when the subject stands on the force plate, squats then push rapidly, and the difference between the force recording during the rapid push to extend the legs and that during the quiet standing is the amount of force (F) in Newtons generated by the lower extremity muscles during the rapid standing (Fig. 1). The peak velocity (V) in meters per second is also determined during this time. Power (P) in W is the product of F and V in Newton meters per second ($P = F \times V$ in Nm/s). The maximum power generated (PJP) was computed using custom-written computer code (Matlab from MathWorks, Natick, MA, USA) and divided by the subject body mass to give a result in W/kg. All participants were asked to perform at least five jumps for the subject's data to be included for analysis. The time frame for performing all of the jumps was self-selected by the patient and was usually completed within 3 min, with a pause between each jump. The highest PJP produced was used for the data analysis. A staff person flanked either side of the subject in case they were not able to stand by themselves, but each subject performed the maneuver using their own power and unaided by staff.

Statistical analysis for subject characteristics and PJP was performed using IBM SPSS Statistics for Windows, Version 20.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean $\pm$ standard deviation (SD). A significance level threshold, alpha, was set at 0.05 for all statistical tests. Differences between the subject groupings were determined by a one-way analysis of variance (ANOVA), followed by a Tukey's post hoc test and testing of assumptions. A receiver operating characteristic curve (ROC) was also generated to determine the suitability of PJP as a corresponding clinical threshold for determining patient disability. In order to generate an ROC threshold value, individuals within the healthy control and ambulatory competent groups were considered "negative" and the ambulatory weakness and ambulatory assistance groups considered "positive" for disability.

Results

Subject recruitment occurred between March 2009 and July 2012 with each healthy control or patient being represented only once (Table 1). A total of 88 healthy controls and 115 patients were recruited with each being able to adequately perform the testing protocol. The age of healthy controls ranged from 3 to 65 years of age. The age of neuromuscular

Fig. 1 Force (N; newtons) versus time (frames where 1 frame = 1/120 s) graph representing stages during a jump. All subjects were asked to perform a jump without countermovement. Some of our patients with declines in ambulatory ability were unable to perform the jump maneuver due to severity of muscle weakness – in which a modified jump was performed (absent flight phase). *Green area*

highlighted following the initiation of the jump provides the force exceeding the individuals' body mass due to gravity. The area generated by this force is then quantified as power by using the velocity of the movement. Each subject's peak jump power (PJP) was computed using custom-written computer code and divided by the subject body mass to give a result in watts (W) per kilogram

Table 1 Subject characteristics at the time of peak jump power (PJP) assessment

Subject characteristics	Healthy controls	Ambulatory competent	Ambulatory weakness	Ambulatory assistance
Sample size	88	41	46	28
Age (years)	24.3 ± 17.0	35.5 ± 16.9	40.7 ± 17.0	40.7 ± 22.9
Gender	M = 37; F = 51	M = 24; F = 17	M = 22; F = 24	M = 10; F = 18
Body mass (kg)	53.7 ± 25.3	70.1 ± 25.0	66.4 ± 20.4	61.3 ± 25.6
Peak power output (W)	1,164.1 ± 758.8	1,334.0 ± 688.4	799.9 ± 496.2	404.4 ± 371.6
PJP (W/kg)	20.5 ± 7.0 ^a	19.0 ± 7.4 ^a	11.7 ± 15.1 ^b	5.8 ± 3.2 ^c

Peak power output and PJP were computed using custom-written computer code (Matlab, MathWorks). Ambulatory competent – no perceived physical impairment; ambulatory weakness – perceived physical impairment; and ambulatory assistance – use of a mobility aid. Ambulatory ability was self-reported by patients. A total of nine patients within the ambulatory assistance group operated a wheelchair in order to ambulate $p < 0.001$ if superscripts are dissimilar (^a, ^b, and ^c) based on Tukey's, data are mean ± SD

patients ranged from 4 to 83 years of age. We found that children under 3 years of age in general were not able to jump on demand consistently in the setting of a clinical lab and therefore recommend 3 years of age as the lower limit

for participation. Females comprised 58% of the healthy control group and 51% of the neuromuscular patients, respectively. Out of the 115 patients recruited, 61 had mitochondrial disease (diagnoses available in supplementary

Fig. 2 Scatterplot of entire healthy control and patient population comparing PJP and age (years). Each subject grouping is denoted by a different color and is compared to the mean PJP for the healthy control group of 20.5 W/kg as well as the proposed PJP cutoff value of 10.0 W/kg

Table S1). The remainder of patients had DMD (Duchene muscular dystrophy), GSD (glycogen storage disease type V or VII), Pompe disease, Fabry disease, rhabdomyolysis, MPS-I or II (mucopolysaccharide storage disease), DCMA (dilated cardiomyopathy with ataxia), MS (multiple sclerosis), FSHD (facioscapulohumeral muscular dystrophy), or nonspecific myopathy. None of the patients had cause for muscle weakness localized to the spine such as spinal cord injury. A total of nine patients received no diagnosis (“other”) but still had symptoms of weakness. Patients were subsequently divided based on their self-reported/observed ambulatory ability (Table 1). The total number of patients within the ambulatory competent group was 41, the ambulatory weakness group 46, and the ambulatory assistance group 28. There were no adverse events in any subject from performing the jumping maneuvers. Statistical assumptions were met as data from each ambulatory ability grouping was normally distributed and homogeneity of variances was verified.

A scatterplot of PJP across all ambulatory groups (Fig. 2) depicts representation of both children and adults in the control group, with all control subjects yielding a PJP above 10.0 W/kg. The highest measurement was 44.1 W/kg. The PJP in healthy controls was not significantly different to subjects within the ambulatory competent group (20.5 ± 7.0 W/kg vs. 19.0 ± 7.4 W/kg, $p = 0.601$; mean $\pm$ SD). Subjects in the ambulatory weakness group had a significantly lower PJP than both healthy and ambulatory competent groups, respectively (11.7 ± 5.1 W/kg, $p < 0.001$). Those subjects within the ambulatory assistance group demonstrated significantly lower PJP than all other

groups (5.8 ± 3.2 W/kg, $p < 0.001$) (Table 1). A receiver operating characteristic curve (ROC) was generated using PJP and whether or not ambulatory assistance was needed for walking (Fig. 3). The area under the ROC curve was 0.888 with a 95% confidence interval of 0.841–0.935, which indicates that PJP is a good to excellent test to discriminate subjects who are ambulatory competent versus those in either ambulatory weakness or ambulatory assistance groupings (Fig. 3). Furthermore, utilizing the empirical PJP threshold value of 10.0 W/kg resulted in a highly sensitive clinical test (sensitivity 95.8%, specificity 52.1%).

Discussion

The range of PJP values for our healthy control group was between 10.0 and 44.1 W/kg which compares closely with other studies that have looked separately at adults (Rittweger et al. 2004; Dionyssiotis et al. 2010) and children (Taylor et al. 2010; Veilleux and Rauch 2010). In our healthy control group, values for maximum power (unadjusted for body mass) ranged from 210 to 3,402 W with lower values being found in children. However, normalizing power to body mass by using PJP (W/kg) showed that this method is highly comparable across age ranges and may be a more useful measure for longitudinal comparisons in clinic populations. A mild decline was seen in subjects over 60 years of age which likely represents early stages of declining jump power seen with sarcopenia as previously reported (Buehring et al. 2010). Overall, the results from the controls

Fig. 3 Receiver operating characteristic curve (ROC) used to correlate PJP and level of subject disability. Sensitivity of PJP is plotted on the y-axis and 1-specificity (false positivity rate) is plotted on the x-axis. The established PJP cutoff value is listed along with the

corresponding sensitivity (sens) and specificity (spec) values. AUROC; area under the ROC curve along with 95% confidence interval

show consistent application of the technique which is essential before comparison to the clinic population.

We show that jumping power reflects different degrees of ambulatory ability. Specifically, we found that if subjects possessed an underlying diagnosis of a neuromuscular disease but no physical limitation or symptoms, their PJP was no different from healthy controls. This finding is relevant since simply having a diagnosis of a neuromuscular disease does not imply that a patient had loss of ambulatory ability and their PJP can distinguish this. The perception of weakness, which is affected by many factors such as fatigue, sleep, and pain, need not imply that the muscle is not able to perform work. In the clinical setting, this can direct care to providing relief of symptoms, encouraging treatments to sustain ambulation. Patients with impairments in ambulatory ability demonstrated a lower PJP compared to patients who did not report weakness. In this group, more detailed evaluations can be performed to evaluate for the risk of falling, effects on quality of life, and interventions undertaken to improve function depending on the underlying cause. Furthermore, patients who use ambulatory aids have PJP values even lower than those with just muscle weakness. Interventions used could be monitored using PJP to see if improvements are taking place or whether declines are still occurring that may confine a patient to a wheelchair.

The ROC analysis showed that PJP was an excellent discriminator of ambulatory ability. The threshold value of 10.0 W/kg adequately separates all healthy controls from

patients possessing varying impairments in ambulatory ability – ambulatory weakness and ambulatory assistance groups. This threshold value, which applies to patients across a wide range of ages, may be used as a quick and easy quantitative clinical assessment of neuromuscular disease progression resulting in declines in ambulatory ability. The threshold value of 10.0 W/kg provides a high sensitivity of 95.8%. As with many tests, high sensitivity can come at the cost of specificity; this cutoff of 10.0 W/kg may select some subjects who do not show impairment in ambulation but also not select out any patient who does. The latter is typically the goal in the clinical setting. Depending on the clinical goal, whether it is high sensitivity to not miss any subjects who have disability versus high specificity to avoid false positives, different thresholds can be selected on the ROC curve.

Although various measures of ambulatory ability have been previously described, this is the first application of jump power in a clinical setting of patients with muscle, nerve, and joint disease. Furthermore, many of our patients are unable to perform existing measures of ambulatory ability such as the timed chair up and go or 6MWT. In all cases, PJP could be performed in a few minutes, requires no preparation and even some patients who were dependent on a wheelchair could perform the modified jump attempt (generating jumping power but with the feet still on the ground). No subjects developed problems from the repeated jumps including those with very limited ambulatory ability.

Our objectives in this study were to target ambulatory ability in the usual clinical setting. Studies in elderly patients show that PJP can decline with aging (Rittweger et al. 2004; Dionyssiotis et al. 2010; Runge et al. 2004) but in general those patients are much older than our control group where the oldest subject was 65 years of age. In the control population, we did not find a trend of PJP versus age. A longitudinal study may be better able to delineate this. In athletic Tunisian children, the fat-free body mass is related to jump power (Aouichaoui et al. 2012). Other studies have shown that in healthy controls, PJP has the lowest inter- and intra-subject variation and highest degree of reproducibility compared to traditional methods of assessing physical ability (Rittweger et al. 2003, 2004; Veilleux and Rauch 2010). Although we attempted to try and perform test retest analysis, many of our subjects with underlying disease reported gradually declining muscle performance with time and difficulty returning to the lab for repeated measures. However, test retest analysis on select patients exhibiting static disease showed an average of 8% variability in PJP ($n = 6$, unpublished data). The major limitation in this study was that some the PJP may have been overestimated because if subjects did a counter-movement during some of their jumps thereby decreasing their stretch shortening cycle (SSC; active stretch of a muscle-eccentric contraction followed by an immediate shortening of the same muscle-concentric contraction) (Gerodimos et al. 2008). Children and adults with these rare diseases, however, are going to naturally perform a jumping maneuver in the way that is most comfortable for them. In most cases, the biomechanics in an individual subject cannot be modified. Our data show that the clinical correlation still holds and the procedure can be applied in an actual clinic setting without patients being required to modify how they jump.

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Compliance with Ethics Guidelines

Conflict of Interest

Christopher Newell, Barbara Ramage, Ion Robu, and Aneal Khan declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (Enright and Sherrill 1998). Informed consent was obtained from all patients for being included in the study.

Author Contributions

Christopher Newell collected and analyzed data, generated figures, and helped develop the manuscript. Alberto Nettel-Aguirre assisted in the development of the primary study design, statistical analysis, interpretation of results, and contribution to the manuscript. Barbara Ramage, Ion Robu, and Aneal Khan contributed to the study design, methodologies described, administration of the study on subjects, data analysis, and manuscript content. Aneal Khan made the primary study design, was the principal investigator, and had primary responsibility for final content. All authors read and approved the final manuscript.

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