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Kraft und Ausdauer bei Patienten mit Muskeldystrophie Duchenne: Stellenwert von Mechanographie und 6-Minuten Gehtest als Untersuchungsinstrumente

Dissertation

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Martin Rodrigues

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München, den 03.06.2025 Martin Rodrigues

Für
Miriam
Rosalie und Raphael

INHALTSVERZEICHNIS

1. Abkürzungen

DMD	Muskeldystrophie Duchenne
6MWT	6 Minute Walk Test
s2LJ	Single two-legged jump
CRT	Chair raising test
SMA	Spinale Muskelatrophie

2. EINLEITUNG

Die Duchenne-Muskeldystrophie (DMD) ist eine X-chromosomale vererbte Muskelerkrankung, die einen von 3.500 neugeborenen Jungen betrifft (1). Mutationen im Dystrophin-Gen (2) führen zum Verlust des Strukturproteins Dystrophin in der Muskelfasermembran (2) und verursachen eine fortschreitende Muskelschwäche, die zum Verlust der Gehfähigkeit spätestens in der Adoleszenz führt (3) (4). In späteren Stadien der Erkrankung geht auch die Kraft der oberen Extremitäten und des Rumpfes verloren und es kommt zur Manifestation einer restriktiven Ventilationsstörung und einer Kardiomyopathie (5).

Dystrophin ist ein strukturelles Schlüsselprotein in der Muskelfaser. In gesunden Muskelfasern stellt der Dystrophin-Glykoprotein-Komplex eine Verbindung zwischen extrazellulärer Matrix und Zytoskelett her. Die primäre Funktion des Dystrophin-assoziierten Proteinkomplexes ist die Stabilisierung der Plasmamembran. Bei Patienten mit DMD führt der Mangel an Dystrophin zur Destabilisierung dieser Verbindung, was zur Degeneration der Muskelfasern durch mechanisch induzierte Schädigung mit fortschreitendem bindegewebig-proliferativen Muskelumbau und Narbenbildung führt (1). Histopathologisch sind veränderte Regeneration, Entzündung und gestörte Gefäßadaptation darstellbar. Diese Mikroläsionen führen letztlich zu einer unausgeglichenen Kalziumhomöostase und zum Zelltod (6).

Klinisch fallen die betroffenen Jungen meist im Kindergartenalter mit einer motorischen Entwicklungsverzögerung auf. Schwierigkeiten beim Treppensteigen und häufige Stürze stehen oft im Vordergrund. Zur frühen klinischen Präsentation gehören auch ein watschelnder Gang und Schwierigkeiten beim Aufstehen (positives Gowers-Zeichen), wobei sich die Patienten beim Aufstehen mit den Armen auf den Oberschenkeln abstützen. Häufig ist eine Pseudohypertrophie der Waden zu beobachten (7) (8).

Die betroffenen Jungen machen in der Regel bis zum frühen Grundschulalter motorische Fortschritte (wenn auch in geringerem Maße als ihre Altersgenossen), danach kommt es zu

einer Plateauphase und schließlich zum Rückgang der motorischen Fähigkeiten. Eine Beeinträchtigung der kognitiven Fähigkeiten ist häufig (9) (10).

Diagnostisch steht bei klinischem Verdacht zunächst die Bestimmung der Kreatinkinase im Vordergrund, diese ist bei der Muskeldystrophie Duchenne im Kindesalter stets massiv erhöht. Als Bestätigungsdiagnostik steht die molekulargenetische Untersuchung an erster Stelle. Zunächst wird eine MLPA (Multiplex Ligation-dependent Probe Amplification) durchgeführt, um große Deletionen oder Duplikationen zu identifizieren, die etwa 70% der ursächlichen Mutationen ausmachen. Kann keine Deletion oder Duplikation nachgewiesen werden, ist die Suche nach einer Punktmutation mittels Sequenzierung des Gens indiziert (Flanigan, et al., 2003).

Da das Dystrophin-Gen sehr groß ist, ist methodisch die klassische Sanger-Sequenzierung mittlerweile der Hochdurchsatzsequenzierung unterlegen, die kosteneffizient bei negativem Ergebnis auch seltenere Formen der Muskeldystrophie differentialdiagnostisch einschließt (11). Die häufigsten krankheitsverursachenden Deletions-Hotspots bei der DMD umfassen die Exone 45-55 und 2-19 (12). Eine Muskelbiopsie ist nur noch bei persistierendem Verdacht ohne Mutationsnachweis indiziert.

Die Lebenserwartung der DMD Patienten hat sich in den letzten Jahren erheblich verbessert und die Patienten können im Mittel ein Lebensalter von 30 – 40 Jahren erreichen (13) (14). Dabei ist in der Versorgung der Patienten ein multidisziplinärer Ansatz für die optimale Behandlung der primären Manifestation und der sekundären Komplikationen essentiell. Der aktuelle Behandlungsstandard ist geprägt vom frühen Einsatz therapeutischer Maßnahmen, die das Potential haben, Lebensdauer und Lebensqualität der Patienten zu verbessern. Diese betreffen Atmung, Herz, Knochengesundheit, orthopädisches und chirurgisches Management, Maßnahmen der Rehabilitation, endokrine Aspekte (Wachstum, Pubertät und Nebenniereninsuffizienz) und gastrointestinale Komplikationen (einschließlich Ernährung und Dysphagie), unter Berücksichtigung der Auswirkungen einer langfristigen Glukokortikoid-Therapie auf den natürlichen Krankheitsverlauf der DMD.

Neue Themen durch die verlängerte Lebenserwartung sind soziale Integration, Primärversorgung und Notfallmanagement der erwachsenen Patienten und Transition (15-17).

Was die pharmakologische Behandlung betrifft, so sind bislang noch die Kortikosteroide Deflazacort und Prednison/Prednisolon der Goldstandard der Behandlung. Sie verlangsamen das Fortschreiten der Erkrankung (18) (19). Seit 2015 ist zudem die Substanz Ataluren verfügbar, die bei DMD-Patienten mit Nonsense-Mutationen das Fortschreiten der Erkrankung im Vergleich zu Placebo verlangsamt, am deutlichsten bei Patienten mit einer 6-Minuten Gehstrecke von ≥300-<400 m bei Behandlungsbeginn (20, 21).

Eteplirsen ist ein Therapeutikum für DMD-Patienten mit speziellen Mutationen, die durch Skippen von Exon 51 des DMD-Gens außer Kraft gesetzt werden können. Weitere, sich allerdings noch in der Erprobung befindliche Therapieansätze umfassen optimierte Antisense-Oligonukleotide, mitochondriale Fibrose-Prävention und gentherapeutische Wiederherstellung der Dystrophin-Expression (22) (23) (24).

3. ZIELSETZUNG DER ARBEIT

Durch die stetige Erprobung neuer medikamentöser Therapieansätze für die Muskeldystrophie Duchenne in klinischen Studien (25) gewinnt die Quantifizierung der Muskelkraft und der körperlichen Leistungsfähigkeit bei den betroffenen Kindern immer weiter an Bedeutung (26). Die Behandlung der DMD wird sich voraussichtlich nochmals erheblich verändern, wenn neue genetische und molekulare Therapien verfügbar werden. Im Rahmen klinischer pharmakologischer Studien wird fortlaufend die Wirksamkeit neuer therapeutischer Ansätze untersucht. Um den Effekt dieser neuen Therapien evaluieren zu können, sind geeignete klinische Messinstrumente notwendig. Bislang wird der 6 Minuten Gehtest am häufigsten in klinischen Studien zur primären Outcome-Messung eingesetzt (27) (28).

Der Test ist ebenfalls Standard bei anderen neuromuskulären Erkrankungen, wie z.B. der spinalen Muskelatrophie (SMA). Bei der SMA zeigten sich in klinischen Studien Hinweise auf das Auftreten von belastungsinduzierter Ermüdung während des 6MWT. Eine Studie aus dem April 2018 maß das Auftreten von belastungsinduzierter Ermüdung („Fatigue“) bei pharmakologisch behandelten Kindern mit SMA, welche als einer der Outcome Parameter für den Behandlungseffekt von Nusinersen verwendet wurde (29). Fatigue im Rahmen des 6MWT gilt auch als vielversprechender Outcome Parameter für die Bewertung der therapeutischen Wirksamkeit bei pharmakologischen Studien für andere neuromuskuläre Erkrankungen (30) (31).

Das Ziel einer der beiden Studien im Rahmen dieses Promotionsprojektes war es, den diagnostischen Wert einer eventuell auch bei der DMD im Rahmen des 6MWT auftretenden Fatigue zu untersuchen. Neben dem 6MWT kommen bislang auch andere Zeitfunktionstests bei der physikalischen Testung der muskulären Performance der Patienten zum Einsatz. Klassische Parameter sind z.B. die benötigte Zeit zum Aufstehen vom Boden aus Rückenlage, bei der Bewältigung von vier Treppenstufen oder für eine 10 Meter Rennstrecke. Weitere quantitative Informationen über die Funktion des neuromuskulären Systems können mit Hilfe von Bodenreaktionskraftplatten gewonnen werden, die in der Lage sind, dynamische Informationen

zu erfassen. Aus der Bodenreaktionskraft während der Gegenbewegung bzw. der Aufstehphase einer Bewegung wird die maximale Leistung, bezogen auf die Körpermasse, berechnet, die als Indikator für die motorische Funktion herangezogen werden kann. Im Leistungssportbereich wird die Mechanographie bereits seit einigen Jahren eingesetzt (32) (33). Sie ermöglicht eine effiziente Quantifizierung von Kraft, Leistung und Bewegungsabläufen im ambulanten Setting (34) (35). Die Reproduzierbarkeit der Ergebnisse aus der Mechanographie hat sich als gut erwiesen (36) (34) (37). Referenzwerte im Kindesalter sind alters- und geschlechtsspezifisch vorhanden (38) (39) (40). Die Mechanographie wird auch zunehmend im medizinischen Bereich eingesetzt, wobei bislang der Schwerpunkt auf Erkrankungen des knöchernen Systems liegt (41-47). Im Bereich der neuropädiatrischen und/oder neuromuskulären Erkrankungen wurde die Mechanographie bislang nur sporadisch eingesetzt (11) (48) (49) und es gibt für diese Patientengruppen bisher nur wenige Daten.

Das Ziel der zweiten Studie, die im Rahmen des vorliegenden Promotionsprojektes durchgeführt wurde, war es, zwei mechanographische Tests, die die Kraft der unteren Extremitäten mittels Zwei-Bein-Sprung bzw. Aufsteh-Test quantifizieren, mit bereits etablierten Zeitfunktionstests in einer Kohorte von gehfähigen Jungen mit DMD zu vergleichen.

Eigenanteil

Alle Patienten dieses Promotionsprojektes wurden regelmäßig im sozialpädiatrischen Zentrum des Dr. von Haunerschen Kinderspitals der Ludwig-Maximilians-Universität München betreut. Die physikalischen Testungen wurden im Rahmen der regelmäßigen Routineuntersuchungen von den Physiotherapeuten der Abteilung durchgeführt.

Der geleistete Eigenanteil des promovierenden Studenten an diesen Studien belief sich auf die Extraktion der erhobenen Daten, ihrer statistischen und deskriptiven Auswertung, sowie ihrer graphischen und tabellarischen Darstellung für die beiden Publikationen.

Die Leistung der Patienten P_{max}rel (SI-Einheit ist W/kg) wurde beim CRT und beim S2LJ gemessen. P_{maxr}el spiegelt die körperliche Leistung in Watt im Verhältnis zum Körpergewicht wider. Dafür wurde das System Leonardo Mechanograph® GRFP STD (Novotec Medical GmbH, Pforzheim, Deutschland) verwendet. Er besteht aus einer geteilten Bodenreaktionskraft-Plattform (GRFP), die mit einem Computer verbunden ist. Die Ergebnisse wurden mittels der Leonardo Mechanography Software Version 4.3 erhoben. Nach Extraktion und Übertragung wurden die Ergebnisse der Mechanographie mit den Ergebnissen der Zeitfunktionstests und des 6MWT mittels linearer Regression korreliert. Die Analyse wurde mit Excel (Microsoft, Redmond, Washington, USA) durchgeführt. Auch die statistische Analyse bzgl. Fatigue im 6MWT erfolgte mittels Microsoft Excel.

4. ZUSAMMENFASSUNG

4.1 DEUTSCH

Eine der häufigsten neuromuskulären Erkrankungen im Kindesalter ist die Muskeldystrophie Duchenne (DMD). Die Anzahl der klinischen Studien für diese Erkrankung hat in den vergangenen Jahren stark zugenommen. Es werden, insbesondere in Anbetracht der Manifestation im frühen Kindesalter, geeignete klinische Messinstrumente benötigt, um die natural history, das Fortschreiten der Erkrankung und die Wirksamkeit potentieller neuer Wirkstoffe zu erfassen.

In der vorliegenden kumulativen Doktorarbeit, basierend auf zwei Publikationen, wurde eine Kohorte kindlicher DMD Patienten retrospektiv hinsichtlich pathologischer Ermüdbarkeit in einem etablierten Testverfahren untersucht. Zudem wurden herkömmliche Testverfahren mit neueren physikalischen Tests verglichen, um die Validität letzterer zu erforschen.

In der ersten Studie („Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy?“) wurden untersucht, ob Patienten mit DMD eine vorzeitige pathologische belastungsinduzierte Ermüdung („Fatigue“) zeigen, die als geeigneter Ergebnisparameter bei anderen neuromuskulären Erkrankungen wie der spinalen Muskelatrophie gilt. Hierfür wurden die Testergebnisse einer Kohorte von 55 DMD-Patienten, die insgesamt 241 6-Minuten Gehtests („6-minute-walk-test“; 6MWT) absolviert hatten, retrospektiv ausgewertet. Die pathologische, vorzeitige belastungsinduzierte Ermüdung wurde durch das Verhältnis zwischen der erreichten Distanz in der sechsten Minute und der Distanz in der der zweiten Minute des 6MWT definiert. Es zeigte sich, dass der durchschnittliche Ermüdungsquotient in der gesamten Patientenkohorte bei 1,0 lag und somit die Fatigue bei der DMD keine relevante Rolle spielt und entsprechend auch keinen nützlichen Outcome-Parameter für klinische Studien darstellt.

In einer Subgruppenanalyse konnte noch gezeigt werden, dass kein Einfluss von Alter, Steroidtherapie, Atalurentherapie, Grad der Behinderung oder der Distanz 6MWT auf das Auftreten von Fatigue bei DMD-Patienten besteht.

In der zweiten Studie („Jumping Mechanography is a Suitable Complementary Method to Assess Motor Function in Ambulatory Boys with Duchenne Muscular Dystrophy“) wurde die verhältnismäßig neue Methodik der Mechanographie mit dem 6MWT und klassischen Zeitfunktionstestungen (50) verglichen. Die Mechanographie ist ein medizinisches Diagnoseverfahren zur Bewegungsanalyse, welches in der Lage ist, körperliche Leistungsfähigkeit zu quantifizieren.

Hierfür wurden die Ergebnisse einer Kohorte von 41 gehfähigen Jungen mit DMD, die insgesamt 95 Aufsteh-Tests („chair rising test“; CRT) und 76 Zweibeinsprünge („single two-legged jump“; S2LJ) auf einer Mechanographie-Plattform absolviert hatten, mit der Distanz aus dem 6MWT sowie der Zeit, die benötigt wurde, um 10 Meter zu laufen, der Zeit, die benötigt wurde um aus einer in Rückenlage liegenden Position aufzustehen und der Zeit, die benötigt wurde um vier Treppenstufen zu steigen, korreliert. Die Messergebnisse wurden jeweils im gleichen Untersuchungssetting erhoben.

Es zeigte sich eine hohe Korrelation zwischen den Mechanographie-Tests und den Zeitfunktionstestungen mit r=0,51-0,62. Die Korrelation zwischen der Mechanographie und dem 6MWT war nur moderat mit r=0,38 -0,39.

Es konnte geschlussfolgert werden, dass die Mechanographie eine valide Methode ist, die zusätzliche Informationen über die Leistungsfähigkeit bei Bewegungen mit höherer Leistung liefert und insbesondere in Kombination mit dem 6MWT für physikalische Endpunktmessungen in klinischen Studien verwendet werden kann.

4.1 ENGLISH

One of the most common neuromuscular diseases in childhood is Duchenne muscular dystrophy (DMD). The number of clinical studies for this disease has increased significantly in recent years. Appropriate clinical measurement tools are needed, especially given the manifestation of the disease in early childhood, to capture natural history, disease progression and efficacy of potential new agents.

In the present cumulative thesis, based on two publications, a cohort of infantile DMD patients was retrospectively assessed for fatigability in anestablished testing procedure. In addition, established testing procedures were compared with newer physical tests to explore the validity of the latter.

The first study ("Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy?") investigated whether patients with DMD show premature pathological exercise-induced fatigue, which isconsidered a suitable outcome parameter in other neuromuscular diseasessuch as spinal muscular atrophy. For this purpose, the test results of a cohort of 55 DMD patients who had completed a total of 241 6-minute walk tests (6MWT) were retrospectively analyzed. Pathological premature exercise-induced fatigue was defined by the ratio between the distance achieved in the sixth minute and the distance in the second minute of the 6MWT. It was demonstrated that the average fatigue quotient in the entire patient cohort was 1.0 and thus fatigue does not play a relevant role in DMD and, accordingly, is not a useful outcome parameter for clinical trials.

In a subgroup analysis, it was demonstrated that there was no influence of age, steroid therapy, ataluren therapy, degree of disability, or distance in the 6-minute walk test (6MWT)on the occurrence of fatigue in DMD patients.

In the second study ("Jumping Mechanography is a Suitable Complementary Method to Assess Motor Function in Ambulatory Boys withDuchenne Muscular Dystrophy"), the relatively new

methodology of mechanography was compared with 6MWT and classical time functiontests. Mechanography is a medical diagnostic method for movement analysis, which is able to quantify physical performance. For this purpose, the results of a cohort of 41 ambulatory boys with DMDwho had completed a total of 95 chair rising tests ("CRT") and 76 singletwo-legged jumps ("S2LJ") on a mechanography platform were correlated with the distance from the 6MWT as well as the time required to walk 10meters, the time required to stand up from a supine position, and the time required to climb four stairs.

The measurement results were always collected in the same study setting. There was a high correlation between the mechanography tests and the time function tests (r=0.51-0.62). The correlation between themechanography and the 6MWT was only moderate with r=0.38 -0.39.It could be concluded that mechanography is a valid method providing additional information about performance in higher power movements and can be used especially in combination with the 6MWT for physical endpoint measurements in clinical trials.

5. PUBLIKATIONEN

5.1

Blaschek, A.*, M. Rodrigues*, L. Ille, M. Idriess, T. Well, B. Warken, C. Muller, I. Hannibal, M. Tacke, W. Muller-Felber, and K. Vill. 2020. 'Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy?', *Neuropediatrics*, 51: 342-48. * contributed equally

Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy?

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Abstract

Objective Duchenne muscular dystrophy (DMD) is a devastating X-linked muscular disorder. The number of studies investigating new therapeutic approaches is substantially increasing. This study aims to investigate the impact and diagnostic value of exercise-induced fatigue in DMD, which has been proposed as a suitable outcome parameter in other conditions like spinal muscular atrophy.

Patients and Methods A cohort of 55 DMD patients (49 of them treated with steroids and 9 with ataluren) underwent a total of 241 6MWT (mean 4.4 tests/patient) which were retrospectively analyzed. Exercise-induced fatigue was assessed by the ratio between the distance achieved in the sixth minute and the distance in the second minute of the 6MWT. In previous studies a quotient above 1 was defined as a sign of fatigue.

Results The average fatigue quotient in the whole cohort of patients was 1.0. In a further analysis no impact of age, steroid therapy, ataluren therapy, overall disability, and distance in the 6-minute walk test (6MWT) on fatigue in DMD patients could be shown.

Conclusion Our data show that fatigue does not play a relevant role in DMD. Analysis of fatigue is not a useful outcome parameter in DMD studies. For this reason we suggest the 2MWT, which is better accepted by the patients, as an alternative to the commonly 6MWT.

Keywords
- Duchenne muscular dystrophy
- outcome measures
- clinical trials
- 6-minute walk test
- fatigue

Introduction

Duchenne muscular dystrophy (DMD) is a devastating X-linked muscular disorder affecting approximately 1 in 3,500 newborn boys.[1] The disease is caused by mutations in the dystrophin gene, leading to a loss of the dystrophin protein in muscle cells,[2] resulting in progressive weakness and loss of ambulation during childhood and early adolescence,[3,4] followed by loss of function of upper extremity and trunk. Respiratory and cardiac functions decline during adolescence. Under supportive therapy of cardiomyopathy and assisted ventilation, the median age of survival is approximately 35 years.[5–7]

Established pharmacological treatment in DMD is mainly limited to corticosteroids, which slightly prolong ambulation.[8] The number of studies investigating basic disease mechanisms in animal models as well as testing these concepts in human clinical trials have substantially increased over the last decade.

Probable therapeutic targets range from exon skipping with new antisense oligonucleotides, vector-based gene

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replacement to downstream modifications of consequences of dystrophin loss.[9–11]

To evaluate the effect of new therapeutic targets, suitable clinical instruments are mandatory. Currently, the 6-minute walk test (6MWT) is often chosen as a primary outcome parameter in clinical studies.[12,13] The test is also becoming standard in other neuromuscular diseases like spinal muscular atrophy (SMA) and Pompe disease.

In SMA there is evidence of exercise-induced fatigue in patients during the 6MWT. A study from April 2018, for example, measured fatigue in Nusinersen-treated children with SMA. Fatigue was thereby defined as the change in the distance covered by patients during the 6th minute compared with that within the 1st minute.

Exercise-induced fatigue was used as one of the outcome measures for the treatment effect of Nusinersen. The authors concluded that the 6MWT was sensitive to fatigue-related changes in SMA and suggested it to be a promising outcome measure for clinical trials in ambulatory patients with SMA.[14,15] Fatigability, measured by the 6MWT, was as well recently proposed to be a promising end point for evaluating therapeutic efficacy in a pharmacological trial in patients with RYR1-associated myopathy.[16]

The aim of our study is to investigate the impact and diagnostic value of exercise-induced fatigue in DMD which has been proposed as a suitable outcome parameter for other conditions.

Patients and Methods

A cohort of 55 ambulant DMD patients (age 4.6–13.6 years, mean 8.0 years, median 8.2 years) with genetically proven DMD was repeatedly investigated. Forty-nine patients were treated with steroids, 45 of them in a 10 days on/10 days off scheme. Nine patients received ataluren therapy. Patient data including motor milestones, genetic findings and treatment are listed in ►**Table 1**. Six-minute walk test (6MWT) was performed on a routine basis in our neuromuscular outpatient clinic. Data of the 6MWT in DMD boys between 2013 and 2018 were analyzed retrospectively. The patients usually underwent the 6MWT in 3 to 6 monthly intervals.

Table 1 Patient's characteristics

Patient no.	Genetic findings	Age walking independently	Treatment with prednisolone	Treatment with deflazacort	Steroid treatment scheme	Treatment with ataluren
			From age	From age		From age
1	Deletion exon 45–52	24 mo	8 y	9.17 y	Daily	–
2	Deletion exon 45–52	"Delayed"	8 y	–	10 d on/off	–
3	Nonsense mutation c4084 C > T, p. Gln1362*	20 mo	5–6.5 y	6.5 y	10 d on/off	5 y
4	Deletion exon 44	24 mo	9.5 y	–	10 d on/off	–
5	Deletion exon 52	18 mo	5–8 y	8 y	10 d on/off	–
6	Duplication exon 17	18 mo	6–12 y	–	10 d on/off	–
7	Deletion exon 8–13	16 mo	5.9 y	–	10 d on/off	–
8	Deletion exon 45–50	22 mo	9 y	–	10 d on/off	–
9	Deletion exon 51–55	20 mo	5 y	–	10 d on/off	–
10	Deletion exon 3–48	24 mo	–	5 y	Daily	–
11	Deletion exon 44	14 mo	5.8–12 y	–	10 d on/off	–
12	Deletion exon 3–13	18 mo	–	–	–	–
13	Deletion exon 49–52	20 mo	6.8 y	–	10 d on/off	–
14	Deletion exon 5–17	13 mo	6.5–13 y	–	10 d on/off	–
15	Deletion exon 49–52	15 mo	7.5 y	–	10 d on/off	–
16	Deletion exon 52	24 mo	5 y	–	10 d on/off	–
17	Nonsense mutation c.3544G > T, p.Glu1182*	14 mo	5.5 y	–	10 d on/off	6 y
18	Nonsense mutation c.3544G > T, p.Glu1182*	13–14 mo	5.25 y	–	10 d on/off	5 y
19	Nonsense mutation c.3544G > T, p.Glu1182*	24 mo	5.75 y	–	10 d on/off	5 y
20	Deletion exon 49–50	24 mo	6 y	–	10 d on/off	–
21	Deletion exon 45	18 mo	6 y	–	10 d on/off	–

Table 1 (*Continued*)

Patient no.	Genetic findings	Age walking independently	Treatment with prednisolone	Treatment with deflazacort	Steroid treatment scheme	Treatment with ataluren
22	Deletion exon 13–43	30 mo	–	–	–	–
23	Nonsense mutation c.453 T > G	12 mo	8–10.75 y	–	10 d on/off	8.34–9.75 y
24	DMD gene: no evidence of mutation. Complete lack of dystrophin in muscle biopsy.	24 mo	10–13 y	–	10 d on/off	–
25	Nonsense mutation c.3242C > A	36 mo	–	–	–	11.5 y
26	Deletion exon 51	19 mo	6.25–7.25 y	–	7 d on/off	–
27	c.101411C > T	24 mo	8.5 y	–	10 d on/off	–
28	Deletion exon 48–52	18–24 mo	5.25–6 y and 7–10.25 y	10.25 y	10 d on/off	–
29	c.del559del G	15 mo	6.25–9 y	9–9.5 y	10 d on/off	–
30	c.7661-?_7872 + ?del	18 mo	5.5 y	–	10 d on/off	–
31	Deletion exon 46–47	14 mo	–	9–9.5 y	10 d on/off	–
32	c.4016_4019dupTAAT	16 mo	–	–	–	–
33	Nonsense mutation c.5131C > T	22 mo	5 y	–	10 d on/off	5 y
34	c.10033C > T	24 mo	6–9.5 y	–	10 d on/off	–
35	Deletion exon 49–50	21 mo	5 y (took break because of chemotherapy)	–	10 d on/off	–
36	Nonsense mutation c.433C > T	16 mo	9–13 y	–	10 d on/off	11–13 y
37	c.(6438 + 1_6439–1)_ (7200 + 1_7201–1) del	14 mo	5.5 y	–	10 d on/off	–
38	Deletion exon 49–50	21 mo	–	–	–	–
39	Deletion exon 44	?	5.5–11 y	–	10 d on/off	–
40	c.6557delG	18 mo	5.25 y	–	10 d on/off	–
41	Nonsense mutation c.5026 G > T (Glu1676*)	18 mo	6.5–11.5 y	–	10 d on/off	–
42	Deletion exon 48–50	19 mo	7.5 y	5.5–7.5 y	daily	–
43	Deletion exon 45–50	14 mo	5.5 y	–	10 d on/off	–
44	Deletion exon 53–55	17 mo	5.1 y	–	–	–
45	Duplikation (n.a.)	12 mo	6.2 y	–	10 d on/off	–
46	Deletion exon 53–55	15 mo	5.33 y	–	10 d on/off	–
47	Deletion exon 3–30	15 mo	5 y	–	10 d on/off	–
48	Deletion exon 48–50	18 mo	5 y	–	10 d on/off	–
49	Deletion exon 8–9	19 mo	11–11.5 y	–	10 d on/off	–
50	Deletion exon 46–51	17 mo	5.8 y	–	10 d on/off	–
51	Deletion exon 45–50	20 mo	–	5 y	10 d on/off	–
52	Deletion exon 49–54	14 mo	5 y	–	10 d on/off	–
53	c.6762 + 1G > T	18 mo	5.5–6 y	6 y	10 d on/off	–
54	Nonsense mutation c.7630C > T	18 mo	6.8 y	–	10d on/off	6.5 y
55	Deletion exon 45–50	18 mo	8 y	–	10 d on/off	–

*Indicates "Stop" or "Ter".

Participating patients absolved the testing in those intervals between one and eleven times (mean 4.4 times). Tests without sufficient cooperation or with falls were not included in the calculation. Outliers were checked for plausibility and if necessary eliminated ($n = 2$). The testing was performed as part of the standard follow-up program in our center for neuromuscular diseases in childhood. The testing followed standardized procedures according to the American Thoracic Society recommendations for 6MWT without pulse oximetry.[17] As developed in other studies with DMD patients,[12] a physiotherapist walked behind the patient to provide encouragement and to assist in the event of falling. The walking distance was assessed in meters. Distance was measured at 1-minute intervals. The walking distance and the walking speed were calculated for every single minute.

Since a previous study[18] of ours showed that—due to reasons of motivation—the speed during the first minute of the 6MWT was constantly higher than in the following minutes, we selected the ratio between the second and the sixth minute of the 6MWT for the assessment of fatigue due to neuromuscular problems. A ratio of (distance min 2)/(distance min 6) >1 was used as an indicator of exercise-induced fatigue. Levels of significance were calculated using a double sided *t*-test.

All patients were examined by trained physiotherapists with a vast experience in trials with neuromuscular disorders. Statistical analysis was performed by using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washighton, United States). The study was approved by the local ethics committee of the Ludwig Maximilians University of Munich (internal N°: UE 141–14).

Results

In total 241 tests were analyzed. Analysis of all tests revealed an average fatigue ratio of exactly 1.0 (mean 1.01; median 1.00, standard deviation 0.19; variance 0.04) indicating that there was no loss of speed within 6 minutes. To get an idea whether fatigue occurs only in certain stages of the disease, the fatigue ratio was compared with the age of the patients (►**Fig. 1C**) and to the neuromuscular functioning as shown by the Vignos scale of the lower extremities (►**Fig. 1A**). There was no increase in fatigue with age and with increase of disability.

While the overall distance which could be achieved during the 6MWT declined in the course of the disease, there appeared no increased fatigue during the worsening of DMD.

When fatigue was plotted according to the Vignos scale for lower extremity—higher scale grades indicate higher disability—there was, again, no significant increase in fatigue. Neither the distance which could be achieved during 2 minutes nor the one which could be achieved in 6 minutes correlated to fatigue (►**Fig. 1B, D**). The slight decline in the trend line in the 6-m walk distance (6MWD)/fatigue graph in contrast to the 2MWD/fatigue graph is caused by a handful of single outliers with fluctuating speed, due to distraction, during the individual minute sections.

Six patients who did not receive steroid therapy absolved in total several 25 walks and nine patients who did receive ataluren therapy absolved in total several 48 walks. The analysis of these two subgroups yielded identical results to the analysis of the entire cohort, displaying fatigue values

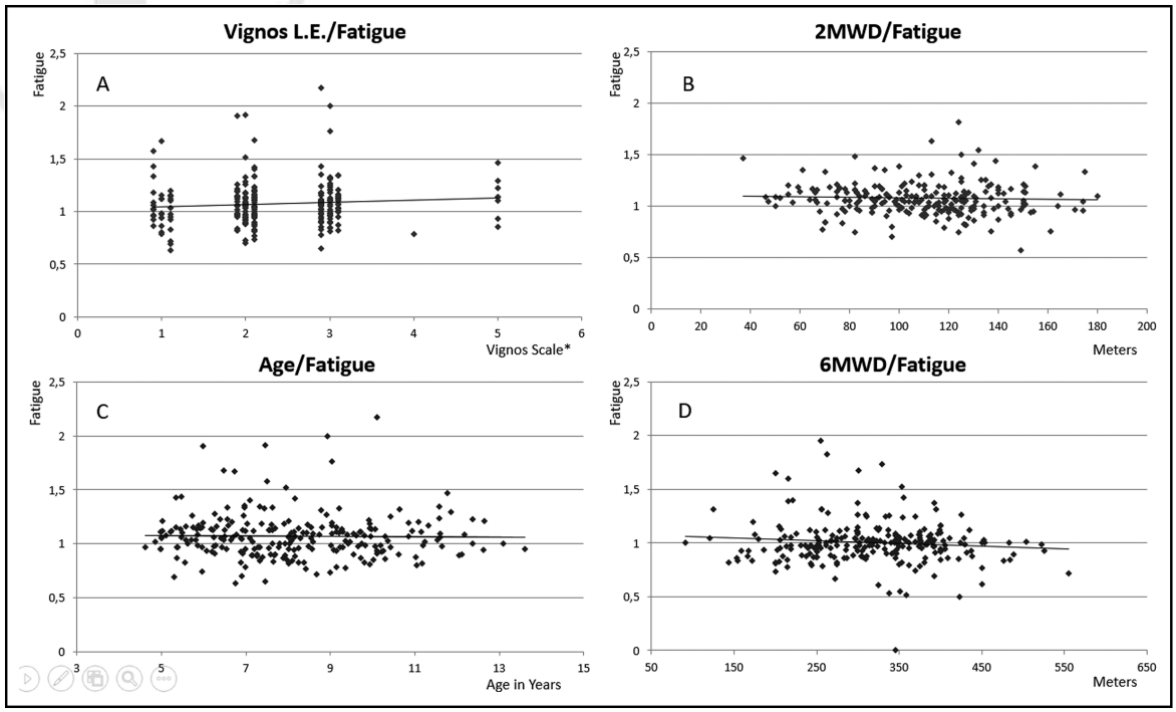

Fig. 1 Plotting of the fatigue quotients with different disease stages defined by the Vignos scale for lower extremity (**A**) and age (**C**), 2-minute walk distance (**B**) and 6-minute walk distance (**D**).

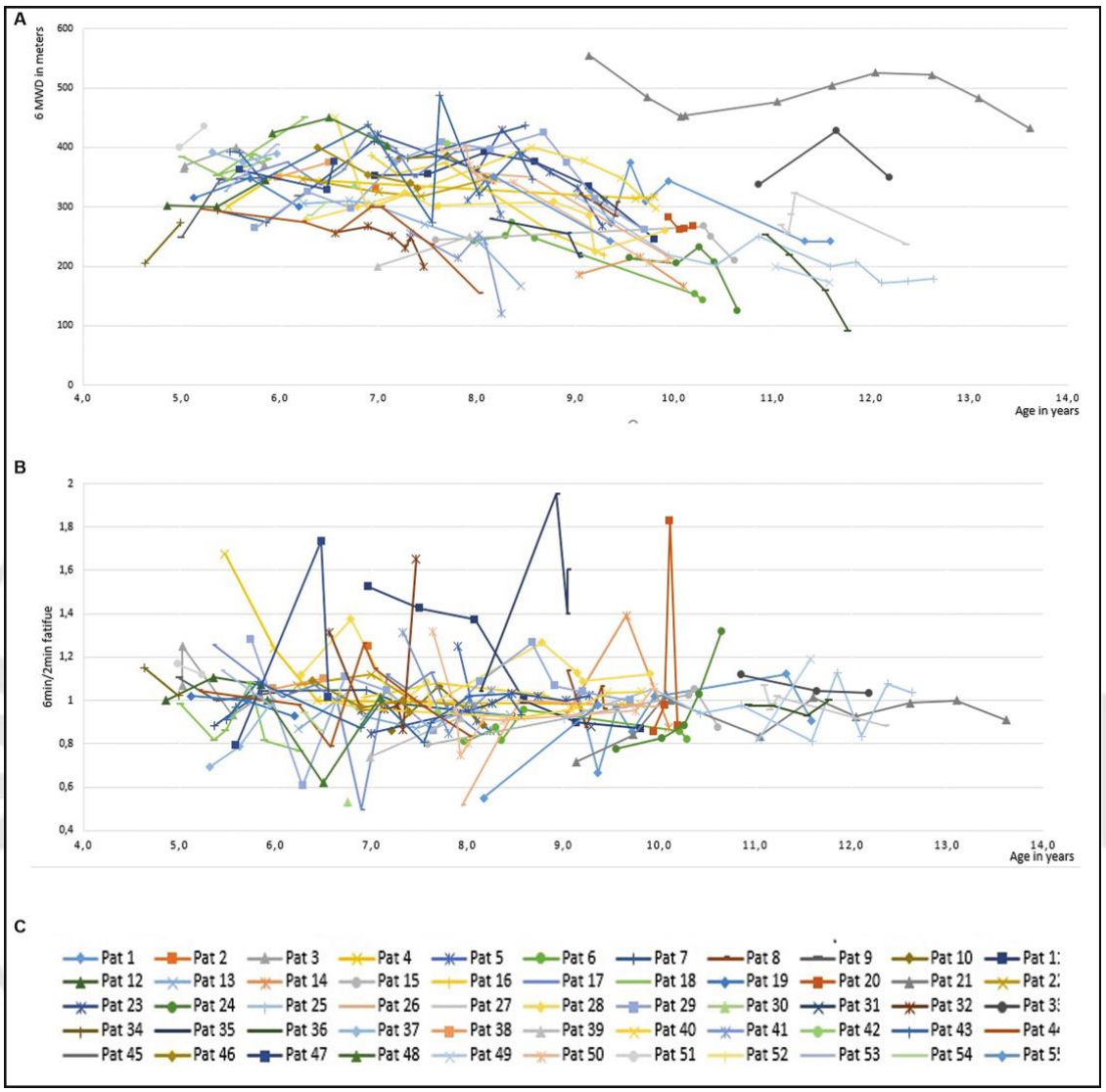

Fig. 2 (A) Intraindividual course of the 6-minute walk distance (MWD) of all 55 patients and (B) intraindividual course of fatigue quotients. While the 6MWD clearly declines over time, fatigue does not increase with higher disability. (C) indicates the patient's graphs.

with a mean quotient of 1.01 and a median of 0.99 in the nonsteroid-group and a mean quotient of 0.98 and a median of 1.01 in the ataluren-group.

To get an idea of the development of the 6MWT and of fatigue in individual patients, the values were plotted over time (►**Fig. 2A**). As expected the decline in the distance can be observed, while the fatigue quotients did not follow the same pattern and did not show any significant decrease in walking distance with increasing disability (►**Fig. 2B**). In four patients there were some intermittent outliers which returned to the previous values at the next visits, indicating that cooperation provides sometimes a problem in individual patients. This underlines why sufficient time and an adequate number of patients are necessary to draw valid conclusions.

Discussion

6MWT is the most established outcome measure in children with neuromuscular diseases in a variety of diseases. It is used as a primary outcome measure in many pediatric neuromuscular studies,[19–22] especially in DMD. A multicenter study from 2013, including 116 DMD boys[23] showed that amongst various clinical scales the 6MWT was the most reliable test.[24]

One of the biggest problems designing DMD trials is the lack of standardized tests before the age of 6 years. The widely used 6MWT is mainly suitable to boys from age 6 to 9 years. There is a big inter- and intraindividual variability, which makes outcome measures based on a physiotherapeutic testing extremely challenging, especially in younger

boys. Commonly observed mental retardation and behavioral problems in DMD[25] reduce the number of children being able to perform the 6MWT in a reproducible manner. For this reason we showed in another study that a 2MWT might be a variant avoiding the necessity to motivate these boys for a 6-minute task. The only information that would be missed in such a setting is about fatigue during prolonged activity as seen in other neuromuscular conditions.

The purpose of this study was consequently to evaluate whether prolonged activity has an impact on speed during a 6MWT at different stages of the disease.

Further literature in NMD and fatigue is rare. A study of Montes et al from 2013 included 114 patients with various neuromuscular diseases[15] and most recently Whitherspoon et al presented data from a population of RYR1-associated myopathy patients.[16]

The authors of the first study found that in the longitudinal course the distance walked by patients declined in Duchenne/Becker muscular dystrophy whereas fatigue did not. In contrast to that weakness in SMA did not change while fatigue increased significantly. Analogue to these previous findings in SMA, walking speed in our cohort of 55 DMD boys stayed stable with an average exercise-induced fatigue quotient of exactly 1.0 (mean 1.01; median 1.00). Comparing second and sixth minute quotients showed no significant decrease ($p > 0.0001$). The findings suggest different mechanisms underlying weakness and fatigue. High frequency discharging motoneurons in neurogenic diseases[14] may be underlying or, respectively, the change of the resting potential in channelopathies.

Does Corticosteroid or Ataluren Therapy Have an Influence on Fatigue in DMD?

As corticosteroids in DMD improve muscle strength and function, the question is whether this treatment could influence endurance. To address this, we performed a subgroup analysis of the six patients (25 walks, age 4.6–13.4 years) without steroid therapy. Since the same results were obtained with a median fatigue of 0.99 and a mean fatigue quotient of 1.01, we do not assume that our observations and conclusions are falsified by the steroid therapy. The same applies to Ataluren; the analysis of 48 walks in the such treated subgroup also showed no change in their results.

Do We See Progredient Fatigue in the Intraindividual Course of the Disease with Longer Duration of the Disease and Progredient Weakness?

Additional subanalyses did not show a relationship of fatigue and age or disability (►**Fig. 1A, C**) With the results of our recent study we can hereby report that there is no significant exercise-induced fatigue in neither one of the subanalyses. For double-check of this statement, we analyzed if there is progredient fatigue in the intraindividual course of the disease with longer duration of the disease and progredient weakness. We analyzed fatigue in the intraindividual course (►**Fig. 2A, B**) and came to the same result. In contrast, a constant decrease in walking speed was observed with increasing degree of disability: Patients Level Vignos 1 walked on average 3.9/3.8 km/h (mean/median) in the second minute and 3.9/3.9 km/h in the sixth minute, patients Level Vignos 3 walked 2.6/2.5 in the second minute and 2.6/2.6 km/h in the sixth minute. Shortly before the loss of walking ability (Vignos Level 5), the patients showed an average walking speed of only 1.9/1.9 km/h in the second minute and 1.9/1.8 km/h in the sixth minute.

Can Exercise-Induced Fatigue Therefore Be a Parameter for Measuring Outcome in Clinical Trials?

According to our data fatigue cannot be used as a parameter for more severely affected patients or younger children with DMD. Our findings, however, represent a strong argument that shortening the walking distance would not be associated with a relevant loss of informative value.[18]

Is Exercise-Induced Fatigue Therefore an Argument against the Establishment of the 2MWT As a Primary Outcome Parameter?

We propose to discuss the establishment of the 2MWT as a primary outcome parameter in DMD. Yet little is known about the usefulness of the 2MWT especially in pediatric population, but recent studies support the ability of the 2MWD to predict the 6MWD, specifically in the pediatric neuromuscular disease population.[18,26] Our results give further evidence, that a 2MWT might be a suitable alternative. Shortening the test would lower the risk of falling and increase motivation, which is a severe problem especially in patients with more advanced stages of DMD. Furthermore, younger and less cooperative patients and patients with lower motoric abilities might be included in clinical studies by using the 2MWT instead of the 6MWT.

A couple of years ago, the reproducibility and correlation of the 100MWT was published in patients with respiratory diseases and the correlation of the time taken over the third 100 m was as the walking pace and proven to correlate highly with a 12-minute walking distance.[27] This work supports our observation that a faster speed is chosen at the beginning of the walk test. The third 100 meters in the 6MWT in our collective, depending on the severity of disability, are absolved between the third and sixth minute.

The combination of their statement that the walking speed between 200 and 400 m correlates with a 12-minute walking distance and our observation that the walking speed is extremely constant from the 2nd minute onward, supports our demand for a shortened test for DMD.

Study limitations: Our study was performed in patients, mainly treated with steroids in a 10 days on/10 days off scheme. Even if it seems very likely, it can be discussed whether the results can be transferred automatically to DMD patients undergoing other treatment schemes.

Conclusion

In our cohort of 55 DMD patients exercise-induced fatigue is not a relevant finding. For this reason we believe that 2MWT increases the number of patients being able to perform the test and reduces the risk of inadvertent falls without losing additional information.

Conflict of Interest
None declared.

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Jumping Mechanography is a Suitable Complementary Method to Assess Motor Function in Ambulatory Boys with Duchenne Muscular Dystrophy

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Abstract

Objective The number of clinical trials for Duchenne muscular dystrophy (DMD) has increased substantially lately, therefore appropriate clinical instruments are needed to measure disease progression and drug efficacy. Jumping mechanography is a medical diagnostic method for motion analysis, which allows to quantify physical parameters. In this study, we compared mechanography with timed function tests (TFTs).

Methods 41 ambulatory DMD patients performed a total of 95 chair rising tests (CRT) and a total of 76 single two-legged jumps (S2LJ) on a mechanography ground reaction force platform. The results were correlated with a 6-minute walk test (6MWT) and the time required to run 10 meters, stand up from a supine position, and climb four stairs, all performed in the same setting.

Results Our measurements show a high correlation between mechanography and the TFTs: S2LJ/10-m run, $r = 0.62$; CRT/10-m run, $r = 0.61$; S2LJ/standing up from supine, $r = 0.48$; CRT/standing up from supine, $r = 0.58$; S2LJ/climb four stairs, $r = 0.55$; CRT/climb four stairs, $r = 0.51$. The correlation between mechanography and the 6MWT was only moderate with $r = 0.38$ for S2LJ/6MWT and $r = 0.39$ for CRT/6MWT.

Interpretation Jumping mechanography is a reliable additional method, which can be used for physical endpoint measurements in clinical trials. We confirmed our assumption, that the method provides additional information concerning performance at movement with higher power output. We suggest using the S2LJ as a first-choice tandem tool combined with the 6MWT. In patients with higher disability, the CRT is an alternative measuring method, because with the progression of the disease this is longer feasible.

Keywords
- jumping mechanography
- Duchenne muscular dystrophy
- outcome measure
- chair rising test
- single two-legged jump
- timed function tests

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Introduction

Duchenne muscular dystrophy (DMD) is a devastating X-linked muscular disorder affecting one in 3,500 newborn boys.[1] Mutations in the dystrophin gene[2] cause progressive weakness resulting in loss of ambulation during adolescence.[3] During later stages of the disease, upper extremity and trunk stability become severely impaired and ventilation and cardiac function become insufficient.[4,5]

In the healthy muscle fibers, the dystrophin–glycoprotein complex provides a link between extracellular matrix and cytoskeleton. In patients with DMD, the lack of dystrophin is known to compromise this link, leading to muscle fiber degeneration with consecutive deterioration of muscular function.[6–8]

Regarding pharmacological treatment, the corticosteroids deflazacort and prednisone/prednisolone are the gold standard of treatment, as they slow disease progression.[9] Ataluren is known to slow disease progression versus placebo in DMD patients with nonsense mutations, most evident in patients with a baseline 6-minute walk test (6MWT) $\geq$300 m to $<$400 m.[10] Eteplirsen is a therapeutic drug for DMD patients with special mutations, that can be overridden by skipping exon 51 of the DMD gene. Eteplirsen showed evidence of muscle cell penetration, exon skipping, and induction of novel dystrophin expression.[11] Currently, new drugs are under investigation[12] and the numbers of studies investigating basic disease mechanisms in animal models and testing these concepts in human clinical trials have substantially increased over the last decade. Targets of interest encompass optimized antisense oligonucleotides for exon skipping, mitochondrial pathways, prevention of fibrosis, and gene therapeutic restoration of dystrophin expression.[13–15]

Suitable clinical instruments are mandatory to measure and evaluate the natural history of the disease and the effect of new therapeutic targets.

To evaluate motor skills in ambulatory DMD patients, one of the current gold standards is the 6MWT. It was initially used to monitor adult patients with cardiopulmonary diseases. This test is meanwhile widely used as a primary outcome parameter to measure natural history and drug efficiency in many neuromuscular conditions in children.

Reference values for the 6MWT in healthy children and adolescents are available from the age of 5 years onward. Classical timed function tests (TFTs) such as time to walk or run 10 m, to climb four steps, or to rise from a supine position are other widely used parameters.[16] Other methods are newer motor function tests, for example, the North Star Ambulatory Assessment (NSAA: containing classical TFTs) or the Revised Upper Limb Module (testing upper limb function).

Further quantitative information on the function of the neuromuscular system can be obtained by using ground reaction force plates, which are able to acquire dynamic information of an individual jump or chair rise. Maximum power relative to body mass (P_{max}rel) is calculated from the dynamic ground reaction force during the counter movement or rise period, which is used as an indicator for motor function. So far primarily applied in sports,[17,18] it is an easy, safe, and reliable tool to measure lower-limb musculoskeletal function.[19,20] Reproducibility is reported to be good.[19,21,22] Reference values have been assessed in several cohorts each including more than 300 children and adolescents for counter movement jumps and chair rising tests (CRT),[23] for a single two-legged jump (S2LJ: nonrestricted counter movement jump),[24] and for grip force, one leg whole body stiffness, and multiple one leg hopping.[25] Mechanography is also increasingly used in the medical field with a focus on bone-related diseases.[26–32]

Rittweger et al reported a strong correlation between mechanography and other time function assessment indices including walking speed, the "timed up & go test," and the "chair rising test" in adults.[21]

There is a significant gender-dependent difference in the age-depending normative values at the age of 12 years and over.[33] When assessing the effects of aging on the measurements in mechanography, a high correlation between age and P_{max}rel was reported for both genders. An assessment index called the Esslinger Fitness Index (EFI) was developed,[24,34] which is calculated as an age- and gender-matched percentage of the standard performance in motor function.[18,35]

So far, mechanography was sporadically used to measure motor function in patients with neuropediatric and/or neuromuscular conditions.[36–38] However, rather little data exist for these groups so far.

The purpose of this study was to compare mechanography, measuring lower-limb force when performing an S2LJ and a CRT, to already established TFTs in a cohort of ambulatory boys with DMD.

Patients and Methods

At our center since 2013, the S2LJ and the CRT are part of the routine survey of ambulatory DMD patients in addition to performing TFTs to measure disease progression.

In this study the data we obtained between November 2013 and January 2018 were evaluated, to support the hypothesis of a correlation between the two mechanography tests and the classical TFTs.

A cohort of 41 ambulatory patients (patients' age at examination 3.9 to 13.6 years, mean 7.5 years, median 7.0 years) was retrospectively analyzed.

Because some patients were examined several times and some patients were examined only once, this study provides a mixture of cross-sectional and longitudinal follow-up data. All tests are summarized to correlate the mechanographic results and the TFT results. The intraindividual course of six patients (pat 15, 18, 21, 25, 35, 36), who underwent four or more test series, was graphically worked up for all subtests.

All patients were under regular medical care in our pediatric neuromuscular center at the Dr. v. Hauner Children's Hospital, Ludwig-Maximilian University of Munich, Germany.

Inclusion criteria were a genetic proof of DMD and the physical and intellectual ability to perform all tests correctly. Patient's clinical and genetic characteristics, age, and level of disability, shown by the Vignos scale for lower extremities, are listed in ►**Supplementary Table 1**.

All the tests took place in our outpatient clinic on a single day and were part of the routine follow-up of DMD patients. Standardized conditions were guaranteed by using the same order and sufficient resting time (2 minutes) between the individual units. The order of performance was S2LJ and CRT first, followed by 6MWT, climbing four stairs, 10-m run, and getting up from supine. Trained physiotherapists with long-standing experience in clinical trials in the field of neuromuscular disorders examined all patients.

The 6MWT was performed according to the American Thoracic Society recommendations without pulse oximetry, and the distance was assessed in meters.

For the TFTs, the patients were instructed to climb four stairs, to run 10 meters, and to get up from a supine position as quickly as possible, whereat the results were measured in seconds. For the stair-climbing test, a standardized four-step model was used, adjusted as required for the NSAA. For mechanography, the system Leonardo Mechanograph GRFP STD (Novotec Medical GmbH, Pforzheim, Germany) was used. It consists of a split ground reaction force platform connected to a computer. The force was analyzed using the Leonardo Mechanography Software Version 4.3.

The platform was zero-adjusted prior to each patient's measurement session. For jumping, the patients were advised to jump as high as possible trying to land on their forefeet. Every patient performed the S2LJ test comprising three consecutive jumps. For the CRT, a bench was installed on the platform, which serves as a seat with a sitting height that produces a 90° angle in the patient's knees. Patients were instructed to stand up as quickly as possible until the knees were fully extended and to sit down again. The arms had to be crossed over the chest. CRT was performed five times and the mean value was used for statistical analysis. P_{max}rel (SI unit is W/kg) was measured from CRT and from S2LJ. P_{max}rel reflects the physical performance in watt, in relation to the body weight. To complete an S2LJ and a CRT, it took ~5 minutes in practice.

All results acquired by the software were manually reviewed (correct measurements of start, end, and validity of the test) by an engineer of the company (coauthor RR).

Statistical Analysis

The results of mechanography were correlated with the results of the TFTs and the 6MWT using linear regression. The analysis was performed with Excel (Microsoft, Redmond, Washington, United States).

The local ethics committee of the Ludwig Maximillian's University of Munich approved the study (internal N°: UE 141–14).

Results

41 patients performed the test session once or repeatedly up to nine times. This cohort represents ~75% of the total ambulatory DMD cohort at our center during that period; the rest were physically or mentally unable to follow the test protocol and therefore not included in the study. No patient refused the tests, hence the acceptance of mechanography was very good.

The reduced performance of this study cohort compared with healthy peers was shown by the EFI with values of 15 to 80%.

In total, 105 test settings were performed and 95 CRT and 76 S2LJ exams were included in the study. In 69 settings, both tests could be performed; five more had to be excluded due to irregularities (mainly compliance problems with extremely varying results within the same setting).

In 36 settings only one of the two methods were completed and in 28 of them, this was only the CRT because the CRT is able to measure even very low wattages, whereas the S2LJ is invalid if the patient can no longer perform a jump with lifting the feet from the ground.

In eight settings, only the S2LJ was performed. The degree of disability corresponded to levels 1 to 3 on the Vignos scale for lower extremities (in 27 settings, the patients' Vignos scale was 1; in 58 settings, the patients' Vignos scale was 2; and in 20 settings, the patients' Vignos scale was 3).

The age distribution and the distances in 6MWT down to which mechanography was possible or no longer possible are provided in Supplementary Table 2. On average, the performed 6MWT, when the CRT was no longer possible to be measured, was 260 m (range: 121–455 m), and for the S2LJ, 316 m (range: 153–455 m). On average, patients at the age of 9.3 years were the latest possible to perform the CRT and 8.7 years to perform the S2LJ.

Significant correlation between both mechanography tests and the TFTs was observed: Arising from the floor compared with the S2LJ revealed a correlation coefficient of 0.48 and 0.58 compared with the CRT. The correlation with the time required to climb four steps was 0.51 for the S2LJ and 0.52 for the CRT. Respectively, the comparison between the S2LJ/the CRT and the 10-m run showed the highest correlation of 0.62 and 0.61. Unfortunately, one inadvertent fall occurred during a 10-m run, so this measurement was rejected.

Correlation between the 6MWT and the S2LJ or the CRT showed a comparable lower correlation coefficient of 0.38 and 0.39. All results are visualized in ►**Fig. 1**.

The intraindividual course of six patients (pat 15, 18, 21, 25, 35, 36), who underwent four or more test series, has graphically been worked up for all subtests. The curves show an overall tendency; however, different grades of progression can be worked out for the different subtests. While the 6MWT results remain comparatively stable over the test period, the speed of getting up and climbing stairs show a clearer deterioration over the same period (in some cases after improvement at earlier age before reaching the motor plateau). The same can be observed in the two mechanography tests. All graphs also clearly show that individual patients in individual subtests intermittently show outliers in their performance (the 6MWT turns out to have the most stable results in this small cohort).

Discussion

Potential new drugs are currently being developed for DMD. To evaluate the effects of new therapeutic targets, suitable clinical test instruments to quantify physical performance are mandatory. We retrospectively analyzed a cohort of ambulatory boys with DMD and compared the results of

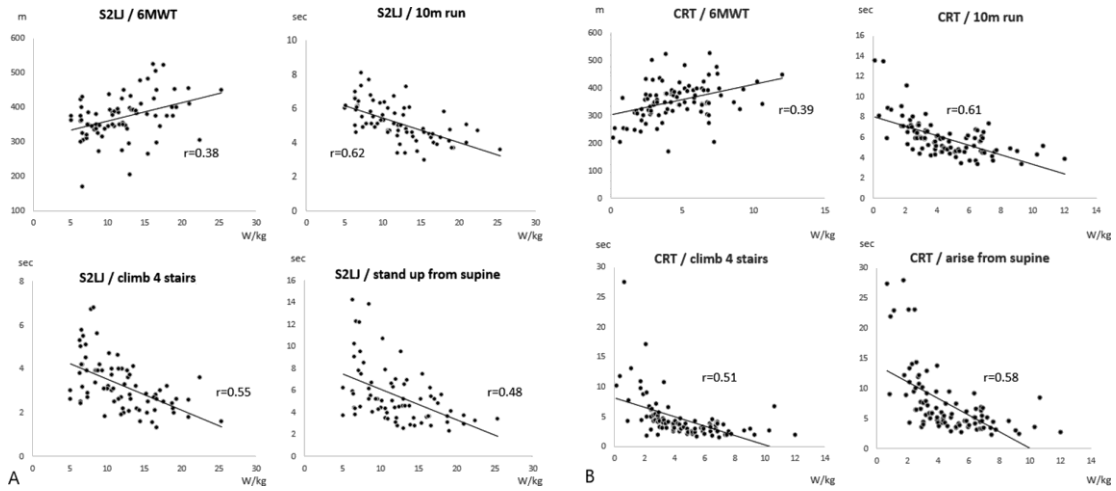

Fig. 1 Correlation of chair rising tests (CRT) (A) and single two-legged jumps (S2LJ) (B) with 6-minute walk test (MWT) and time function testing. Correlation calculated by linear regression; *x*-axis = mechanography; *y*-axis = time function tests; *r* = correlation coefficient.

TFTs and the 6MWT with two mechanography tests: the CRT and the S2LJ.

The 6MWT is so far the best-established test instrument for children with neuromuscular diseases.[39] It is known to be accurate, reproducible, and generally well accepted.[16] Nevertheless, the walking distance is only one parameter for assessing motor skills. In General, the 6MWT measures low power and endurance and quantifies majorly aerobic performance, focusing more on slow-twitch muscle fibers.

The S2LJ and CRT mainly depend on functioning proximal muscles of the pelvic girdle and the legs. It measures short time movements requiring high muscle power, and therefore quantify anaerobic performance with a focus on fast-twitch muscle fibers.

The muscles of the pelvic girdle, in particular the gluteus maximus, which are required for jumping, are especially weak in DMD patients. The S2LJ correlates best with the 10-m run, which might be due to very similar movement characteristics. This would as well explain why CRT and S2LJ correlate less with the 6MWT than with getting up from the floor and running 10 m, as both similarly target pelvic girdle and fast-twitch muscle fibers.

In general, the S2LJ is more challenging in terms of coordination than the CRT. One of the reasons for this is that a counter movement and a good/fast stretching and shortening cycle in the muscle[40] is essential for an effective maximum jump.

Our results can be summarized as followed:

- Mechanography is suitable for quantification of strength in DMD patients up to an age of ~8 to 9 years, down to a quite variable walking distance (in this study of 125–455 m) and a 1 to 3 degrees of disability on the Vignos scale for lower extremities.
- Lowest correlation was observed between mechanography and the 6MWT, probably because mechanography is focused on short-term high-performance muscle work, while the 6MWT evaluates endurance during long-term low-intensity activity. This suggests that mechanography is a good complement to the 6MWT.
- Best correlations were observed between the S2LJ and the 10-m run as well as with climbing stairs, since similar muscle groups (especially thigh and gluteus) and high performance (high power per body mass levels) are evaluated.
- Also, very good correlations were observed between CRT and the 10-m run as well as with getting up from supine. Again, for these tests, similar muscle groups and high power are required. However, the technique of getting up from the floor in DMD is slightly different, since these patients help with their arms (Gowers sign).

Tools like the NSAA, which is currently the most complex composite score and specifically designed for ambulant children with DMD, include TFTs like arising from supine and 10-m running, targeting movements at high power output and including the hip-surrounding muscles. However, scales or methods to quantify performance at movements with high power output have not been established so far in DMD.

Studies that investigate the usefulness of mechanography in pediatric patients with neuromuscular disorders are extremely rare. In a previous publication, our study group could show that the CRT and the S2LJ correlate well with classical TFTs like 10-m run and the time to arise from a supine position in pediatric patients with hereditary motor and sensory neuropathy.[36]

We confirm these results in patients with DMD. The CRT has the advantage that patients with declining motor function are longer able to perform it, compared with the S2LJ. In addition, the S2LJ is more demanding in terms of coordination, so the CRT is in general easier to complete. We assume that the S2LJ reflects earlier stages of the disease quite well.

Since the S2LJ is known to be a specific parameter to assess maximum anaerobic peak power[25] and therefore provides additional information on muscular function, our final

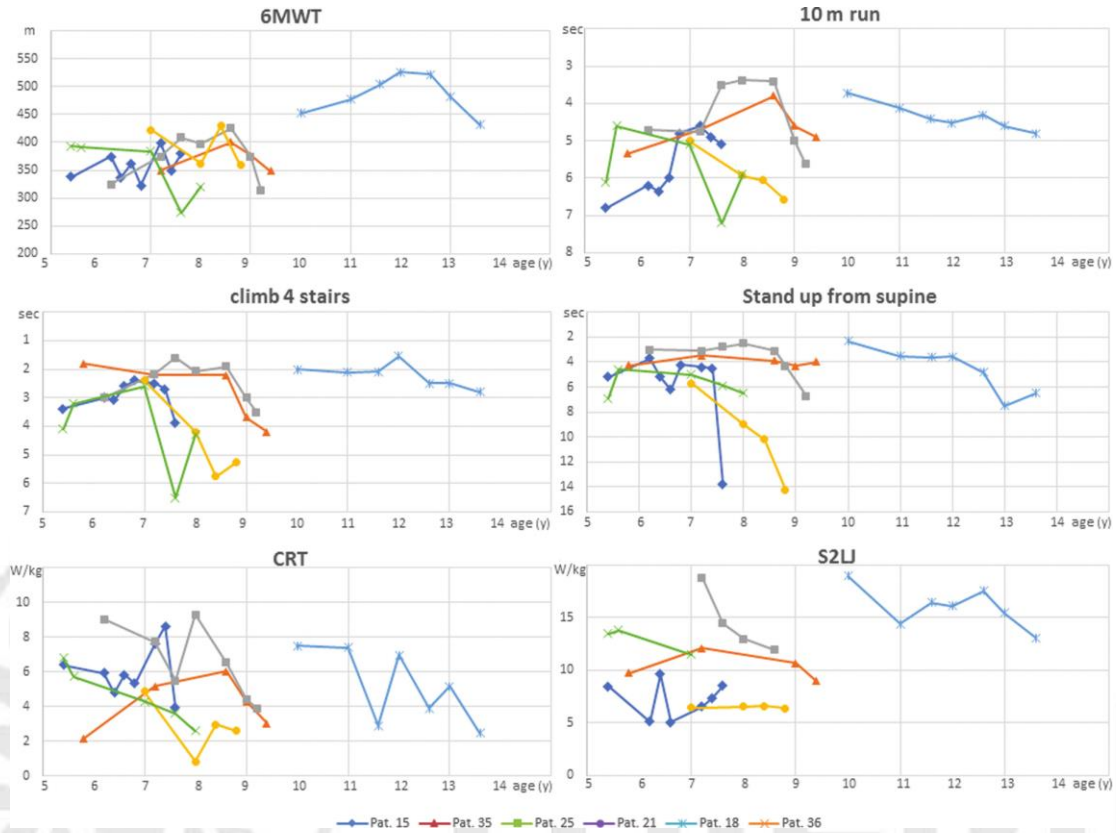

Fig. 2 Intraindividual course of Mechanography tests and TFTs in six patients, who underwent four or more test series.

recommendation is to perform a tandem of 6MWT and S2LJ, and, if not possible, to choose the CRT as a second-choice tool for mechanography.

For the future, it would certainly be interesting to investigate the correlation of mechanography with composite scores like the NSAA, ideally in a prospective setting.

Of course, it must be taken into account that not all DMD patients are actually able to complete the test protocol including a bipedal jump. However, our study cohort for this analysis represents 75% of our center's ambulatory DMD cohort over the chosen time period, which is certainly an argument for the use of mechanography.

A further indicative argument for the combination of the 6MWT and an additional quantitative force measurement results from our ►**Fig. 2**: in the small cohort of six selected patients, in which longitudinal data are available, the 6MWT proved to be the most stable value, comparatively favorable with respect to outliers, but also quite rigid concerning intraindividual changes over several years.

Conclusion

Our results demonstrate that jumping mechanography is a beneficial tool in quantifying motor function in DMD. The S2LJ is a very valid outcome measure; however, the CRT is more suitable in patients with higher grades of disability. Exact force can be quantified and intraindividual comparisons over time or with normative data are possible.[24,34]

The method provides valuable information on performance at high-power motor tasks and expands, especially in combination with the 6MWT, our knowledge on motor function in DMD.

Highlights

- We demonstrate a good correlation of mechanography with established TFTs in ambulatory DMD patients.
- Jumping mechanography adds further quantitative information about neuromuscular function.
- The CRT and the S2LJ provide additional information about movements at higher power (chair rise, stair climb, jumping) compared with endurance-oriented movements as quantified in the 6MWT.
- This is why we consider them as useful tandem tools together with the 6MWT.
- The CRT can be tested even when a higher grade of disability is present; however, the S2LJ is the more specific method.

Conflict of Interest

Dr. Rawer is an employee of Novotec Medical GmbH, Pforzheim, Germany. Wolfgang Müller-Felber received a project-specific grant from PTC. All the other authors report no conflict of interest.

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