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Different K^+-release in distal myogenic and neurogenic muscular weakness during non-ischemic exercise

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ABSTRACT

Introduction: In myotonic dystrophy, an increased potassium release upon ischemic forearm exercise has been previously described. However, it remains unclear whether this is specific for myotonic dystrophies or just due to distal muscular weakness.

Methods: Non-ischemic forearm test (NIFET) was performed and venous K^+ concentration was measured at rest and at three different force levels (20–30%, 50–60%, 70–80%) related to maximal contraction force (MCF) in patients with distal myogenic ($n = 7$), neurogenic ($n = 7$) muscular weakness and healthy volunteers ($n = 12$). The specific K^+ release was defined as K^+ increase related to workload as force-time-integral during repetitive contraction.

Results: Workload was lower at all force levels in both disease groups compared to the control group. With increasing workload, the K^+ concentrations increased in all study groups. Analysing individual force levels related to the maximum contraction force (MCF), a higher specific K^+ release was measured at low force levels in myopathies (20–30% MCF) in comparison to higher force levels ($p = 0.02$). At 20–30% MCF, the specific K^+ release was significantly higher in myogenic compared to neurogenic muscular weakness ($p = 0.005$). At 50–60% and 70–80% MCF, the specific K^+ values converged and did not significantly differ between the three groups ($p = 0.09$ and $p = 0.37$).

Discussion: At low force levels, K^+ efflux related to workload is higher in patients with myogenic in comparison to neurogenic distal paresis. Our results indicate a different regulation of K^+ balance in neurogenic and myogenic muscular weakness possibly due to a different recruitment behaviour of motor units and the firing rate of motor neurons.

1. Introduction

Skeletal muscle function depends on the precise regulation of intra- and extracellular potassium concentration. A disturbed regulation of the potassium balance in skeletal muscle can lead to muscle pain, weakness and tetany [1,2]. Myotonia can be influenced by the extracellular K^+ concentration and it has been assumed that extracellular K^+ increase might be responsible for myotonia in myotonic dystrophies [3]. In patients with clinically defined myotonic dystrophy, a strong increase of the plasma K^+ concentration has been observed after ischemic exercise. This was not observed in patients with other neuromuscular diseases [4]. In this study, the myotonic dystrophy patients had a significantly lower forearm force and performed with a significantly lower workload than healthy volunteers and patients with other neuromuscular diseases. Therefore, it remains unclear whether this is specific for myotonic dystrophies or characteristic for distal muscular weakness in general. Additionally, at that time the genetic differentiation of myopathies, e.g. myotonic dystrophy type 1 and 2 was not possible yet. Furthermore, the authors used an ischemic forearm test, which may induce muscle pain during the measurement and even rhabdomyolysis [5]. In patients with McArdle disease, similar results as for the ischemic test were obtained performing a non-ischemic forearm exercise test (NIFET) and it was better tolerated [10]. Thus, NIFET might be more suitable for measuring exercise-induced K^+ release.

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In muscle contraction, two different mechanisms are discussed to increase muscle strength: 1) the recruitment of previously inactive motor units and 2) increase in motor neuron firing rate [8]. Which mechanism is primarily activated depends on the force to be achieved and the underlying pathology in myogenic and neurogenic paresis. However, the exact involvement of these mechanisms is unclear, especially under pathophysiological conditions. In addition to electrophysiological studies, differences in electrolyte balance, especially potassium, in neurogenic and myogenic paresis could provide clues as to the role of recruitment and firing rate of motor units in muscle strength.

This provided the impetus for conducting an explorative study to compare work-related potassium release in patients with pronounced distal muscular weakness of myogenic and neurogenic origin.

2. Methods

2.1. Patient recruitment

Eligible were patients with significant distal muscular weakness of the upper extremities (grade $\leq$ 4 of MRC scale [16]). The weakness of the extremities had to exist for at least 1 year. Patients had to be able to apply a reproducible force in hand closure, so patients with very severe paresis could not participate in the study. According to diagnosis, patients were assigned to either the group with myogenic or neurogenic muscular weakness (Tables 1, 2). The latter group included patients with polyneuropathy as well as motor neuron disease. For simplicity, this group will be referred to as the "neuropathy group" regardless of etiology. An accompanying sensory polyneuropathy of the lower extremities was allowed in the myopathy group. All patients were recruited from the Department of Neurology, University Hospital Halle (Saale) and gave written informed consent for participation. The healthy volunteers consisted of current or former employees of the Department of Neurology who also gave written informed consent. Subjects in the control group also underwent clinical examination e.g. to rule out paresis. The local ethics committee (University of Halle-Wittenberg) approved the conduct of this study.

2.2. Exercise test

All patients and healthy volunteers performed a non-ischemic forearm exercise test. It included in measuring blocks of 3 min each a handgrip exercise with a target frequency of 1 Hz, which was indicated by a repeating sound signal. The contraction force was continuously recorded by a dynamometer device connected to a laptop, which allowed constant visual control of the force applied during the test. The device was designed at the Centre for Basic Medical Research, Martin-Luther-University Halle-Wittenberg (data acquisition software: LabVIEW, National Instrument, Texas, USA). At the beginning, the maximum contraction force (MCF) was determined as the highest value from three measurements with one maximum contraction each. This value was chosen as reference. After that, three measurement runs followed, each lasting 3 min with 20–30%, 40–50% and 60–70% of MCF. The patient was able to control the contraction force by a reference line on the laptop screen indicating the actual force. There was a resting period of at least 15 min between each measurement. Blood samples for potassium analysis were collected from a cubital vein catheter before each exercise and at minute one, two and three during exercise. The workload [kN*s] was calculated as the area under the force-time curve for the duration of one measurement block (3 min.). The specific K^+ release [mmol/l/kN*s] was defined as the venous K^+ increase [mmol/l] related to the workload. The mean values of K^+ concentrations after minutes 1, 2 and 3 were used for further calculation. All included patients and subjects in the control group were able to maintain the exercise protocol within the 3-min window.

2.3. K^+ determination

The blood samples were always taken under non-ischemic conditions, without vein congestion from a cubital vein catheter. The blood was collected into a monovette prefilled with lithium-heparin (S-Monovette® 4.9 ml LH-gel, Sarstedt AG und Co. KG, Nümbrecht, Germany). The potassium concentration was determined potentiometrically using a full automation system (Cobas® 8100 system, Roche Deutschland Holding GmbH, Grenzach-Wyhlen, Germany).

2.4. Statistical analysis

Differences among the study groups were analysed using One Way ANOVA; post-test analysis was done using Mann-Whitney-U Rank-sum test. For linear regression, Pearson correlation was utilized with a subsequent two-sided significance test. For statistical analysis and figure preparation Sigma Plot 13.0 (Systat Software Inc., San Jose, CA, USA) was used.

3. Results

3.1. Study population

Eight patients with a myopathy, eight with a neuropathy and twelve subjects in the control group became eligible to the study. One patient

Table 1
Clinical and electrophysiological data of the study patients with neurogenic paresis included in the data analysis (UL – upper limbs; LL – lower limbs; PNP – polyneuropathy; ALS – amyotrophic lateral sclerosis).

Age, sex	Diagnosis	Yrs.[a]	Main clinical symptoms	Severity of paresis (prox./dist.)	EMG findings
56 yrs., female	Demyelinating sensorimotor PNP	2	paraesthesia and muscular weakness	UL: 5/4 LL: 5/4	Mild chronic neurogenic pattern, delayed recruitment
78 yrs., female	Axonal and demyelinating sensorimotor PNP	3	Initially distal limb paraesthesia, later distal muscular weakness	UL: 4/3 LL: 3/1	Marked acute and chronic neurogenic pattern
60 yrs., male	Definitive ALS	1	Progressive tetraparesis with marked spasticity	UL: 4/3 LL: 5/3	In several areas increased spontaneous discharges, delayed recruitment
56 yrs., female	Demyelinating sensorimotor PNP	2	Neuropathic pain (lower legs), in the course muscular weakness	UL: 4/3 LL: 5/4 (asymmetrical, right accentuated)	Mild chronic neurogenic pattern
72 yrs., female	Definitive ALS	1	Progressive tetraparesis with marked spasticity, bulbar paralysis	UL: 4/3 LL: 3/3	In several areas fasciculation, markedly delayed recruitment
82 yrs., male	Probable ALS, initial flail-arm syndrome	6	Initially right arm paresis, later increasing axial weakness and bulbar paralysis	UL: 3/4 LL: 5/4	Mild chronic neurogenic pattern
38 yrs., male	Definitive ALS	2	Bulbar paralysis, gait disorder, impairment of fine motor skills of the hands	UL: 5/4 LL: 5/5	In several areas pronounced spontaneous discharges, delayed recruitment

[a] Years since the first presentation of disease-related symptoms.

Table 2
Clinical and electrophysiological data of the study patients with myogenic paresis included in the data analysis (abbreviations see Table 1).

Age, sex	Diagnosis	Yrs.[a]	Main clinical symptoms and/or examination findings	Severity of paresis (prox./dist.)	EMG findings
68 yrs., male	Polymyositis	4	Gait disturbance, myalgia, fine motor disturbance of the hands	UL: 5/4 LL: 4/4	low-amplitude and polyphasic potentials, early recruitment, dense interference pattern
44 yrs., male	Myotonic dystrophy type I (genetically proved)	>10	Distal tetraparesis, facies myopathica, myotonic symptoms in the hands	UL: 5/3 LL: 5/4	N/A (external diagnostic, no valid data available)
56 yrs., female	Inflammatory myopathy (Mi2-positive)	3	exercise-induced limb girdle muscular weakness, fine motor disorder of the hands	UL: 5/4 LL: 4/4	pathological spontaneous activity, polyphasic potentials (14–41%), early recruitment, various interference pattern (dense or thinned)
43 yrs., female	Paramyotonia congenita (SCN4A mutation)	2	Myotonic symptoms and fine motor disturbance of the hands,	UL: 4/4 LL: 4/5	In various muscles myotonic discharges, normal interference pattern, normal single unit potentials
43 yrs., male	Myotonic dystrophy type I (genetically proved)	1	cold-induced muscle tension, fine motor disturbance of the hands	UL: 5/4 LL: 5/5	Moderately developed fibrillations and fasciculations, early recruitment
43 yrs., female	Distal myopathy (unknown etiology)	8	exercise-induced painful muscle tension	UL: 5/4 LL: 5/5	early recruitment in some locations, polyphasic potentials with low amplitudes
29 yrs., male	Myofibrillar myopathy (pathogenic mutation in the desmin gene)	5	Initially exercise-induced muscle pain, later progressive tetraparesis, cardiomyopathy	UL: 5/4 LL: 4/3	N/A (external diagnostic, no valid data available)

[a] Years since the first presentation of disease-related symptoms.

with a myopathy was excluded from the study as the measurement was stopped due to muscle pain. One dataset from a patient with a neuropathy was not analysable due to technical issues. The key clinical and electrophysiological data of the included patients, if available, are shown in Tables 1 and 2. The mean age numerically differed between the three groups with the highest mean age in the neuropathy group (myopathy: 48.4 yrs., neuropathy: 60.9 yrs., controls: 51.0 yrs.; $p = 0.33$, One Way ANOVA).

3.2. Maximum contraction force (MCF) and workload

All patients included in the study were able to perform the 3 min lasting test. With the exception of fatigue and moderate pain in the working limb, no other symptoms, such as myotonia, occurred. Values of workload, MCF, and serum potassium concentrations are shown in Table 3. Maximum contraction force and workload were significantly lower in both myopathy and neuropathy groups compared to the control group ($p < 0.001$, $p = 0.001$, Mann-Whitney U Test). The maximum contraction force ($p < 0.001$, One-Way ANOVA) and the workloads within each force level differed significantly between the groups (20–30%: $p = 0.001$; 50–60%: $p = 0.001$, 70–80%: $p < 0.001$, One-Way ANOVA). The workload tended to be lower in the myopathy group than in the neuropathy group at 20–30% MCF ($p = 0.08$, Mann-Whitney U Test). Only two patients from the neuropathy group and no one from the myopathy group had a maximum contraction force within the range of the healthy volunteers.

3.3. Venous K^+ concentrations

The venous K^+ concentrations at rest in both myopathy and neuropathy groups were significantly higher compared to the control group ($p = 0.002$, One-Way-ANOVA; $p = 0.008$ and $p = 0.003$, Mann-Whitney U Test). Comparing the K^+ concentrations during the exercise, there was no significant difference between minutes 1, 2 and 3 of the exercises in all study groups. This applied to all force levels. Thus, all K^+ values in Table 3 are given as the mean K^+ of the values at minutes 1, 2 and 3.

With increasing workload, the absolute venous K^+ concentration increased in all three groups compared to the resting period (Fig. 1). Quantified by a linear proportionality model, this relationship was most pronounced for the myopathies and also significant in the control group, but not in the neuropathies. The linear regression coefficient r was 0.87 for myopathies ($p < 0.001$), 0.70 in the control group ($p < 0.001$) and 0.40 for neuropathies ($p = 0.08$). Saturation kinetics could not be excluded when the workload was more than 10 kN*s in the control group. The global specific K^+ release that was defined as K^+ increase per workload represent the slopes of the regression lines in Fig. 1 and it was most pronounced in the myopathy group.

The workloads of individual subjects overlap in Fig. 1, because the maximum contraction forces (MCF) differ. The specific K^+ release in relation to the workload is illustrated in Fig. 2A. Since the workloads between the study groups differed considerably, the specific K^+ release was analysed at three different relative strength levels (20–30%, 50–60% and 70–80%), which were based on the individual maximum strength (Fig. 2B). The specific K^+ release was significantly different between the study groups at 20–30% MCF ($p = 0.02$, One-Way ANOVA; Fig. 2A, B). This difference decreased at higher force levels and was not statistically significant (50–60%: $p = 0.09$; 70–80%: $p = 0.37$; One-Way ANOVA). The specific K^+ release was significantly higher in myopathies compared to neuropathies in 20–30% MCF ($p = 0.005$, Mann-Whitney U Test), and in neuropathies there was a trend towards lower values compared to the control group ($p = 0.08$, Mann-Whitney U Test). Comparing the three force levels, there was a significant decrease in

Table 3
Workload and venous potassium concentrations within the force levels.

	Force level	Myopathies	Neuropathies	Controls	p value (ANOVA)
Maximum contraction force [N]	100%	135 ± 43; range: 45–266	155 ± 79; range: 44–173	345 ± 80; range: 191–502	<0.001
Workload [kN*s][a]	20–30%	2.61 ± 1.11	3.76 ± 1.18	5.71 ± 2.20	0.001
	50–60%	4.92 ± 4.50	7.06 ± 2.48	13.08 ± 3.66	0.001
	70–80%	7.60 ± 2.48	9.67 ± 5.01	16.81 ± 7.10	<0.001
K^+ [mmol/l][a]	at rest	4.06 ± 0.41	4.13 ± 0.56	3.52 ± 0.27	0.002
Absolute K^+ increase [mmol/l][a]	20–30%	0.41 ± 0.15	0.18 ± 0.15	0.65 ± 0.34	0.04
	50–60%	0.57 ± 0.24	0.41 ± 0.32	1.21 ± 0.36	0.01
	70–80%	0.76 ± 0.29	0.62 ± 0.51	1.48 ± 0.33	0.001

[a] Values are given as mean and standard deviation (SD). The three study groups were compared using one-way-ANOVA.

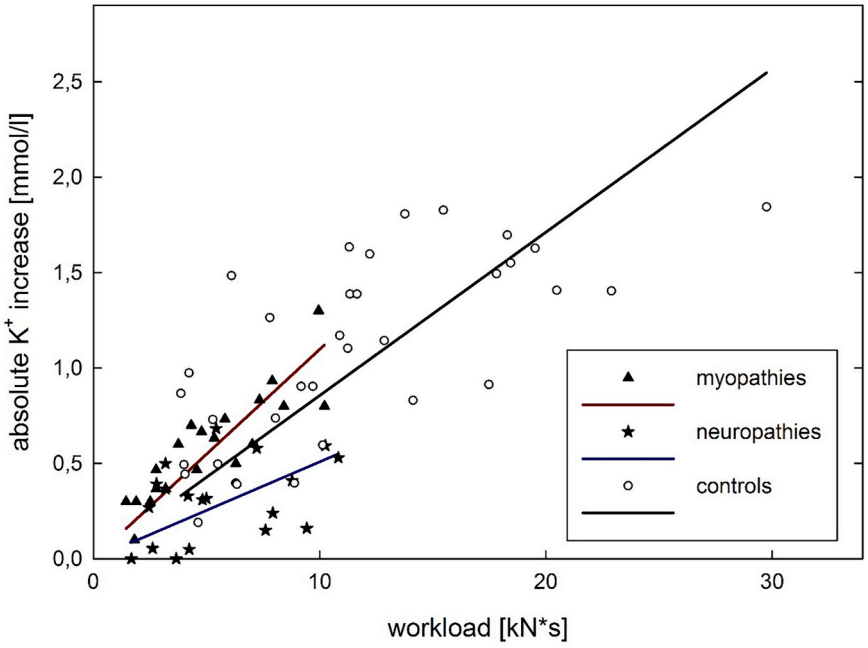

Fig. 1. Absolute K^+ increase depending on the workload.
Increase in venous K^+ concentration (compared to the resting period) depending on the workload. The groups were not sorted by individual force levels, so the subjects in each group can overlap. It was assumed that all regression plots pass through the origin.

specific K^+ release in the myopathy group with increasing workload ($p = 0.02$, One-Way ANOVA), but no differences occurred in the control and neuropathy groups ($p = 0.75$ and $p = 0.52$, One-Way ANOVA).

4. Discussion

In this explorative study, K^+ release related to workload in patients with myogenic and neurogenic muscular weakness compared to healthy controls was examined using a non-ischemic forearm test. MCF and workload in both groups were markedly reduced in comparison to the control group. This indicates that muscular force of the patients in both study groups was significantly diminished, even though the pareses were clinically classified as only mild in some patients (Tables 1 and 2). As a main result, different K^+ release in relation to muscle work occurred in myopathies compared to neuropathies. First, K^+ release was significantly more pronounced in myopathies compared with neuropathies as absolute workload increased. Second, in the myopathies, K^+ release at low forces relative to maximal force was significantly higher than in the neuropathies. Thus, in terms of the individual patient with a myogenic muscular weakness, there does not appear to be a linear relationship between potassium release and work done. The K^+ release was highest within low force levels. In neuropathies, the opposite seems to be true, i.e., a lower potassium release at low forces.

The specific K^+ release results from the K^+ efflux due to muscle work and the activity of proteins transporting it back into the cell. As maximum contraction force and workload were comparably reduced in both myopathy and neuropathy groups compared to controls, severe distal paresis and muscular inactivity in general cannot explain the different work-related K^+ balance. Our results suggest a different regulation of Na^+-K^+-ATPases in neurogenic and myogenic muscular weakness. The Na^+-K^+-pumps represent highly regulated proteins with short- and long-term processes playing a role [6,7]. A reduced amount of Na^+-K^+-ATPases in the cell membrane was shown histologically for patients with myotonic dystrophy and Mc-Ardle disease [7]. It is unclear whether this also applies to patients with neurogenic muscular weakness. However, it may generally occur in patients with muscular inactivity and atrophy [15]. A reduced amount of Na^+-K^+-ATPases can lead to higher extracellular K^+ concentration in myopathies compared to neuropathies as found in our study (Fig. 1). But why did specific K^+ drop in myopathies with increasing individual force level as displayed in Fig. 2? We suspect that this is caused by different recruitment behaviour of motor units and firing rates of motor neurons. In neurogenic muscular weakness, muscle strength is primarily enhanced by an increased firing rate of motor neurons already at low force levels as the number of available motor units is reduced [8]. An increased firing rate may lead to an increase in the intracellular Na^+ concentration in muscle cells. This represents a short-term and pronounced stimulus for Na^+-K^+-ATPases [9] leading to enhanced transport of K^+ into the muscle cell. Thus, the specific K^+ increase in neuropathies is small at low force levels. In myopathies, the Na^+-K^+-ATPases are not stimulated as much, so less K^+ is transported into the cell. Here, early recruitment of motor units occurs and an increased firing rate becomes more relevant at higher forces stimulating the Na^+-K^+-ATPases and enhancing the return transport of K^+ into the cell. At higher force levels, both processes, that is motor unit recruitment and increased firing rate, contribute to force development in all groups thereby reducing the differences in specific potassium release. Thus, in myopathies at high forces the specific K^+ increase drops.

Various potassium channels are also involved in the regulation of the muscular K^+ balance. Experimental data indicate that drugs affecting K^+-transporting proteins, especially Ca^{2+}-dependent and ATP-dependent K^+-channels, influence muscle force and fatigue [11–14]. As the difference in specific K^+ release occurs at low force levels, we do not assume a significant drop in intracellular [ATP] leading to higher K^+ efflux from the muscle cells. Voltage-activated potassium channels terminating action potentials are also involved in the regulation of potassium efflux from the muscle cell [11]. They are stimulated by high-frequent action potentials. Thus, we would expect a higher channel activity with increased extracellular K^+ especially in neuropathies that was not observed in our experiments. However, we cannot exclude the involvement of potassium channels in the results, as we did not investigate them in detail.

The K^+ concentration at rest was significantly lower in the control group than in the patient groups. Currently, we cannot explain this difference. However, this should have no influence on the K^+ release in

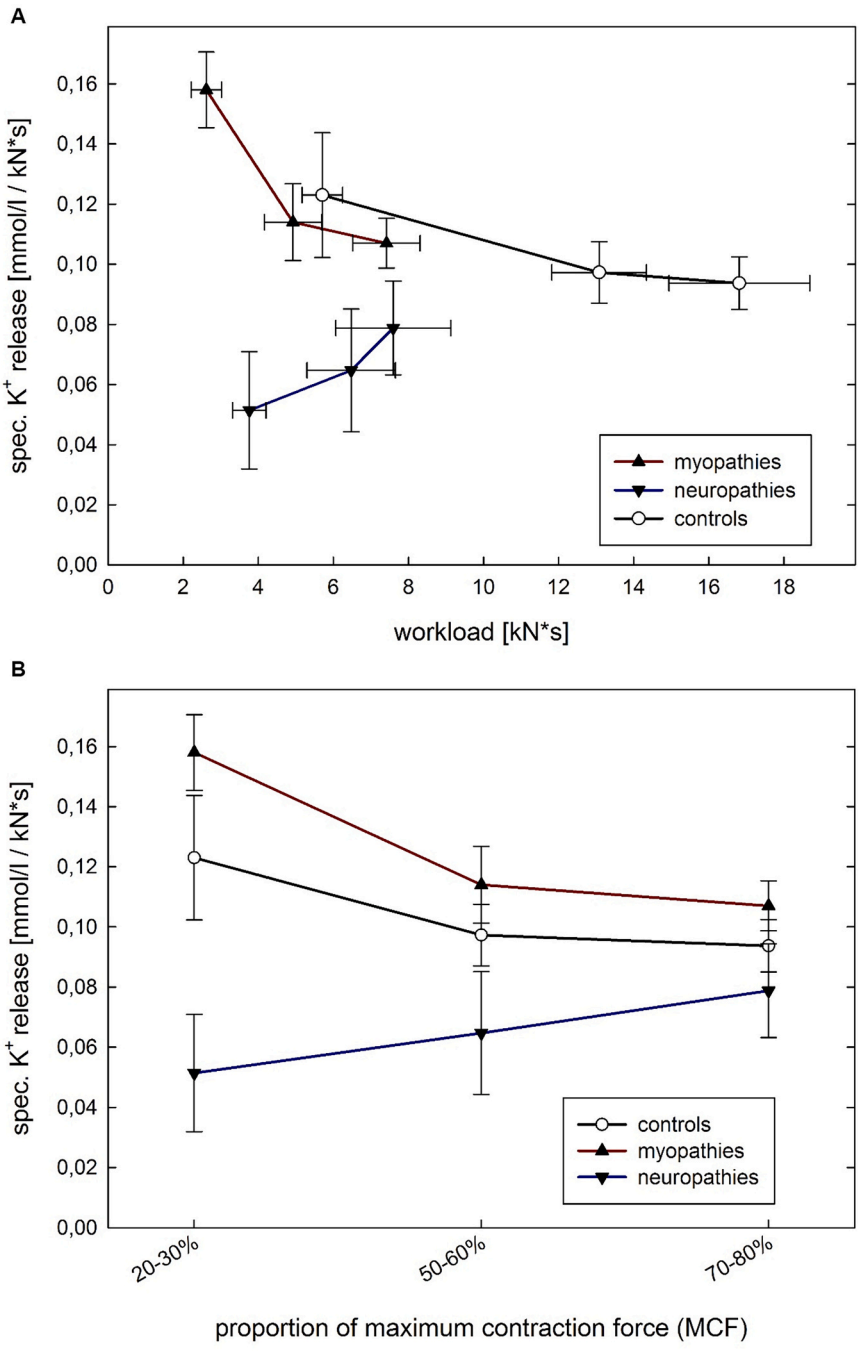

Fig. 2. Specific K^+ release depending on workload and individual force levels.
Specific K^+ release depending on the workload (A) and the individual force levels as proportions of the individual maximum contraction force (B). In A, the three measurement points for each group refer to the proportions of maximum force. In B, the workload is normalized to the individual force levels. All values are presented as mean and standard error (SEM).

myo- and neuropathies as K^+ at rest for these two groups did not differ.

Because the study groups were small, no conclusions can be drawn about specific diseases. The groups were inhomogeneous with regard to the diseases, the severity of the paresis, and the presence of spastic or flaccid paresis. In the group with neurogenic paresis, both lower motor neuron diseases and ALS as a combined upper and lower motor neuron disease are included. It is still unclear whether this leads to differences in frequency behaviour and recruitment of motor units in neurogenic paresis. In this connection, De Carvalho et al. [17] found a similar firing rate, but a higher variability of motor unit discharges in a group of patients with sensorimotor PNP and ALS as a possible sign of LMN dysfunction in comparison to UMN disorders and a control group without a neuropathy. However, the results cannot be directly applied to this study because paretic muscles were not examined by De Carvalho. The EMGs performed in the current study were performed within routine clinical practice and mostly allow for qualitative conclusions only. Furthermore, ion channel inhibitory drugs could affect excitability and potassium balance. One participant in each of the neuropathy and myopathy groups took a sodium channel inhibitor (carbamazepine), and calcium channel inhibitors (gabapentin or pregabalin) were taken by 2 patients in the neuropathy group and 1 patient in the myopathy group. This was not further evaluated in this study.

5. Conclusion

Taken together, our study point to a different regulation of K^+ balance in neurogenic and myogenic muscular weakness. It emphasizes the highly discussed thesis of different mechanisms of muscle force development (early recruitment versus high action potential frequency [8]) between these groups. More studies including genetic, biochemical and

electrophysiological analyses may help to clarify this issue.

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Ethical publication statement

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

Declaration of Competing Interest

None.

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