Article

The Adaptive Force as Potential Biomechanical Parameter in the Recovery Process of Patients with Long COVID

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Abstract:

Neuromuscular symptoms in long COVID patients are common. Since adequate diagnostics are still missing, investigating muscle function might be beneficial. The holding capacity (maximal isometric Adaptive Force; $AFiso_{max}$) was previously suggested to be especially vulnerable for impairments. This longitudinal, non-clinical study aimed to investigate the AF in long COVID patients in recovery process. AF parameters of elbow/hip flexors were assessed in 17 patients at three timepoints (pre: long COVID state, post: immediately after first treatment, end: recovery) by an objectified manual muscle test. The tester applied an increasing force on the limb of the patient, who had to resist isometrically for as long as possible. The intensity of 13 common symptoms were queried. At pre, patients started to lengthen their muscles at ~50% of the maximal AF (AF_{max}), which was then reached during eccentric motion, indicating unstable adaptation. At post and end, $AFiso_{max}$ increased significantly to ~99% and 100% of AF_{max}, respectively, reflecting stable adaptation. AF_{max} was statistically similar for all three timepoints. Symptoms intensity decreased significantly from pre to end. In conclusion, maximal holding capacity seems to be impaired in long COVID patients and increases with substantial health improvement. $AFiso_{max}$ might be a suitable sensitive functional parameter to assess long COVID patients and to support therapy process.

Keywords: Adaptive Force; maximal isometric Adaptive Force; holding capacity; muscle function; Long COVID; post COVID syndrome; muscle weakness; fatigue; neuromuscular control; biomechanical parameter

1. Introduction

Long term sequelae of SARS-CoV-2 infections increasingly challenge the medical, social and economic systems worldwide. Different terms are used to define persisting post-infectious symptoms such as 'long COVID', 'post-COVID syndrome', 'post-acute COVID' or 'persistent post-COVID' mostly depending on the duration of symptoms after acute infections. For simplification, the term 'long COVID' will be used in the following for patients suffering from symptoms at least 4 weeks after acute infection. Reports on the amount of patients with at least one persistent symptom after SARS-CoV-2 infection range from 10% to 57%, or even up to 87% in hospitalized patients depending on the time span after acute infection or hospitalization vs. non-hospitalization [1–19]. Long COVID occurs in 10% to 35% of non-hospitalized patients [1,18], which is most important, since only 5% to 7% of patients are hospitalized [20]. Current data show a lower rate of long COVID after infection with omicron variants than with delta (4.5% vs. 10.8%)[21]. Infection severity was found to be not a major factor for the development of long COVID [16,22]. According to 'COVID-19 data Explorer' of Johns Hopkins University, more than 570 million

SARS-CoV-2 cases were confirmed worldwide (Europe, Asia, North America, South America, Africa, Australia) from 22nd January 2020 to 28th July 2022. Assuming that at least 10% of them develop long term sequelae, more than 57 million people suffer or suffered from long COVID. The socioeconomic relevance gets clear thereby.

The medical community is rather describing characteristics of long COVID, pathomechanisms or the causality are not sufficiently known [6,23]. Not to mention the lack of diagnostic and therapeutic approaches, which are urgently needed to intercept the large amount of sick leave [1,24].

Post-infectious syndromes also occur after other viral infections [25–30] and are known since decades. They partly result in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [11,25,26,30–33], which is closely connected to long COVID. Symptoms of long COVID range from fatigue, tiredness, muscle weakness, joint and muscle pain, cognitive impairments ('brain fog'), depression and anxiety, dyspnoea, chest pain and tightness, cough, loss of taste and smell, headache, cardiac symptoms, insomnia, diarrhoea and more [1,2,11,13,14,19,34–36]. As can be seen thereby, different systems are involved as the "respiratory, cardiovascular, musculoskeletal, integumentary, gastrointestinal, endocrine, and neurological systems"[14]. A dysfunction of the autonomous nervous system (ANS) was discussed previously as cause for the symptoms or at least to be involved in long COVID [25,26,30,31,37–39]. However, the diagnosis of post-infectious syndromes is difficult and usually based on diagnosis of exclusion [24,40]. Patients frequently report to be not taken seriously by their doctors [34], which even increases the helplessness and anxiety.

A possible supportive diagnostic approach could be to investigate the neuromuscular system since muscle weakness and musculoskeletal pain occur frequently in long COVID patients. This idea is not new. Some researchers examined the maximal voluntary isometric contraction (MVIC, e.g., hand grip force) in patients with post-infectious syndromes. Inconclusive findings were reported. Two studies (MVIC of quadriceps femoris muscle and of elbow flexors) reported of non-significant difference between patients and controls [41,42]. Further two studies revealed a significantly reduced hand grip force in ME/CFS [43,44]. However, in Meuss et al. gender effects were not considered [44]. Females were overrepresented in ME/CFS group (96% vs. 62% in controls) [44], which might explain the lower strength. The findings are inconclusive and highlight that common maximal strength assessments might not be that appropriate to investigate muscle dysfunction in post-infectious states.

The Adaptive Force (AF) was inaugurated as a special neuromuscular function, which was found to be sensitive to impairments. The AF characterizes the capacity of the neuromuscular system to adapt to external varying forces in an isometric holding manner [45–52]. It can be assessed by a technical device using pneumatics [45–47] or by an objectified manual muscle test (MMT) using a handheld device which measures dynamics and kinematics during the MMT [48,51–53]. For the latter, it was shown that the maximal isometric AF ($AFiso_{max}$; maximal holding capacity) was significantly reduced in reaction to negative stimuli such as unpleasant emotional imagery or odors in healthy participants [48,49,52]. The $AFiso_{max}$ instantaneously decreased by perceiving the negative stimulus and switched back immediately to baseline values by applying the positive one. In other words, under disturbing influences the isometric holding capacity broke down to a significantly low level but the overall maximal force value (maximal AF; AF_{max}) reached during the subsequent eccentric action stayed on a similarly high level. At baseline or under positive intervention the muscles stayed stable during the whole force increase up to AF_{max} ($AFiso_{max} \geq 99\%$ of AF_{max}). Thereby, $AFiso_{max}$ was similar to AF_{max} of unstable muscles. Hence, the maximum force was not influenced by the stimuli but the isometric holding function. This was interpreted as a high sensitivity of $AFiso_{max}$ with respect to possibly impairing inputs [48,49,51,52]. Neurophysiological explanations were given previously.

This longitudinal study aimed to investigate the AF in patients with long COVID in a non-clinical setting. For that, AF parameters were assessed in the course of long COVID:

(1) in long COVID state (pre), (2) after first treatment (post) and (3) after recovery (end). The received individual treatments were not part of the study. It is not a clinical trial and therefore not aimed to measure the efficacy of any treatment. However, the treatments were queried and described to get an impression of possibly helpful approaches without any claim of evidence.

Based on the current scientific knowledge on AF and on therapeutical experience, we hypothesize that the holding capacity will be significantly reduced in patients with long COVID and will stabilize, thus increase, in the recovery process. In case this will be verified positively, it might provide first data that AF might be a useful biomechanical parameter to examine patients with long COVID and to find the purposeful treatment approach, which will be explained and discussed.

2. Materials and Methods

This longitudinal non-clinical study investigated patients in long COVID state and in the course of their recovery process. The patients were not acquired specifically. They consulted the practice for Integrative Medicine (Potsdam, Germany; complementary medicine) on personal initiative. In case they had the medical diagnosis post-COVID syndrome or long COVID they were asked for permission to participate in the present study. AF data were measured anyway for diagnostic purposes in daily practice. The treatments were neither subject nor part of the investigation. We only aimed to investigate the AF in those patients and its behavior during the recovery process. Therefore, a control group was not part of the study. The measurements took place at the practice of Integrative Medicine and were conducted by researchers of the University of Potsdam (Potsdam, Germany).

2.1 Patients

Until July 2022, 37 patients with diagnosis long COVID attended the above-mentioned practice for consultation and were measured initially using a handheld device. The only inclusion criterion was the medical diagnosis "post-COVID-syndrome' or 'long COVID', which the patients received from medical doctors before they consulted the practice. Exclusion criteria were pre-existing complaints of arm, shoulder, hip, or knee of the measured side. 17 patients were included in this study since they reported a substantially improved or regained health state until July 2022. The remaining 20 patients were still in therapy or cancelled further therapy because of various reasons (long distance between home and practice, difficulties in finding appointments, other ongoing treatments and rehabilitation or unknown reasons).

The 17 measured patients included 14 females (age: 44.43 ± 14.78 yrs., body height: 168.75 ± 5.23 cm, body mass: 69.93 ± 13.18 kg) and 3 males (49.00 ± 7.94 yrs., 187.5 ± 3.54 cm, 94.75 ± 0.35 kg). Further information on patients (intensity of acute infection, duration from acute SARS-CoV-2 infection to first measurement, symptoms and others) are given in results section.

The study was conducted according to the declaration of Helsinki and permission of local ethics committee of the University of Potsdam (Germany) was given (no. 70/2021, date: 16th February 2022). Each participant gave written informed consent.

2.2 Questionnaires

The patients filled out two questionnaires. The first one assessed information with respect to acute SARS-CoV-2 infection: duration, medical diagnosis and examination, symptoms and degree of severity (0 = symptom free, 1 = mild, 2 = moderate, 3 = severe but without hospitalization, 4 = hospitalization without intensive care, 5 = hospitalization with intensive care without invasive ventilation, 6 = intensive care with invasive ventilation); as well as concerning long COVID state: period between acute infection and onset of long

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COVID, periods of improvement, symptoms, diagnosis, medical examinations, experience with health care, treatments and their effects.

The second questionnaire queried the intensity of common symptoms during long COVID using a scale from 0 (no) to 10 (very strong). The assessed symptoms were fatigue, breathing difficulties, cough, chest pain, chest tightness, memory and concentration problems, headache, muscle pain, fast or strong heartbeat, loss of smell or taste, depression/anxiety, professional and personal stress level, fever, dizziness, post-exertion malaise. The questionnaire should be filled out at least for the following time points: (1) retrospectively for pre-COVID baseline (before acute SARS-CoV-2 infection), (2) in long COVID state (time of input measurement; pre), (3) 1 day after first treatment (post) and (4) after recovery (output measurement; end).

2.3 Handheld device to measure the Adaptive Force

The AF of hip and elbow flexors of one side was assessed by the objectified MMT using the handheld device which was already used in previous studies [48,51–53]. (Figure 1a; development funded by the Federal Ministry of economy Affairs and Energy; project no. ZF4526901TS7). It records simultaneously force and position and was proven to be reliable and valid [51]. Strain gauges (co. Sourcing map, model: a14071900ux0076, precision: 1.0 ± 0.1%, sensitivity: 0.3 mV/V) and kinematic sensor technology (Bosch BNO055, 9-axis absolute orientation sensor, sensitivity: ± 1%) are implemented inside the device. It records the reaction force between tester and patient's limb as well as the linear accelerations and angular velocity during the MMT. The sampling rate was 180 Hz. The data were buffered, A/D converted and sent by Bluetooth 5.0 to a tablet. An app (Sticky notes, comp.: StatConsult) saved the transmitted data [48,51–53].

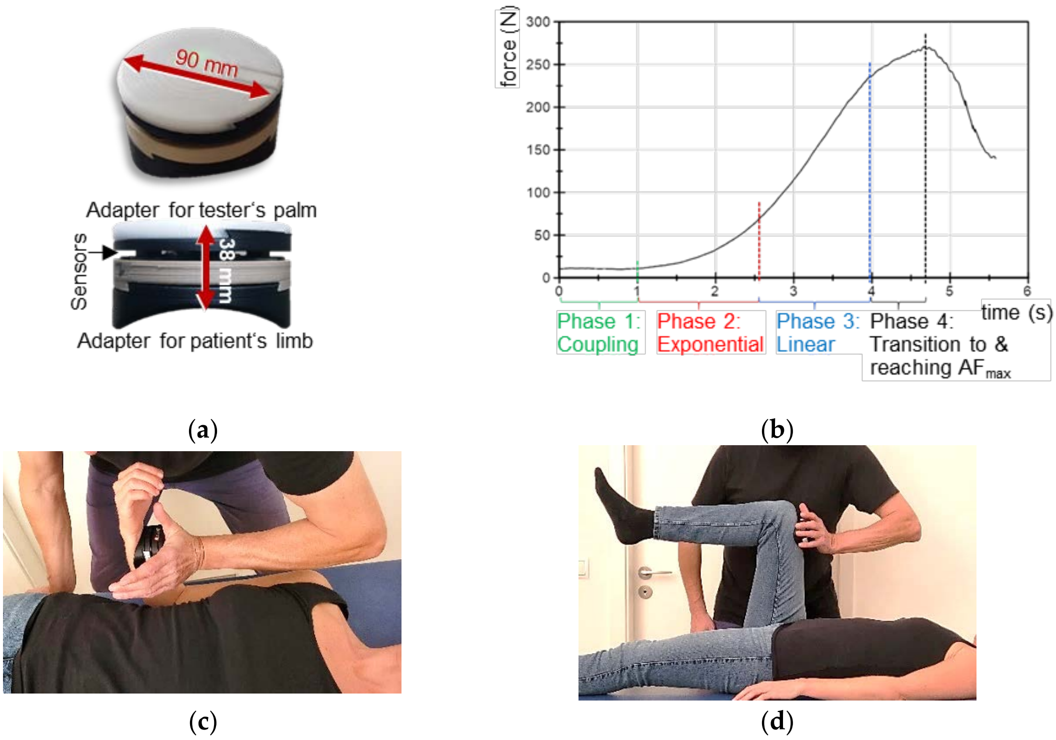

Figure 1. Handheld device and setting. (**a**) Handheld device with size indications; (**b**) Force increase during manual muscle test (MMT) including the decisive phases as was suggested to be optimal by Bittmann et al. [51] and Schaefer et al. [48,52,53]; Starting positions of MMTs of (**c**) elbow flexors and (**d**) hip flexors.

2.4 Manual muscle test to assess the Adaptive Force: procedure and setting

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For testing the AF, the MMT in the sense of a 'break test' was utilized [54], since it enables a flexible and time-saving approach, which is especially necessary in fatigued long COVID patients. The characteristics of MMT were described previously [48,51,53]. Nevertheless, a few essentials should be briefly given. During the MMT, the tester applies an increasing force on the participant's limb, who is prompted to resist in an isometric holding manner. The force increase should be firstly smooth (phase 2, Figure 1b) to give the patient the chance to adapt (for neurophysiological explanations see [51]). Afterwards, a linear increase (phase 3, Figure 1b) should be applied by the tester up to a considerably high force level (phase 4, Figure 1b) [48,51–53]. The whole MMT should last ~4 s. A reproducible force application is a necessary precondition for valid data. Experienced testers are able to perform reliable force profiles over time [51]. Both testers (female, 36 years, 168 cm, 55 kg, 9 yrs. of MMT experience; male, 65 years, 185 cm, 87 kg, 26 yrs. of MMT experience) who assessed the AF of the patients in the present study proofed their ability to test reproducibly previously [51]. Moreover, the force profiles over time of both testers were proofed to match very exactly with each other [51]. If the patient is able to adapt the muscle tension maintaining the isometric position during the entire force increase up to a considerably high force level, the MMT is rated as 'stable' and the maximal AF (AF_{max}) is reached under isometric conditions (AF_{max} = $AFiso_{max}$). If the muscle starts to lengthen during the force increase, the adaptation is considered as 'unstable'. In that case, the maximal holding capacity ($AFiso_{max}$) is substantially lower than $AF_{max,}$ which is then reached during eccentric muscle action. Healthy persons usually show stable adaptation ($\frac{AFiso_{max}}{AFmax}$ ≥ 99%) [48,52,53].

The MMT aims to assess the patient's neuromuscular capacity to adapt to an external force increase. It does not test the maximal strength of the patient in the sense of MVIC. It is decisive that the patient just reacts and adapts to the applied force in a holding manner and that he or she does not push against the tester (for explanation see [48,49,52]).

The settings (starting positions) of the MMTs of elbow and hip flexors including the application of the handheld device are illustrated in Figure 1c and 1d (according to [48,52,53]). The patient laid supine on a practitioner table for both tests. The starting position of elbow flexor test was 90° flexion in elbow joint and maximal supination of the forearm (Figure 1c). The tester held the handheld device in his or her palm and contacted therewith the distal forearm of the patient. The handheld device was cushioned to avoid a possibly painful pressure at the forearm. For hip flexor test, starting position was a hip and knee angle of ~90° (Figure 1d). The contact with the handheld device was at the distal thigh. The heights of contact at the limbs were marked and measured to standardize the lever for retests. The force vector application by the tester was in direction of muscle lengthening of the patient's elbow flexors (elbow extension) or hip flexors (hip extension). The patient had the task to maintain the starting position for as long as possible throughout the entire force increase. Force and limb position were recorded by the handheld device during the MMT. Furthermore, the MMT was rated subjectively by the tester: 0 = unstable: the muscle started to lengthen during force increase, the patient was not able to maintain the isometric position; 1 = stable: the patient was able to maintain the isometric position until an oscillating force equilibrium was reached on a considerably high force level; 2 = unclear: the muscle was neither completely stable nor unstable, slight suspensions were present.

2.5 *Procedure*

At the first appointment, the patient was examined by means of the MMT by one of the two testers. This tester also conducted all subsequent MMTs of the same patient. Four muscle groups of lower and upper extremity on both sides, respectively, were assessed manually (without handheld device) to get an overall impression of the neuromuscular functionality. Afterwards, the input measurements (pre) were performed: AF of hip and elbow flexors of one side were recorded utilizing the handheld device during the MMT for objectification. The measured side was chosen by the patients, or in case of complaints the complaint-free side was used. Both muscle groups were measured consecutively in alternating order three times each starting with hip flexors (~1 min resting period between trials). The subjective assessment of the performed MMT by the tester was noted (0 = unstable; 1 = stable, 2 = unclear). Subsequently, the patients received their individual treatment which was not part of the study. After this treatment (~1h after input measurements), AF of hip and elbow flexors were measured again (post) with the same procedure as for pre-measurements. A treatment period of varying duration and number of treatments followed for each patient. In that phase the patients received their individual treatments, which they would have obtained either way independently from the study. The patients were prompted to contact the testers as soon as they felt substantially better or recovered. Then, the last appointment for end measurements (end) took place. The same measuring procedure as for pre/post was executed. Importantly, at that day no treatment was applied prior to end measurements.

2.6 Data processing and statistical analyses

Data processing and evaluation were performed according to Schaefer et al. [48,52,53] in NI DIAdem 2020 (National Instruments, Austin, Texas, US). The used recorded data (force and gyrometer signals) were transferred from the measuring app (tablet) as csv file to NI DIAdem. They were interpolated (1 kHz) and filtered (Butterworth, filter degree 5, cut-off frequency 20 Hz). For visualization (Figure 2) the angular velocity was additionally filtered (degree: 3, cut-off: 10 Hz) to smoothen the oscillations. The following AF parameters were captured for further evaluation:

1. Maximal Adaptive Force (AF_{max}):
   AF_{max} (N) refers to the maximal force value of a single trial. This could have been reached either during isometric or eccentric muscle action.
2. Maximal isometric Adaptive Force ($AFiso_{max}$):
   $AFiso_{max}$ stands for the highest force value under isometric conditions. In case of a stable MMT, $AFiso_{max} = AF_{max}$. Hence, the patient was able to maintain the isometric position up to the maximal force value of the test. If the muscle started to lengthen in the course of MMT, $AFiso_{max}$ was reached during the force increase before the maximal force value was reached. Consequently, the position of the limb has to be considered to assess $AFiso_{max}$. For that, the gyrometer signal was evaluated. $AFiso_{max}$ was defined as the force at the moment in which the gyrometer signal increased above zero (breaking point). This indicated a yielding of the limb and, accordingly, a muscle lengthening. If the gyrometer signal oscillated around zero during the entire trial, $AF_{max} = AFiso_{max}$, thus, the muscle length/position of the limb stayed stable over the whole MMT. Additionally, the ratio $AFiso_{max}$ to AF_{max} (%) was calculated per trial. In 1 of 256 trials $AFiso_{max}$ was not determinable because of peculiarities in curve shape, hence, this was excluded from evaluation.
3. Adaptive Force at the moment of onset of oscillations (AFosc):
   AFosc (N) characterizes the force at the moment, in which oscillations start to appear regularly. Previous studies [48,52,53] showed that both interacting partners develop an oscillating force equilibrium, especially during stable MMTs. This was indicated by oscillations which arose in the force signal mostly in phase 3 of MMT (linear increase) showing a clearly distinguishable regular oscillatory behavior. During unstable MMTs this oscillatory swing up was missing or occurred if at all attenuated on a considerably higher force level. To evaluate the force at the moment of onsetting oscillations (AFosc (N)) the force signal was checked for oscillations (force maxima) appearing sequentially during force increase. If four force maxima with a time distance $dx < 0.15$ s appeared consecutively, the force value of the first maximum was defined as AFosc. Time delta $dx < 0.15$ s was chosen due to the knowledge that mechanical muscle oscillations occur ~10 Hz [55–64]. In case no oscillatory onset as defined above occurred, $AFosc = AF_{max}$. The ratios AFosc to AF_{max} (%) as well as AFosc

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to $AFiso_{max}$ (%) were also calculated per trial. The latter is based on previous findings that for stable MMTs AFosc arose on a lower level than $AFiso_{max}$, and for unstable MMTs oscillations arose – if at all – after that breaking point. In 2 of 256 trials AFosc was not clearly determinable, hence, they were excluded from evaluation.

4. Slope of force rise
The slope of force increase prior to the breaking point ($AFiso_{max}$) of all trials was evaluated to control the force application by the tester. This has to be similar between the trials for a valid comparison. The difference quotient m = $\frac{y_2-y_1}{x_2-x_1}$ was used to calculate the slope, whereby x refers to the time points and y to the respective force values. Reference points (time, force) were 70% and 100% of the averaged $AFiso_{max}$ of all as unstable assessed MMTs of one patient. The decadic logarithm was taken from slope values (lg(N/s)) since the force rise was exponential. In 11 of 256 trials the slope could not be determined since oscillations occurred too intensive which would have distorted the slope value.

Arithmetic means (M) and standard deviations (SD) of each parameter were calculated in Microsoft Excel (Microsoft 365, Redmond, Washington, US, Microsoft Corp.) of the three trials of each patient, muscle and timepoint (pre, post, end). For statistical evaluation, IBM SPSS Statistics (Windows, Version 28.0. Armonk, NY: IBM Corp) was used. Main objective was to assess the AF parameters in the recovery process, thus between pre, post and end measurements. The following hypotheses were set:

- H0: The slope will show no significant differences between time points (pre, post, end) as prerequisite for the subsequent main hypotheses.
- H1: AF_{max} will show no significant differences between pre, post and end. This assumption is based on the current knowledge that also for unstable MMTs, the maximal reached force value is similar to stable MMTs [48,52,53].
- H2: $AFiso_{max}$ will be significantly lower for pre compared to post and end. This is the main hypothesis as mentioned in the introduction and is based on practical experience that patients with long COVID show a reduced holding capacity in MMT.
- H3: The ratio $AFiso_{max}$ to AF_{max} will be lower for pre vs. post and vs. end, respectively, which consequently follows from the abovementioned hypotheses.
- H4: AFosc will be significantly higher for pre compared to post and end. This is based on previous findings that the onset of oscillations appear on a significantly lower force level in case of stable vs. unstable MMTs [48,52,53].
- H5: The ratios AFosc to AF_{max} as well as AFosc to $AFiso_{max}$ will be significantly higher for pre vs. post and end, respectively.
- H6: Based on the aforementioned hypotheses, no parameter will show a significant difference between post vs. end.

For statistical analyses, firstly, all parameters (AF_{max}, $AFiso_{max}$, AFosc, their ratios and slope) were checked for normal distribution using Shapiro Wilk test. In case of normal distribution repeated measures ANOVA (RM ANOVA) was used to compare the three time points (pre, post, end). In case Mauchly test of sphericity was significant, the Greenhouse-Geisser correction was chosen (F_G). For post-hoc test, Bonferroni correction was applied (adjusted p values are given by p_{adj}). Effect size eta squared (η^2) was given for RM ANOVA and for pairwise comparisons the effect size Cohen's d_z was used, both calculated by SPSS. The effect sizes were interpreted as small (0.2), moderate (0.5), large (0.80) or very large (1.3) [65,66]. Since RM ANOVA is known to be robust against violation of normal distribution [67,68], the Friedman test was only performed to compare the three time points if more than one data set (pre, post or end) was not normally distributed. This applied only for the ratio $AFiso_{max}$ to AF_{max} for both muscles. Bonferroni post-hoc test was applied for pairwise comparisons (p_{adj}) and effect size Pearson's r was calculated by r =

$\left|\frac{z}{\sqrt{n}}\right|$ in Microsoft Excel. Significance level was $\alpha = 0.05$. The 95% confidence intervals (CI) were calculated for all parameters and muscles.

Besides AF parameters, the intensities of the different queried symptoms were evaluated by calculating the arithmetic means and standard deviations. Those values were also compared between the three time points using Friedman test. Furthermore, the percentage of patients who stated the respective symptom with an intensity of at least 2 was calculated for descriptive purposes.

3. Results

3.1 Number of trials and subjective MMT rating by the testers

The hip flexors of all 17 patients were measured at the three time points (pre, post and end). The measurements of elbow flexors were only completed in 14 patients due to reasons like lack of time, shoulder complaints, too exhausted patients or similar. In total, 144 MMTs were performed using the handheld device for hip flexors and 118 for elbow flexors. One patient was only tested twice for both muscles because of lack of time. In two other patients hip and elbow flexors were only measured twice at pre and post because of tiredness. The hip flexors of another patient were assessed only once at end because of hip pain. In total, 141 valid trials were gathered for evaluation for hip and 115 for elbow flexors, since technical issues occurred in six trials (3 x hip, 3 x elbow). In one patient four trials of hip flexors were performed at end because the device indicated an error, but the data were nevertheless transferred and, therefore, used for evaluation.

The female tester assessed ten patients, the male tester seven. The number of as 'unstable', 'stable' and 'unclear' rated MMTs by the testers is given in Table 1.

Table 1. Subjective ratings of manual muscle tests by the testers. The number of MMTs assessed as unstable, stable or as unclear for hip and elbow flexors for each time point is given.

	Hip flexors (n = 144)			Elbow flexors (n = 118)		
MMT rating	**pre**	**post**	**end**	**pre**	**post**	**end**
unstable	48	2	0	39	2	1
stable	0	42	47	0	35	40
unclear	0	3	2	0	1	0

As can be seen at pre all MMTs (100%) were rated as 'unstable'. This reflects that elbow and hip flexors started to lengthen during the force increase, thus, the patients were not able to adapt their muscle length and force adequately during the external force increase in an isometric position. At post and end, the majority of MMTs were rated as 'stable' for both muscles (elbow: 92.1% and 97.6%, respectively; hip: 89.4% and 95.9%, respectively). This indicates the patients were able to adapt to the external force increase in an isometric position in the vast majority of MMTs, the muscles did not yield during force rise. In total, 6 MMTs were rated as 'unclear' by the testers (elbow: 2.6% at post; hip: 6.4% at post, 4.1% at end). This highlights that the MMTs could not be rated as completely stable. The testers mostly described the muscle showed stronger suspensions as usual for a stable MMT or that the muscle started to yield on a very high force level (especially in comparison to pre trials). Those subjective ratings should be verified using the data of handheld device.

3.2 Parameters of Adaptive Force in the course of long COVID

Figure 2 exemplifies force and gyrometer signals of the three MMTs of elbow and hip flexors, respectively, of one female patient (24 years, 168 cm, 65 kg) tested by the male tester at each timepoint pre, post and end, respectively. The uppermost graphs illustrate the force signals of MMTs of all timepoints in one panel for elbow (left) and hip flexors (right), respectively, for slope comparison. As can be seen, except for one curve of a pre-trial, all force rises can be regarded as similar. Table 2 displays M ± SD and borders of 95% CIs of all parameters and the statistical results of RM ANOVA or Friedman test regarding the three timepoints (pre, post, end). The values of each patient are given in supplementary material.

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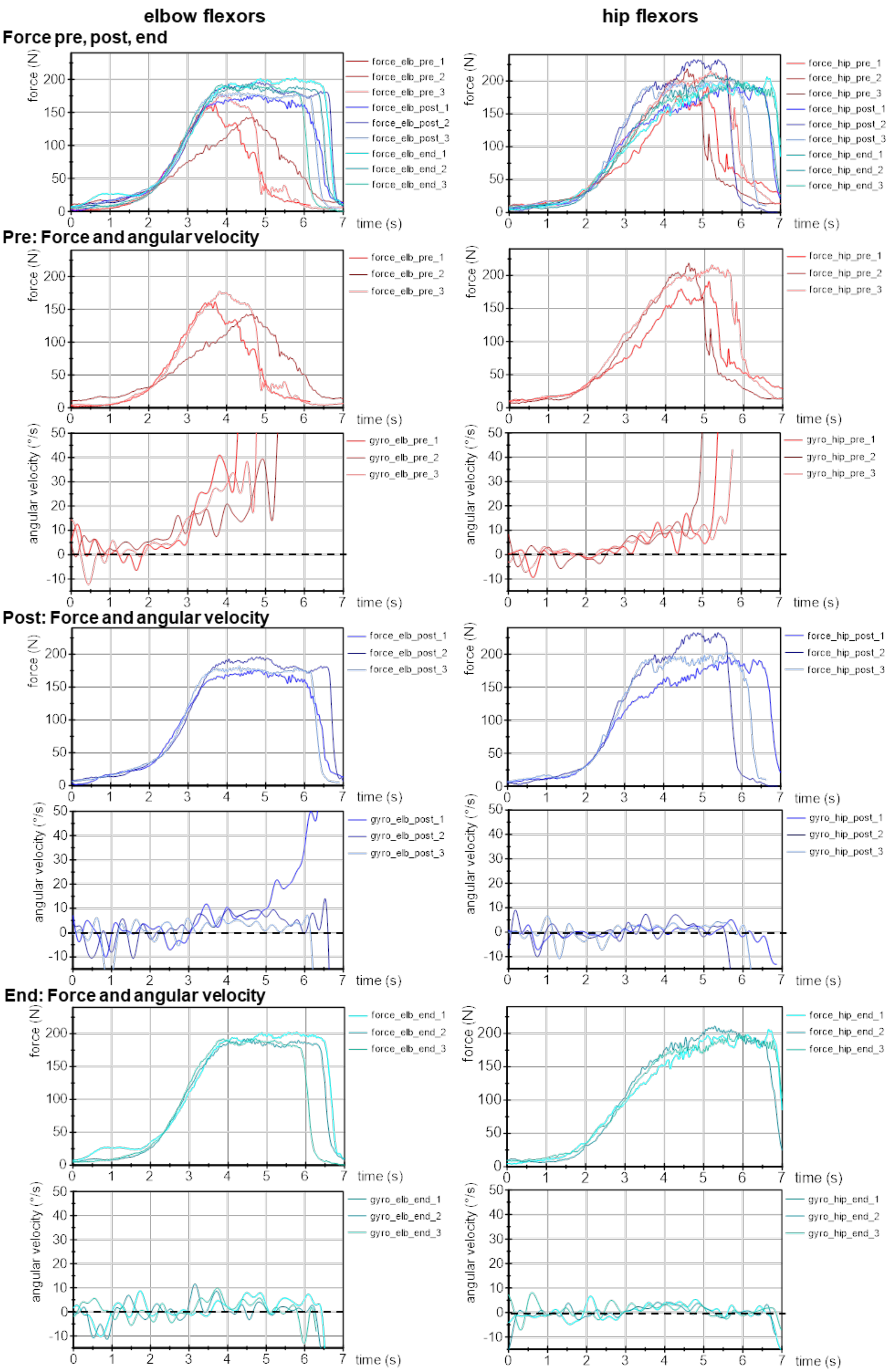

Figure 2. Exemplary force and gyrometer signals. Force and angular velocity of AF measurements of one female patient (24 yrs., 168 cm, 65 kg) measured during each three MMTs at timepoints pre, post and end are displayed.

Table 2. Parameters of Adaptive Force (AF) of elbow and hip flexors. Arithmetic means and standard deviations (M ± SD), lower and upper borders of 95% confidence intervals (CI) and values of RM ANOVA (F-statistics, degrees of freedom (df), significance p and effect size η^2) or of Friedman test (df, p, effect size Kendall's W) for all AF parameters at each timepoint (pre: in long COVID state – before treatment, post: directly after treatment, end: recovery) are given for elbow (n = 14) and hip flexors (n = 17). Parameters: maximal AF (AF_{max}) (N), maximal isometric AF ($AFiso_{max}$) (N), ratio $AFiso_{max}$ to AF_{max} (%), AF at onset of oscillations (AFosc) (N) and the ratios AFosc to AF_{max} (%) and AFosc to $AFiso_{max}$ (%) as well as the slope of force rise (lg(N/s)).

Parameter	Timepoint	M ± SD	95%-CI	F (df_1,df_2) or z (df)	Significance p	η^2 / Kendall's W
			elbow flexors (n = 14)			
AF_{max} (N)	pre	177.02 ± 53.47	149.01; 205.03	1.054 (1.43,18.63)[a]	0.345	-
	post	184.74 ± 39.02	164.27; 205.15			
	end	187.87 ± 52.00	160.63; 215.11			
$AFiso_{max}$ (N)	pre	87.92 ± 54.41	59.42; 116.42	114.772 (2,26)	**< 0.0001**	0.898
	post	182.26 ± 38.58	162.05; 202.47			
	end	187.22 ± 52.15	159.90; 214.53			
Ratio $AFiso_{max}$ to AF_{max} (%)	pre	46.58 ± 15.91	38.25; 54.91	25.064 (2)[b]	**< 0.0001**	0.895[b]
	post	98.73 ± 3.01	97.15; 100.31			
	end	99.62 ± 0.96	99.12; 100.13			
AFosc (N)	pre	170.95 ± 49.17	145.20; 196.71	5.274 (2.26)	**0.012**	0.289
	post	144.54 ± 44.83	121.06; 168.03			
	end	146.51 ± 48.64	121.04; 171.99			
Ratio AFosc to AF_{max} (%)	pre	96.87 ± 2.85	95.38; 98.36	23.403 (2,26)	**< 0.0001**	0.643
	post	76.95 ± 11.89	70.73; 83.18			
	end	76.98 ± 11.09	71.17; 82.79			
Ratio AFosc to $AFiso_{max}$ (%)	pre	258.83 ± 110.74	200.82; 316.84	34.701 (1.02,13.19)[a]	**< 0.0001**	0.727
	post	78.06 ± 12.30	71.62; 84.50			
	end	77.28 ± 10.92	71.55; 83.00			
Slope lg(N/s)	pre	1.85 ± 0.23	1.73; 1.98	1.282 (2,26)	0.294	-
	post	1.87 ± 0.18	1.78; 1.97			
	end	1.90 ± 0.21	1.79; 2.01			
			hip flexors (n = 17)			
AF_{max} (N)	pre	174.98 ± 50.03	148.77; 148.77	0.015 (2,32)[a]	0.952	-
	post	175.67 ± 40.95	154.22; 197.12			
	end	174.21 ± 46.78	149.71; 198.72			
$AFiso_{max}$ (N)	pre	88.30 ± 40.67	66.99; 109.61	88.739 (1.47,23.45)[a]	**< 0.0001**	0.847
	post	173.30 ± 41.75	151.43; 195.18			
	end	174.06 ± 46.80	149.54; 198.58			
Ratio $AFiso_{max}$ to AF_{max} (%)	pre	49.25 ± 12.01	42.96; 55.54	32.109 (2)[b]	**< 0.0001**	0.944[b]
	post	98.54 ± 3.44	96.74; 100.35			
	end	99.91 ± 0.39	99.70; 100.11			
AFosc (N)	pre	167.10 ± 43.80	144.16; 190.04	27.952 (2,32)	**< 0.0001**	0.636
	post	116.47 ± 39.63	95.71; 137.23			
	end	110.06 ± 40.81	88.68; 131.44			
Ratio AFosc to AF_{max} (%)	pre	95.19 ± 5.59	92.26; 98.12	53.417 (2,32)	**< 0.0001**	0.77
	post	65.62 ± 11.56	59.57; 71.68			
	end	62.01 ± 13.74	54.81; 69.21			
Ratio AFosc to $AFiso_{max}$ (%)	pre	223.06 ± 69.65	186.57; 259.54	78.199 (1.07,17.11)[a]	**< 0.0001**	0.83
	post	66.88 ± 13.18	59.97; 73.78			
	end	62.07 ± 13.78	54.85; 69.29			
Slope lg(N/s)	pre	1.85 ± 0.18	1.75; 1.94	3.260 (1.45,21.73)[a]	0.071	-
	post	1.93 ± 0.15	1.85; 2.00			
	end	1.89 ± 0.14	1.81; 1.97			

[a] Greenhouse-Geisser correction was applied for RM ANOVA. [b] Friedman test was performed with effect size Kendall's W. Significant results are displayed in bold.

3.2.1 Slope of force increase

The slope did not differ significantly between the three timepoints; neither for elbow, nor for hip flexors and it was similar for elbow and hip flexors (Table 2, Figure 3). For the latter, RM ANOVA was close to significance with p = 0.071. However, the lowest slope was present for pre trials. Thus, at post and end the challenge for patients to adapt to the external load can be assumed as even higher. The slope can be interpreted as statistically similar between the timepoints, which is the prerequisite to compare the AF parameters.

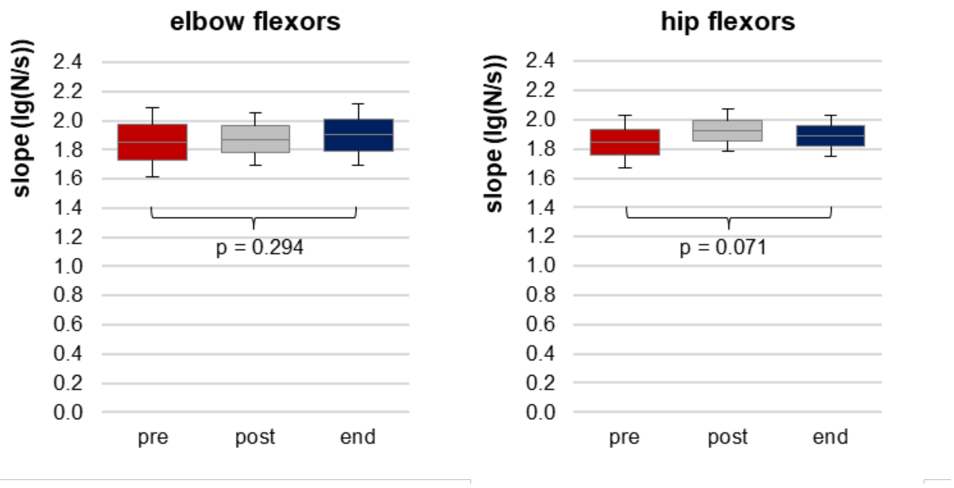

Figure 3. Slope of force increase during AF assessment. Displayed are arithmetic means, standard deviations (error bars) and 95% CIs of logarithmised slope (lg(N/s)) of force increase during manual muscle tests for elbow (left) and hip flexors (right) at each timepoint pre (red), post (grey) and end (blue). RM ANOVA was non-significant, p-values are given.

3.2.2 Maximal Adaptive Force and maximal isometric Adaptive Force

Maximal AF did not differ significantly between the three timepoints for both muscle groups (Table 2, Figure 4). As can be seen, AF_{max} was considerably high at pre measurements with averagely 177.02 ± 53.47 N for elbow and 174.98 ± 50.03 N for hip flexors. One female patient (outlier) showed an extremely low AF_{max} in pre trials with only 61.43 ± 4.86 N for elbow and 67.38 ± 8.66 N for hip flexors. She could increase her AF_{max} immediately at post trials to 146.44 ± 22.05 N for elbow and 162.58 ± 26.01 N. Thus, in her case AF_{max} pre amounted only 42% of post for elbow and 41% for hip flexors, respectively. This is usually not expected and will be discussed later. The other patients showed AF_{max} values between 145.83 to 295.05 N for elbow and 124.10 to 257.27 N for hip flexors. At post and end AF_{max} was considerably high for all patients (Table 2, Figure 4). AF_{max} pre related to post amounted averagely (excl. outlier) 100 ± 14% for elbow and 106 ± 24% for hip flexors, respectively. Similar for post vs. end with 100 ± 10% for elbow and 102 ± 15% for hip, respectively. Hence, AF_{max} seems not to be appropriate to reflect the testers' MMT ratings adequately, which showed a clear difference between pre vs. post and pre vs. end as well as similar ratings for post vs. end (see above). It has to be mentioned that for all pre trials, AF_{max} was reached during muscle lengthening, whereby for the majority of post and end trials, AF_{max} arose during isometric muscle action. Therefore, the suggested main parameter to quantify the manually found difference is the maximal force during isometric muscle action (holding capacity; $AFiso_{max}$).

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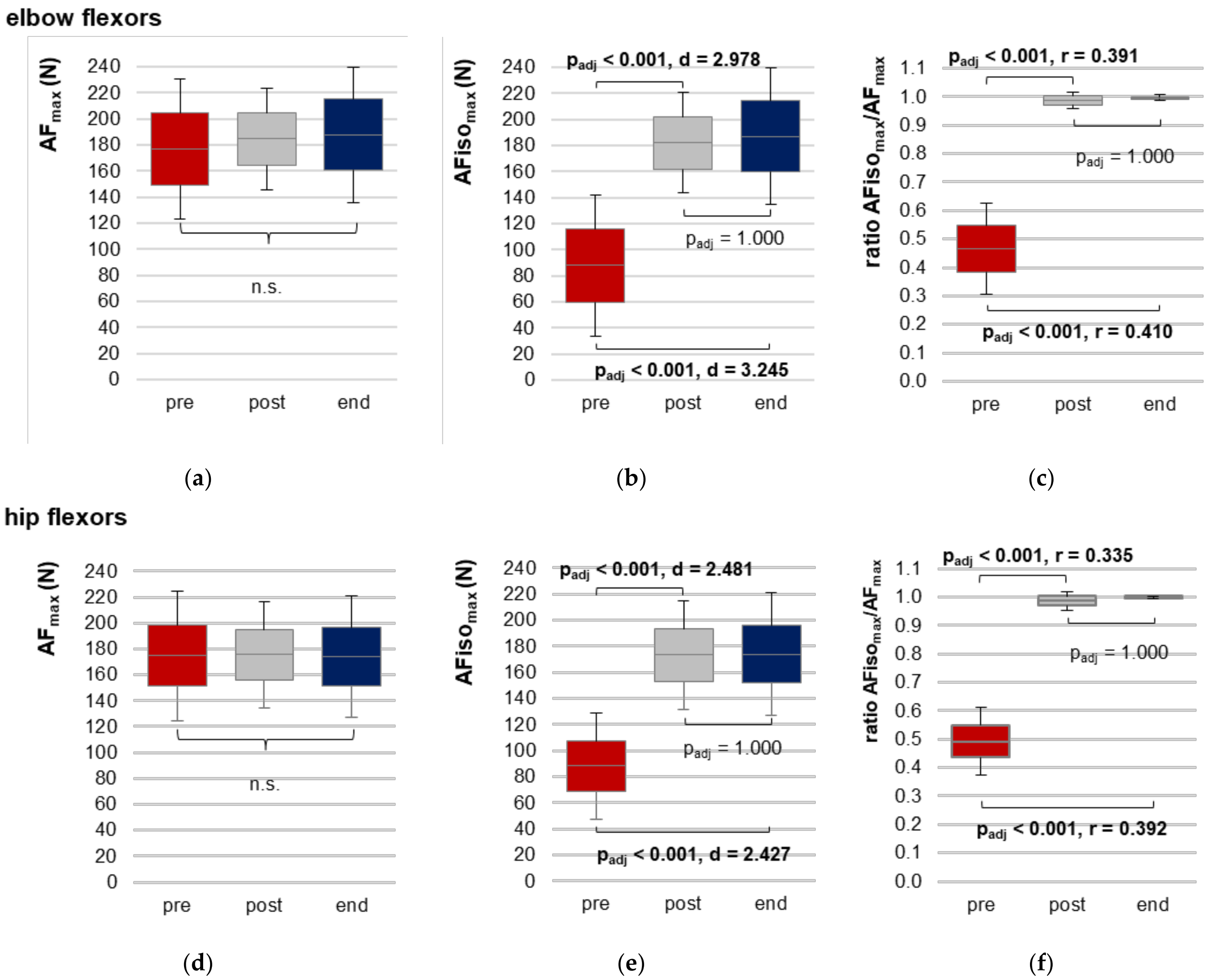

Figure 4. Maximal Adaptive Force and maximal isometric Adaptive Force. Displayed are the arithmetic means, standard deviations (error bars) and 95% CIs of AF parameters of both muscles at each timepoint: pre (red), post (grey) and end (blue). Elbow flexors: (**a**) Maximal Adaptive Force (AF_{max}); (**b**) maximal isometric AF ($AFiso_{max}$) and (**c**) the ratio of $AFiso_{max}$ to AF_{max}; hip flexors: (**d**) AF_{max}; (**e**) $AFiso_{max}$ and (**f**) ratio of $AFiso_{max}$ to AF_{max}. The adjusted p-values (Bonferroni correction) for RM ANOVA as well as for Friedman test and the respective effect sizes Cohen's d or Pearson's r are given in case of significance.

As displayed in Table 2 and Figure 4, $AFiso_{max}$ was clearly lower for pre vs. post and vs. end trials. RM ANOVA revealed a significant main effect. For both muscles, pairwise comparisons revealed clearly and significantly lower values for pre vs. post (elbow: t(13) = -11.144, $p_{adj} < 0.0001$, d = 2.978; hip: t(16) = -10.228, $p_{adj} < 0.0001$, d = 2.481; one-tailed) as well as for pre vs. end (elbow: t(13) = -12.140, $p_{adj} < 0.0001$, d = 3.245; hip: t(16) = -10.007, $p_{adj} < 0.0001$, d = 2.427, one-tailed). For post vs. end pairwise comparisons did not differ significantly (elbow: $p_{adj} = 1.000$; hip: $p_{adj} = 1.000$). For elbow flexors, four patients reached $AFiso_{max}$ below 60 N for pre (range 20.56 to 58.66 N), which has to be considered as extremely low; hereby, the outlier mentioned above, showed the lowest value. Another patient showed a very high value with $AFiso_{max}$ = 229.94 N. The others ranged between 62.21 to 156.30 N. All patients showed considerably high $AFiso_{max}$ values at post and end (Table 2, Figure 4).

For hip flexors, three patients showed $AFiso_{max}$ values below 60 N at pre (range 27.36 to 52.00 N), whereby again the mentioned outlier showed the lowest. The highest $AFiso_{max}$

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for pre was 166.73 N, which was reached by the same patient who showed the highest value in elbow flexors. For post and end measurements, $AFiso_{max}$ was considerably high for all patients.

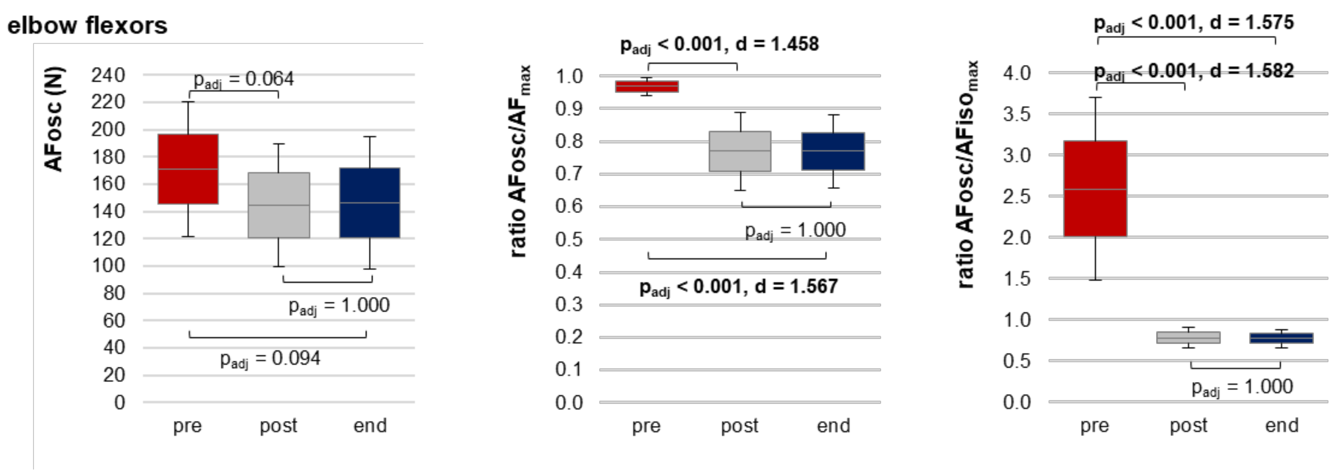
This is mirrored furthermore by the ratio $AFiso_{max}$ to AF_{max} (Table 2, Figure 4). For elbow flexors the range was 23% to 78% at pre, 89% to 100% at post and 97% to 100% at end; for hip flexors it was 28% to 69% at pre, 87% to 100% at post and 98% to 100% at end. This indicates that for pre trials, the patients started to lengthen their muscles already at 47 ± 16% of their maximal force (AF_{max}) for elbow flexors and 49 ± 12% for hip flexors. They were not able to demand their maximal strengths at this stage. Some patients showed an extremely low ratio in single MMTs at pre. The lowest were 14% and 15% for elbow and hip flexors, respectively. In 15 of 36 MMTs for elbow flexors and 13 of 46 MMTs for hip flexors, the ratio amounted less than 40%. In 11 and 13 MMTs, respectively, it was > 60%. The others were in-between 40% and 60%.

At post, already 12 of 14 patients were able to fetch at least 98% of AF_{max} for elbow flexors, two patients reached values below (89% and 96%). Similar for hip flexors, whereby 14 of 17 patients were able to demand at least 98% of AF_{max}, three showed values below (87%, 93%, 97%). In all trials at end, the patients were able to reach 100% of AF_{max} in an isometric holding position, except for two patients who showed values of ~97% or ~98% for elbow flexors and one who reached ~98% for hip flexors.

The values of the ratio $AFiso_{max}$ to AF_{max} clearly indicate that in long COVID state before treatment, the patients were not able to maintain the isometric position while trying to adapt to the force increase. Already directly after treatment (post) and especially at with substantial health improvement (end), the patients were able to adapt to the external force increase in an isometric holding manner up to a significantly high force level.

3.2.3 Onset of oscillations during force increase

The values of force at onset of oscillations (AFosc) as well as statistical tests are given in Table 2. Comparing the three timepoints, RM ANOVA showed a significant main effect for both muscles. For elbow flexors, oscillations started on an 18% and 17% higher force level comparing pre vs. post and pre vs. end, respectively. Pairwise comparisons missed significance after Bonferroni correction (Figure 5). For hip flexors, oscillations occurred on a 43% and 52% higher force level comparing pre to post and pre to end, respectively. Pairwise comparisons were highly significant for pre vs. post ($t(16) = 5.997$, $p_{adj} < 0.0001$, $d = 1.454$) and for pre vs. end ($t(16) = 5.892$, $p_{adj} < 0.0001$, $d = 1.429$). For post vs. end, pairwise comparison was non-significant ($p_{adj} = 1.000$).



(a) (b) (c)

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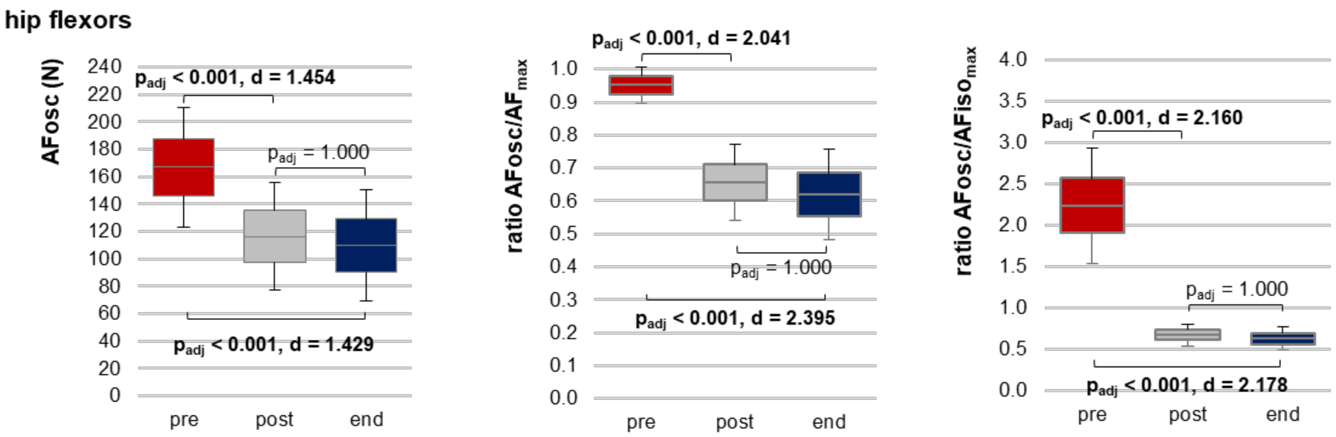

(**d**) (**e**) (**f**)

Figure 5. Adaptive Force at onset of oscillations. Displayed are the arithmetic means, standard deviations (error bars) and 95% CIs of AF parameters with regard to the onset of oscillations during MMT for both muscles at each timepoint pre (red), post (grey) and end (blue). Elbow flexors: (**a**) AF at onset of oscillation (AFosc); (**b**) ratio AFosc to AF_{max} and (**c**) ratio of AFosc to the $AFiso_{max}$; hip flexors: (**d**) AFosc; (**e**) AFosc to AF_{max} and (**f**) ratio of AFosc to $AFiso_{max}$. The adjusted p-values after Bonferroni correction for RM ANOVA as well as effect sizes Cohen's d are given in case of significance.

The above-mentioned outlier regarding to AF_{max} showed an extremely low AFosc for both muscles already at pre measurements with 60.84 (elbow) and 66.48 N (hip). For elbow flexors, AFosc increased to 100.94 N at post and to 100.90 N at end; for hip flexors it was similarly low comparing pre (66.48 N) vs. post (62.88 N) and vs. end (69.89 N). The other patients (excl. outlier) showed AFosc values for elbow flexors in the range of 145.69 to 272.70 N at pre, from 62.98 to 217.69 N at post and from 52.00 to 236.84 N at end. For hip flexors AFosc ranged from 116.90 to 242.17 N at pre (without outlier), from 62.88 to 188.86 N at post and from 29.86 to 191.76 N at end. The coefficient of variation (CV; average of pre, post and end) between patients was very large with ~31 ± 2% for elbow and ~32 ± 6% for hip flexors. The intraindividual CV was considerably lower with 5.8 ± 2.8% at pre, 12.1 ± 8.3% at post and 12.8 ± 5.3% at end for elbow flexors and 6.1 ± 4.1% at pre, 12.3 ± 7.03% at post and 16.5 ± 15.1% at end for hip flexors.

The ratio AFosc to AF_{max} was clearly and significantly higher at pre vs. post and vs. end for both muscles (Table 2, Figure 5). This reflects that the oscillations occurred on a high force level at pre and arose on a clearly and significantly lower force level at post and end (elbow: pre vs. post: $t(13) = 5.455$, $p_{adj} < 0.0001$, $d = 1.458$; pre vs. end: $t(13) = 5.863$, $p_{adj} < 0.0001$, $d = 1.567$; hip: pre vs. post: $t(16) = 8.306$, $p_{adj} < 0.0001$, $d = 2.014$; pre vs. end: $t(16) = 9.876$, $p_{adj} < 0.0001$, $d = 2.395$). At post vs. end no significant differences were present.

Displayed by the ratio AFosc to $AFiso_{max}$, for each patient and both muscles the oscillations arose consistently after the breaking point ($AFiso_{max}$) at pre measurements whereby they occurred before $AFiso_{max}$ at post and end (Table 2, Figure 5). Only in one MMT of elbow flexors the oscillations arose just with $AFiso_{max}$ at post ($AFosc/AFiso_{max}$ = 100%). RM ANOVA regarding the ratio AFosc to $AFiso_{max}$ turned out to be significant for elbow and hip flexors, respectively (Table 2). The pairwise comparisons revealed highly significant results after Bonferroni correction for pre vs. post (elbow: $t(13) = 5.918$, $p_{adj} < 0.0001$, $d = 1.582$; hip: $t(16) = 8.905$, $p_{adj} < 0.0001$, $d = 2.160$) and pre vs. end for both muscles (elbow: $t(13) = 5.892$, $p_{adj} < 0.0001$, $d = 1.575$; hip: $t(17) = 8.979$, $p_{adj} < 0.0001$, $d = 2.178$). Post vs. end showed no significant differences ($p_{adj} = 1.000$ for both muscles). This might point out that the oscillation could be a prerequisite for stable adaptation towards an external increasing load as was suggested previously [48,52,53].

3.3 Patients characteristics regarding long COVID

The patients' professions ranged from teachers/educators (6) over students/trainees (2), IT specialist (1), editor (1), lawyer (1), filmmaker (1), social insurance clerk (1), physiotherapist (1), business economist (1), manager of a corona test center (1) to one pensioner (1). From the 16 actually still working patients, 14 were incapacitated for work due to long COVID at the first appointment (pre), one just started to work again and one had no sick leave at all. At end measurement (end), 8 from the 14 incapacitated patients worked again, 6 wanted to start to work again soon. One was still in sick leave.

The acute SARS-CoV-infection lasted averagely 15.29 ± 9.40 days (range: 7 to 40, n = 17). The median of the individual assessment of the severity of acute infection on the scale from 0 (symptom free) to 6 (invasive ventilation) was 2.25 (range 0 to 4, n = 16). One patient was admitted to hospital due to vertigo, another one because of suspect of heart attack (nevertheless, she rated the intensity with 1). Overall, the symptom intensity has to be interpreted as mild.

The duration from acute infection to first measurement (pre) was averagely 274.88 ± 210.70 days (range: 32 to 688). From pre to end the duration amounted 71.06 ± 44.43 days (range: 26 to 166 days). The patients had averagely 3.29 ± 1.79 (range: 1 to 7, n = 17) treatment appointments in the practice from pre to end measurement. At end, four patients were completely recovered and had no further appointments. 13 patients reported to feel sustainably better but wanted to receive further treatments. For 10 of those 13 patients the treatments were completed after averagely 2.80 ± 1.99 further treatments. Three patients were still in treatment (July 2022), since they have not gained their full quality of life back or they wanted to stabilize their health further, especially with regard to mental stability.

The patients reported a large variety of symptoms for long COVID state, which were not all included in the symptoms questionnaire. Beyond the queried symptoms, the patients reported of the following symptoms: recurrent 'crashes', (muscle) weakness, joint stiffness, limb heaviness, feeling of being paralyzed at the whole body, brain fog to black outs, aphasia, forgetfulness, slowed reaction, sensitivity to stimuli as light and noise, hypersomnia or sleeping problems, vertigo, nausea, diarrhea, sore throat, ague, strong sweating, impaired vision, olfactory hallucination, body aches (back, shoulder, neck, heart, lung, tooth, eyes), tingle of nerves/limbs/head/tongue, cold hands/feet, increased convulsion tendency, internal vibrating, inner restlessness, being phlegmatic, high level of irritability, fast overload, mental imbalance, depression, tachycardia, extrasystoles, hair loss, eczemas, herpes, reactivated Epstein-Barr virus infection and tinnitus.

Different considerations regarding the queried symptoms for different timepoints (before SARS-CoV-infection, during long COVID and at end measurement (end)) are given in Figure 6. The upper diagram illustrates the percentage of patients who stated the respective symptom with an intensity of at least 2. As can be seen, no patient reported to have chest pain/tightness, cough, dizziness, loss of smell/taste and fever with such an intensity before COVID. However, the majority of symptoms were already present – at least slightly – before COVID infection in some patients (7.14% to 35.71%, n = 14), whereby depression/anxiety showed the highest percentage before COVID. This is in line with the statements regarding job-related and personal stress before COVID, which were given with an intensity of ≥ 2 in 90.91% and 100%, respectively (n = 11, not all patients answered). Those values declined in long COVID state to 85.71% (n = 14, three patients did not check the boxes because of sick leave) and 88.24% (n = 17), respectively; at end they amounted 30.33% and 50.00% (n = 12), respectively.

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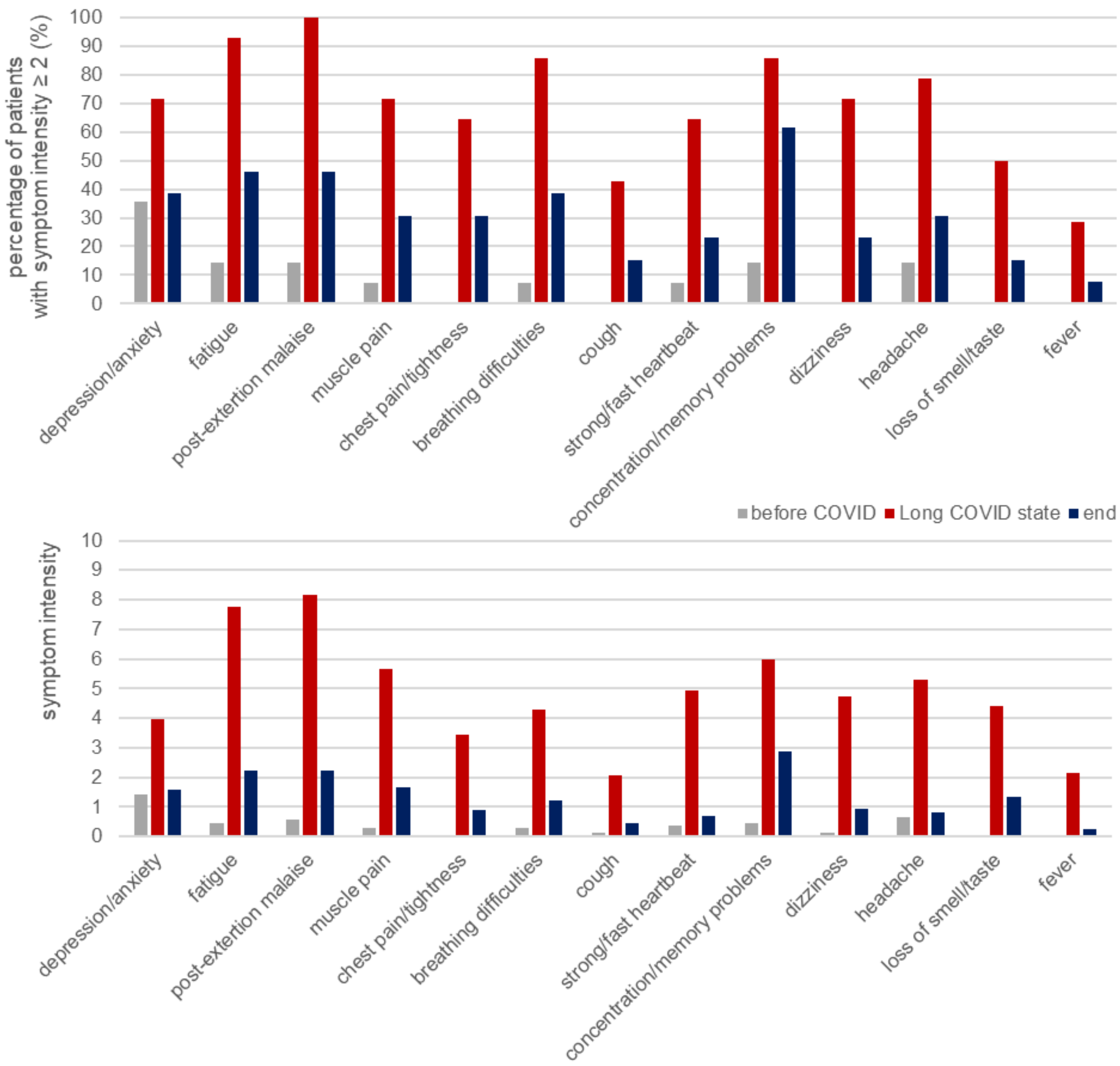

Figure 6. Intensity of symptoms. The upper diagram depicts the percentage of patients who rated the symptom intensity with ≥ 2 (from 10) for each queried symptom. The lower panel illustrates the arithmetic means of symptom intensity on the scale from 0 (no) to 10 (very strong).
Both are given for each timepoint: before COVID (grey, n = 14), long COVID state (red, n = 14, corresponds to pre measurements), end (blue, n = 13, corresponds to end measurements).

The results regarding job-related and personal stress on the scale from 0 (none) to 10 (unbearable) are given in Table 3. Symptoms intensities regarding the different time points (before COVID, during long COVID, end) are displayed in Table 3 and Figure 6 (lower panel). Friedman test was significant for every symptom. From before COVID to long COVID state, the intensities increased significantly for each symptom (pairwise comparisons; $p < 0.001$ to 0.024), except for fever ($p = 0.202$). In long COVID state, all patients reported to suffer from fatigue, post-exertion malaise and breathing difficulties with at least an intensity of 1. The most prominent symptoms were post-exertion-malaise and fatigue with an intensity of averagely 8.1 and 7.8, respectively. The other symptoms did not occur in each patient. Fever was the rarest symptom (4 patients).

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Table 3. Stress level and symptom intensity. Given are the arithmetic means, standard deviations (M ± SD) and range incl. number of patients (n) of job-related and personal stress level as well as of the intensity of queried common long COVID symptoms (from 0 = no, 10 = very strong) for the different timepoints before COVID infection, in long COVID state (corresponds to pre measurements) and at end (end measurement). The values of Friedman test comparing the three timepoints, significance p and effect size Kendall's W are given. The results of pairwise comparisons are indicated by superscript.

Stress M ± SD (range, n)	**before COVID**	**long COVID state (pre)**	**end**	**Friedman test**	**significance p**	**effect size Kendall's W**
Stress level job-related	4.23 ± 2.56 (0 – 9, n = 11)	5.64 ± 2.95 (0 – 10, n = 14*)	2.29 ± 3.17 (0 – 8, n = 12)	0.667	0.717	-
Stress level personal life	3.77 ± 2.70 (2 – 10, n = 12)	4.76 ± 2.75 (0 – 10, n = 17)	3.29 ± 3.53 (0 – 9, n = 12)	4.056	0.132	-
Symptoms M ± SD (range)	**n = 14**	**n = 14**	**n = 13**			
Depression / anxiety	1.43 ± 2.21 (0 – 8)	3.96 ± 3.78 (0 – 10)	1.58 ± 2.33 (0 – 7)	9.389	**0.009**[1,2]	0.361
Fatigue	0.43 ± 0.76 (0 – 2)	7.75 ± 2.50 (1 – 10)	2.23 ± 2.67 (0 – 7.5)	22.217	**< 0.001**[1,2]	0.855
Post-exertion malaise	0.57 ± 1.40 (0 – 5)	8.14 ± 1.96 (3 – 10)	2.23 ± 3.06 (0 – 9)	20.311	**< 0.001**[1,2]	0.781
Muscle pain	0.29 ± 0.61 (0 – 2)	5.64 ± 4.27 (0 – 10)	1.65 ± 2.81 (0 – 8)	14.800	**0.001**[1,2]	0.569
Chest pain / tightness	0.00 ± 0.00	3.43 ± 3.01 (0 – 9.5)	0.88 ± 1.23 (0 – 4)	18.667	**< 0.001**[1,2]	0.718
Breathing difficulties	0.29 ± 0.61 (0 – 2)	4.29 ± 2.37 (1 – 8)	1.23 ± 1.36 (0 – 3)	23.106	**< 0.001**[1,2]	0.889
Cough	0.14 ± 0.36 (0 – 1)	2.23 ± 3.00 (0 – 10)	0.46 ± 0.97 (0 – 3)	16.267	**< 0.001**[1,2]	0.678
Strong / fast heartbeat	0.36 ± 1.08 (0 – 4)	4.93 ± 4.03 (0 – 10)	0.69 ± 1.18 (0 – 3)	17.882	**< 0.001**[1,2]	0.688
Concentration / memory problems	0.43 ± 0.76 (0 – 2)	5.96 ± 3.20 (0 – 10)	2.88 ± 2.60 (0 – 9)	23.130	**< 0.001**[1,2]	0.890
Dizziness	0.14 ± 0.36 (0 – 1)	4.71 ± 3.81 (0 – 10)	0.92 ± 1.98 (0 – 7)	16.800	**< 0.001**[1,2]	0.646
Headache	0.64 ± 1.28 (0 – 4)	5.29 ± 4.07 (0 – 10)	0.81 ± 1.28 (0 – 3)	18.242	**< 0.001**[1,2]	0.702
Loss of smell or taste	0.00 ± 0.00	4.39 ± 4.85 (0 – 10)	1.35 ± 3.16 (0 – 10)	13.923	**0.001**[1]	0.536
Fever	0.00 ± 0.00	2.14 ± 3.66 (0 – 10)	0.23 ± 0.83 (0 – 3)	7.538	**0.023**	0.290

* Three patients made no statement because of sick leave.
[1] Pairwise comparison 'before COVID' vs. 'long COVID state' was significant: $p < 0.05$.
[2] Pairwise comparison 'long COVID state' vs. end was significant: $p < 0.05$.

After the individual treatment period (timepoint end) all symptoms and the percentage of patients who rated the intensity with at least 2 decreased (Figure 6, Table 3). Comparing 'long COVID state' vs. end, the intensity of all symptoms declined, mostly significantly ($p < 0.001$ to 0.031), except for fever ($p = 0.281$) and loss of smell/taste ($p = 0.062$).

From 'before COVID' vs. end, the symptoms' intensities differed not significantly ($p = 0.202$ to 0.922), whereby for concentration/memory problems it was $p = 0.050$. The latter was still present in 11 of 13 patients (3 of them stated an intensity of 1, one patient of 9). One patient stated that elevated temperatur when physically active was partly still present at end measurement (rated fever with intensity 3); after one further treatment this resolved, too.

Although the individual treatments were not part of the evaluation, they should be stated descriptively. 15 of 17 patients filled out the questionnaire with respect to the underwent diagnostics and therapies prior to the first measurement appointment. At least seven patients had large diagnostic assessments in centers or rehabilitation facilities for long COVID syndrome, the others stated to have large diagnostics from medical specialists (pulmonologists, internists and similar). The treatments initiated by them ranged from rehabilitations measures as physiotherapy incl. lymph drainage, manual therapy/massage, reflectory breathing massage, hot role and exercise therapy over (hyperbaric) oxygen therapy, ergotherapy, psychotherapy or psychological guidance, behavioral therapy, speech therapy, concentration training to pharmacological approaches using antibiotics, cortisone, asthma inhaler to dietary changes. The most common advice from the medical specialists was 'pacing'. According to the patients' statements, this was very frustrating. Four patients stated to have no advice or arranged therapy from medical specialists at all. They should 'pace' themself and rest or were not taken seriously. The majority of patients told to have the impression that the conventional medicine had no treatment approach and some told that the medical specialists were 'clueless'. Other reported that as soon as no somatic reason for the condition could be found, the patients were diagnosed to have a psychosomatic disorder. Nevertheless, some patients reported of positive effects regarding reflectory breathing massage and for psychological guidance to cope with the condition. Regarding physiotherapeutic measures, the effects varied largely. Some reported of at least a supporting effect regarding manual therapy which helped reducing some pain short-term. Others stated that lymph drainage worsen the condition. Some also stated that exercise therapy helped for the musculature and cardiovascular system, however, others reported of deterioration after low-intensity exercise therapy.

The mentioned helplessness and – if at all – mostly short-term supporting other therapies have led the patients to try interventions on their own initiative. Those ranged from supplements (mostly vitamins, trace elements) over walks, relaxation techniques or meditation, planning of daily routine, concentration training and rest. At least two patients went to naturopaths or specialists of Traditional Chinese Medicine for support. However, all those measures did not lead to the desirable improvement of the condition. That is why the patients were seeking for further approaches and made an appointment at the practice, where the AF measurements took place. Two of the 17 patients were transferred from a pulmonologist, the others came via other ways. The patients partly still had ongoing therapies elsewhere. The additive treatment at the practice for integrative medicine is based on an individual approach based on the muscular holding capacity. Some regularities regarding the applied treatments were found. For each patient an individualized pulsed electromagnetic field therapy (PEMF) was applied. Based on several studies [31,69–72] an influence on the ANS is assumed thereby. Moreover, 11 of 17 patients were treated for mental stress (persisting or past traumatic situations) using an individualized treatment approach. The lymphatic system was treated in 7 of 17 patients using manual methods as well as individualized PEMF. In some cases, osteopathic and chiropractic techniques for the cranial and/or the musculoskeletal system were applied.

4. Discussion

The present pilot study investigated the AF of elbow and hip flexors by an objectified MMT in patients with long COVID at three timepoints: in long COVID state (pre), after first treatment (post) and after recovery (end). For that, the comprehensibly as subjective criticized MMT was objectified by a handheld device. The anyhow received individual treatments of the patients were not part of the study and were only included descriptively. The evaluation of slope of applied force increase by the tester revealed a non-significant difference between the three timepoints as was hypothesized (H0). Therefore, the results are based on reproducible force increases and can be regarded as valid. Main findings with respect to the hypotheses were the following:

1. AF_{max} was statistically similar for all three timepoints as was assumed (H1). It is suggested thereof that maximal forces as eccentric ones or the MVIC might not be suitable parameters for investigating patients in post-infectious states. However, one outlier existed, who showed extremely low AF_{max} values at pre. This might highlight that in some individuals with post-infectious syndromes or ME/CFS also the common maximal strengths are reduced significantly as was found in [43,44]. Nevertheless, the results on AF_{max} might also explain, why other investigations did not found such differences [41,42].
2. $AFiso_{max}$ was significantly lower with very large effect sizes for pre vs. post and pre vs. end, whereby post vs. end did not differ significantly, according to the hypothesis (H2). In long COVID state (pre), the patients were not able to maintain their muscle length when they should hold the isometric position in reaction to an externally applied force increase. The muscles gave way already at less than a half of the maximal AF. This indicates that the holding capacity in the sense of $AFiso_{max}$ might be more sensitive than the AF_{max} (and presumably also other maximal strengths) with respect to post-infectious states. This is furthermore supported by the findings concerning the ratio $AFiso_{max}$ to AF_{max}, which was significantly lower at pre vs. post and pre vs. end according to the hypothesis (H3). The accordance with the subjective MMT ratings by the tester will be discussed below.
3. The onset of oscillations was found to be on a significantly higher force level (AFosc) for hip flexors at pre vs. post and pre vs. end (post vs. end was n.s.) with very large effect sizes, which was presumed (H4). AFosc for elbow flexors missed significance. However, the differences in oscillatory behavior were underpinned by the ratio AFosc to AF_{max} which was significantly higher for pre vs. post and vs. end with very large effect sizes (post vs. end n.s.) as was hypothesized (H5). Moreover, in all of the 84 MMTs of elbow and hip flexors at pre (rated as unstable) the oscillations arose – if at all – after the breaking point (ratio AFosc to $AFiso_{max}$), thus during muscle lengthening. For the remaining 175 MMTs (elbow and hip, mostly rated as stable) at post and end, the up-swing of oscillations arose regularly during isometric actions. This finding supports previous ones that in case of stability, oscillations occur during isometric muscle action whereby in case of instability, they do not arise. This indicates the oscillations might be a prerequisite for stable adaptation as was suggested previously [48,52,53].

The results support the hypotheses and will be discussed in the following regarding different physiological and practical aspects.

4.1 Comparison of subjective ratings of the manual muscle test and measured AF

The MMT was comprehensibly criticized to be subjective. Not only the applied force increase, but also the rating of MMT as 'stable' or 'unstable' is based on the manual ability and 'feeling' of the tester. By measuring the dynamics and kinematics during the MTT, the force increase and breaking point can be objectified as was recently shown and as was performed in the present study. However, the question remains if the measured AF parameters support the subjective MMT ratings. Since the results of elbow and hip flexor showed similar characteristics, they will be considered together. All 84 MMTs at pre were assessed as 'unstable' by the testers. The MMTs at post and end were rated at 'stable' in the majority of trials (164 of 175), as 'unstable' in 5 of 175 cases and as 'unclear' in 6 of 175 cases. Regarding the MMT rated either as 'unstable', 'stable' or 'unclear', the ratio $AFiso_{max}$ to AF_{max} amounted 50.27 ± 13.15%, 99.69 ± 0.64%, or 97.95 ± 2.61%, respectively. Hence, it can be concluded that the testers' MMT ratings are in accordance with the measured AF data. In unstable conditions, $AFiso_{max}$ was only half of the holding capacity during stable tests. The as unclear rated MMTs are rather in accordance with the stable ones. Obviously, they have a high $AFiso_{max}$, however, during the MMT the testers felt higher suspensions and the muscle resistance felt 'softer'. The values of stable MMTs support previous findings, in which stable MMTs showed a ratio $AFiso_{max}$ to AF_{max} of ≥ 99% [48,52,53]. Unstable MMTs revealed values of ~56%, which is slightly higher than the value of ~50% found here. This might be attributable to the fact that the previous studies were performed in healthy participants which were affected temporarily by disturbing odors or imagery, respectively. Unhealthy individuals with long COVID seem to show – at least in part – even stronger impairments in muscular adaptation. Some patients showed extremely low $AFiso_{max}$ values; the lowest was 15% of AF_{max} for hip flexors and 14% for elbow flexors. This is interpreted as an – partly extremely – impaired muscular adaptation, probably due to long COVID state. However, it cannot be stated if their muscular adaptation was already impaired before SARS-CoV-2 infection. Based on the findings it can be concluded that the MMT ratings of both experienced testers are strongly in accordance with the measured AF values. Therefore, the AF measured by the objectified MMT seems to be a suitable biomechanical parameter to evaluate the muscular function in adaptation to an external increasing force.

4.2 Adapaptive Force in the recovery process of long COVID

Fatigue is considered as the main symptom of long COVID [73–75]. The link between fatigue and muscle weakness has already been raised previously [11,15,30,76–79]. That is why maximal strength is partly investigated in post-infectious syndromes or ME/CFS. As was mentioned above, the findings are inconclusive until now [41–44]. It was questioned if the investigated MVIC might probably not be the suitable parameter to measure the muscle weakness in patients. It was previously proposed that the holding capacity would be a more sensitive biomechanical parameter to assess muscle function. Hence, the main question of this investigation was if the holding capacity would be impaired in long COVID state and would show improvements during recovery process. This must be clearly answered with 'yes'. The significant difference of $AFiso_{max}$ between pre and end apparently indicates that the holding capacity was not only substantially improved, but even fully normalized until recovery. This result has to be discussed independently from possible causations of the improvement. Because the study was non-clinical there was no control group. Therefore, the reasons why health conditions and AF parameters improved remain open. As the main result of the study AF turned out to be a sensitive parameter for long COVID state, because 100% of the patients showed initially clear instability (this was also the case for the not included further 20 patients measured in long COVID state). To the authors' knowledge, only one study assessed muscle strength in SARS-CoV-2 patients [80]. MVIC was measured directly at discharge of elderly hospitalized patients. Thereby, 73% and 86% of patients showed a 'weakness' for biceps brachii and quadriceps femoris muscles, respectively. Muscle weakness was defined if strength "was inferior to 80% of the predicted normal value" based on Andrews et al. [81]. However, those patients are not comparable with the presented ones since the measurements were executed at the end of acute infection after a period of hospitalization (averagely 20.7 days). More than 90% received oxygen supply and all of them were pharmacologically treated. Another

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study investigated hand grip strength in CFS/ME patients which was prior to Corona pandemic. Jäkel et al. revealed a sensitivity of ~70% and ~86% for maximal hand grip strength in CFS/ME patients aged 20-39 years and 50-59 years, respectively [43].

$AFiso_{max}$ of long COVID patients responded immediately at first appointment after treatment with a clear and significant increase. This instant change leads to the assumption that $AFiso_{max}$ does not reflect the maximal strength capacity but a functional aspect of motor control which can be influenced by stimuli and can switch immediately from instability to stability or vice versa. This was shown by previous studies in healthy participants [48,52,53]. Directly after first treatment, the health condition of long COVID-patients was not improved that quickly, but the motor control already responded clearly. For this study only patients were selected who finally recovered – for whatever reasons. All of them showed an early response of their holding capacity after first treatment. It is hypothesized that the motor reaction could have been a first hint on a helpful intervention at least in a share of subjects. The actual causality remains open. There could have been helpful treatment methods but also possible mental factors like an empathetic atmosphere or the like.

Regarding the queried symptoms it was visible that they behave inversely proportional to the holding capacity: At pre, the symptom intensity was significantly higher in most items compared to end ($p < 0.001$ to 0.031; except for fever ($p = 0.281$) and loss of smell/taste ($p = 0.062$)), whereby $AFiso_{max}$ or the ratio $AFiso_{max}$ to AF_{max} was significantly lower at pre vs. end with large effect sizes of > 2.42. This indicates an inverse correlation of health state in long COVID with the holding capacity. The directionality and causation of this connection can only be assumed. Since the holding capacity was improved already at post measurements (directly after first treatment), the holding capacity cannot be a direct indicator for the improvement in health. Moreover, it remains unclear whether that observed instant improvement was sustainable. It seems to be likely the motor response was a more transitional phenomenon at the beginning. MMTs at following treatment appointments showed a fallback to muscular instability for the most patients; however, this was not verified by objective measurements. Because the output-measurements (end) were not done after an immediately preceding treatment the found stability could be interpreted as a part of the improved health state. We assume that the holding capacity is regained prior to the decrease of symptom intensity. Hence, after suitable treatment, the functionality is restored firstly. A probable improvement of health condition is time-delayed and might possibly be dependent on the sustainability of this regain functionality mirrored by the stable muscle function. The holding capacity in the sense of $AFiso_{max}$ might be a suitable sensitive functional parameter to assess the current state of long COVID in a given patient. This can be justified by neurophysiological consideration.

4.3 Neurophysiological considerations with respect to the reaction of AF in long COVID

The discussion on the etiology of long COVID should not be opened here in detail. Brain stem dysfunction [36], a reduced cerebral blood flow [31,82] and the involvement of the ANS [25,26,30,31,37–39] are discussed with respect to long COVID. Recently, preinfection psychological distress was discussed as risk factor for long COVID, too [75,83]. This is in line with the self-reported stress prior to acute infection regarding the patients of the present study. Brain structures as the brain stem, the thalamus, the basal ganglia, the cerebellum, the inferior olivary nucleus, the cingulate cortex and more are involved in processing and controlling nociception, emotions and motor control [84–88]. Hence, the influence of possibly interfering inputs in the complex control circuitries of motor function are conceivable. The adaptive holding capacity in reaction to an external increasing force was suggested to be especially vulnerable regarding such stimuli. The length-tension control with respect to an increasing external force challenge the regulation and control processes of motor control in a specific way (for a detailed discussion see [48,51–53]). Therefore, it is conceivable that a health state like long COVID could influence the holding capacity. Based on the findings of previous studies on the influence of emotions on AF in

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healthy participants [48,52,53] and on long-term practical experience that mental stress can reduce the holding capacity we assume that the motor output in the sense of AF could have been impaired already prior to SARS-CoV-2 infection because of mental stress. This might have affected the functionality of the human system on different levels. Especially an impairment of the immune system is known to be associated with mental distress [83,89–94]. Hence, the individually perceived mental stress could have diminished the resilience of the individual with regard to the virus and, probably, could have impeded the recovery of the acute infection resulting in long COVID. Wang et al. [83] highlighted that the findings that psychological distress is a risk factor for long COVID "should not be misinterpreted as supporting a hypothesis that post-COVID-19 conditions are psychosomatic". We concur with this statement. From our point of view, mental stress might lead to disbalances of different bodily systems, e.g., the immune system [83,89,90] or the ANS [95], which, in turn, leads to a lower resilience. This might favor a long COVID state. We interpret the long COVID state rather as a sign of dysfunction. The found instability of the holding function might be a part of the complex physiological functional disbalance of long COVID patients. Also, the onset of oscillation (AFosc) might reflect an impaired functionality. AFosc occurred on a significantly low force level at post and end compared to pre, where oscillations did not or only slightly occur on a high force level and after the breaking point. The neuromuscular system is known to be characterized by oscillations. From the current knowledge on AF, we assume that the oscillations might be a prerequisite for stable adaptation in the sense of AF. The findings of the present study support this hypothesis and the evidence consolidates that oscillations are playing a major role in neuromuscular adaptation with respect to external forces.

Based on the connection of physiological disbalances and motor control, the AF might be a suitable biomechanical parameter to check for such functional impairments. Due to the immediate response of the holding capacity to supporting or impairing inputs, also the recovery process of long COVID could be controlled, and a potentially supportive therapy approach might be ascertained by assessing the holding capacity.

4.4 Limitations

One limitation was the non-standardized duration from post to end measurements. Due to the individual recovery process this limitation is difficult to resolve. The duration depended on the self-reported health state of the patients. This self-report is another limitation. Further studies could include a more quantitative assessment of the health state. However, the individual feeling of health is the most important one, also for return to work. Furthermore, the study was not blinded. The testers were aware of the patients' health state. However, the evaluation of slope and of maximal AF revealed statistically similar values between the three timepoints and only $AFiso_{max}$ as well as AFosc showed significant differences between pre vs. post and pre vs. end. This strongly indicates that the AF assessment was not influenced by missing blinding.

5. Conclusions

The investigation of the AF in patients with long COVID and in the course of their recovery process revealed that the holding capability was significantly reduced in long COVID state and was stabilized after first treatment and at recovery. AF_{max} did not reflect this difference. The holding capacity seems to be sensitive but is assumed to be not specific for long COVID. Nonetheless, its assessment might support the diagnostics of long COVID and especially choosing the individual helpful treatment, since the holding function seems to change immediately from instability to stability. This should be used to identify a treatment tailored to the patient's individual conditions and requirements. It is concluded that the assessment of $AFiso_{max}$ could be a supportive biomechanical parameter to assess the functional health state, follow up and recovery process in long COVID patients. A next step should be to investigate the mentioned treatment approaches. Based on the present study it cannot be judged if they were the reason for the recovery. Possibly also other received treatments or a spontaneous recovery over time could have led to the improved health state. Clinical studies have to be performed investigating the mentioned treatment approaches. In case they will be verified positively, a big step towards the diagnostics and treatment approaches with regard to long COVID would be made. This would have major socioeconomic implications.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Patients characteristics, COVID specific durations and number of treatments; Table S2: Intensity of symptoms; Table S3: Ratings of manual muscle tests by the tester; Table S4: Maximal Adaptive Force of elbow flexors; Table S5: Maximal isometric Adaptive Force of elbow flexors; Table S6: Adaptive Force at onset of oscillations of elbow flexors; Table S7: Slope of force increase for elbow flexors; Table S8: Maximal Adaptive Force of hip flexors; Table S9: Maximal isometric Adaptive Force of hip flexors; Table S10: Adaptive Force at onset of oscillations of hip flexors; Table S11: Slope of force increase for hip flexors.

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Data Availability Statement: The data presented in this study are available in the article and supplementary material.

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