Isometric Muscle Function

with Specific Respect to Oxygen Supply and Adaptive Force

Cumulative Dissertation

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Thank you,
my supervisors, colleagues, participants, family, friends and love
for your important support!

Table of Contents

Abstract

The cumulative dissertation consists of four original articles. These considered isometric muscle actions in healthy humans from a basic physiological view (oxygen and blood supply) as well as possibilities of their distinction. It includes a novel approach to measure a specific form of isometric holding function which has not been considered in motor science so far. This function is characterized by an adaptation to varying external forces with particular importance in daily activities and sports.

The first part of the research program analyzed how the biceps brachii muscle is supplied with oxygen and blood by adapting to a moderate constant load until task failure (publication 1). In this regard, regulative mechanisms were investigated in relation to the issue of presumably compressed capillaries due to high intramuscular pressures (publication 2).

Furthermore, it was examined if oxygenation and time to task failure (TTF) differs compared to another isometric muscle function (publication 3). This function is mainly of diagnostic interest by measuring the maximal voluntary isometric contraction (MVIC) as a gold standard. For that, a person pulls on or pushes against an insurmountable resistance. However, the underlying pulling or pushing form of isometric muscle action (PIMA) differs compared to the holding one (HIMA).

HIMAs have mainly been examined by using constant loads. In order to quantify the adaptability to varying external forces, a new approach was necessary and considered in the second part of the research program. A device was constructed based on a previously developed pneumatic measurement system. The device should have been able to measure the Adaptive Force (AF) of elbow extensor muscles. The AF determines the adaptability to increasing external forces under isometric (AFiso) and eccentric (AFecc) conditions. At first, it was questioned if these parameters can be reliably assessed by use of the new device (publication 4). Subsequently, the main research question was investigated: Is the maximal AFiso a specific and independent variable of muscle function in comparison to the MVIC? Furthermore, both research parts contained a sub-question of how results can be influenced.

Parameters of local oxygen saturation (SvO_2) and capillary blood filling (rHb) were non-invasively recorded by a spectrophotometer during maximal and submaximal HIMAs and PIMAs.

These were the main findings: Under load, SvO_2 and rHb always adjusted into a steady state after an initial decrease. Nevertheless, their behavior could roughly be categorized into two types. In type I, both parameters behaved nearly parallel to each other. In contrast, their progression over time was partly inverse in type II. The inverse behavior probably depends on the level of deoxygenation since rHb increased reliably at a suggested threshold of about 59% SvO_2. This triggered mechanism and the found homeostatic steady states seem to be in conflict with the concept of mechanically

compressed capillaries and consequently with a restricted blood flow. Anatomical configuration of blood vessels might provide one hypothetical explanation of how blood flow might be maintained. HIMA and PIMA did not differ regarding oxygenation and allocation to the described types. The TTF tended to be longer during PIMA.

As a sub-question, oxygenation and TTF were compared between (HIMA) and intermittent voluntary muscle twitches during a weight holding task. TTF but not oxygenation differed significantly (Twitch > HIMA). A changed neuromuscular control might serve as a speculative explanation of how the results can be explained. This is supported by the finding that the TTF did not correlate significantly with the extent of deoxygenation irrespective of the performed task (HIMA, PIMA or Twitch).

Other neuromuscular aspects of muscle function were considered in second part of the research program. The new device mentioned above detected different force capacities within four trials at two days each. Among AF measurements, the functional counterpart of a concentric muscle action merging into an isometric one was analyzed in comparison to the MVIC.

Based on the results, it can be assumed that a prior concentric muscle action does not influence the MVIC. However, the results were inconsistent and possibly influenced by systematic errors. In contrast, maximal variables of the AF ($AFiso_{max}$ and $AFecc_{max}$) could be measured in a reliable way which is indicated by a high test-retest reliability. Despite substantial correlations between force variables, the $AFiso_{max}$ differed significantly from MVIC and $AF_{max,}$ which was identical with $AFecc_{max}$ in almost all cases. Moreover, $AFiso_{max}$ revealed the highest variability between trials.

These results indicate that maximal force capacities should be assessed separately. The adaptive holding capacity of a muscle can be lower compared to a commonly determined MVIC. This is of relevance since muscles frequently need to respond adequately to external forces. If their response does not correspond to the external impact, the muscle is forced to lengthen. In this scenario, joints are not completely stabilized and an injury may occur. This outlined issue should be addressed in future research in the field of sport and health sciences.

At last, the dissertation presents another possibility to quantify the $AFiso_{max}$ by use of a hand-held device applied in combination with a manual muscle test. This assessment delivers a more practical way for clinical purposes.

Abbreviations

AF	Adaptive Force
$AFecc_{max}$	maximal eccentric AF
$AFiso_{max}$	maximal isometric AF
AF_{max}	maximal AF
ATP	Adenosine Triphosphate
CV	Coefficient of Variation
EF	External Force
EMG	Electromyography
ICC	Intraclass Correlation Coefficient
IF	Internal Force
IMA	Isometric Muscle Action
HIMA	Holding Isometric Muscle Action
M	Mean
Max	Maximum
MMG	Mechanomyography
MTG	Mechanotendinography
MVIC	Maximal Voluntary Isometric Contraction
MVICpri-con	MVIC with a prior concentric contraction
PIMA	Pulling / Pushing Isomeric Muscle Action
pre-MVIC	MVIC at the beginning of measurement series
post-MVIC	MVIC at the end of measurement series
rHb	relative Hemoglobin amount
SD	Standard Deviation
SEM	Standard Error of Measurements (random error)
SvO_2	local capillary-venous Oxygen Saturation
t_1	measuring session at day 1
t_2	measuring session at day 2
TTF	Time to task failure

Preface

According to the requirements of the Faculty of Human Sciences of the University of Potsdam, this cumulative dissertation contains a synopsis of the research program behind the presented joint publications. The research was conducted at the Division of Regulative Physiology and Prevention at the Department of Sport and Health Science of the University of Potsdam. The scientific articles are presented exactly as they have been published. The key points of every publication and an overall discussion is offered.

Some of the ideas and data presented here do not fit to conventional theories in the respective field. Based on studies with small sample sizes, truth claims are – of course – not demanded. However, the ideas are put up for discussion. In this regard, the words of my supervisor, Frank Bittmann, "we will accept what we have found" (translated freely by the author) can be complemented by a statement of Claude Bernard (1927), translated by Henry Copley Greene (1949), pp 40 – 41) [1]):

> "…when we have put forward an idea or a theory in science, our object must not be to preserve it by seeking everything that may support it and setting aside everything that may weaken it. On the contrary, we ought to examine with the greatest care the facts which apparently would overthrow it, because real progress always consists in exchanging an old theory which includes fewer facts for a new one which includes more. Our ideas are only intellectual instruments which we use to break into phenomena; we must change them when they have served their purpose, as we change a blunt lancet that we have used long enough."

1 Introduction

Thinking about function of skeletal muscles, associations like “allowing movements” or “giving stability” might come into mind. Further reflections could point on the provision of heat, storage of energy or transportation of blood towards the heart (muscle pump). This little brainstorm shows that muscle functions are versatile. All in common, they have to work physiologically. Muscular work can be static or dynamic as a consequence of the relation between internal and external forces [2].
The internal force (IF) is a result of a person’s neuromuscular system developing strength in interaction with an object (or another individual). The external force (EF) acts against the person. It can be gravity, inertia but also frictional resistance or generated force of another person. If one force overcomes the other during interaction, a dynamic movement occurs. The muscle shortens if the IF exceeds the EF and lengthens vice versa (IF < EF). A muscle action while shortening is also termed as concentric action and while lengthening as eccentric action, even if these terms do not fit perfectly (see [3]).
Balanced internal and external forces result into static muscular work. The type of muscle action is isometric whereby the overall muscle length does not change irrespective of the generated tension. Muscle actions can also be composed as during the known stretch-shortening cycle (eccentric – concentric) or a measurement of the Adaptive Force (isometric – eccentric) [4]. Another combination could be a concentric contraction running into an isometric one. This composed muscle action was also considered marginally in the research program. However, the isometric muscle action (IMA) is on main focus. Some background of what is known and unknown of this type of muscle action is given in the following.

1.1 Isometric Muscle Action – Muscle Mechanics and Neuromuscular Control

Despite research over more than a century, the IMA is linked to several unsolved mysteries. For instance, it is still unclear what exactly happens within the sarcomere during force generation [5] and how the specific motor process is controlled by the nervous system [6]. Regarding the former, sliding of filaments [7–9] explained by the famous, later called cross-bridge theory of muscle contraction [10–12] does not fit perfectly for IMA (and especially not for eccentrics [13]).

Repeated working strokes during cross-bridge leading to a continuous sliding of filaments and consequently global muscle shortening cannot serve as an explanation of maintained (submaximal) IMA. Sustained cross-bridges between actin and myosin filaments as seen during rigor mortis is traced to a lack of adenosine triphosphate (ATP) regeneration [5]. This universal energy carrier is necessary to detach an actomyosin connection and is also hydrolyzed to adenosine diphosphate and inorganic phosphate during an IMA [14].

Although energy cost is lower during maintaining a force compared to attaining it [15], ATP hydrolyzation would – in theory – lead to another cross-bridge cycle which might be incompatible with isometrically working muscles. Even maximally stimulated fixed-end myofibril bundles of rats and frogs have shown a plateau in length after an initial shortening [16]. In contrast, newer research presume that filament sliding is not necessarily associated with sarcomere shortening, i.e., global isometrics does not mean local isometrics [17–19]. Thus, compliant (elastic) elements of a sarcomere might lengthen while filaments slide under isometric conditions [16,19–23].

In this regard theory of functional unit half-sarcomere could also be of relevance [24]. It assumes that half-sarcomere lengths behave non-uniformly during activation and, therefore, each half sarcomere forms the smallest functional unit. This is supported, e.g., by in vitro video microscopy data of fixed-ends myofibrils of rabbits and guinea pigs activated by physiological calcium solution [24]. It was shown that after an initial shortening of all half-sarcomeres with different velocities during force rise, some shortened further on, others stood isometrically and again others lengthened during the force plateau. However, the half-sarcomeres shortened on average during whole activation time.

Other in vitro experiments found non-uniform but stable (half-)sarcomere lengths after an initial shortening under isometric conditions in myofibrils activated by physiological solutions [25–27]. The observations of initial (half-)sarcomere shortening during IMA might simply be compensated by lengthening of passive components like titin (sarcomeric stabilization) [20]. Moreover, it must be noticed that elasticity of fixations as well as dead (half-)sarcomeres which are unable to contract after dissection contribute to the overall shortening in such passively activated myofibrils [20,25,28,29]. This draws attention to the impeded transferability of in vitro studies to real life conditions [3,28]. However, a minimal invasive in vivo study also supports the complex and possible non-uniform length of (half-)sarcomeres by presenting length variations up to ~20% at a given overall muscle length [30].

Regardless of the inhomogeneity of (half-)sarcomeres, connected in series, each one must transmit the same force [29]. Until now, it is still unknown how the working stroke (swinging lever arm hypothesis) during the cross-bridge cycle is related to force generation [16]. A lever arm swing might be incompatible with sustained isometrically working muscles. Possibly, force generation is a different step in the cross-bridge cycle and separated from the lever arm swing [19]. The swing might only reduce strain in the compliant element of the myosin head after pre-tension [19]. Based on Huxley and Simmons (1971) [11], a speculative idea how (isometric) force is generated was proposed recently [31]. In simple terms, release of adenosine diphosphate and inorganic phosphate in activated weakly bound cross-bridges cause a working stroke and filament sliding. At the end of the stroke, force equals zero. If filaments are hindered to slide, e.g., by a high EF, the myosin head will remain in bent position (no working stroke). However, a compliant cross-bridge spring element is stretched causing the myosin lever arm to exert isometric force on actin. A schematic diagram can be found

in [31]. That idea needs to be tested in future and especially analyzed how many of the myosin heads are connected to actin in the respective state (weakly or strongly bound) as well as for how long [5].

It is also questionable how this approach can be brought together with the fact that muscles oscillate mechanically during isometric actions around 10 Hz to 15 Hz [32–38]. This underpins the idea that pure isometric conditions cannot exist at least on microscopic level. Oscillations have to be preceded by a coordinated activation of muscle fibers. In contrast, independent actions of single fibers would not result in an oscillation. It is currently unknown how myosin heads are coordinated within a single fiber [19]. What we know is that a release of calcium ions is triggered by nerve signals (action potentials) leading to further processes which are needed for binding of myosin to actin [5]. A simultaneous depolarization leads to an activation of the whole fiber [5]. During muscle actions, numerous muscle fibers innervated by several motor neurons working together. It is still unclear how this coordinated process really works.

Technical properties only allow electromyographic discharges of single motor units or fibers via intramuscular needle / wire electrode or collective signals of the whole muscle or muscle groups via surface electrodes [39,40], whereby conclusions on motor drive or motor unit recruitment are difficult to draw by interpreting surface EMG [41]. During recruitment, the motor units possibly attain the discharge frequency of previously active ones [40], inducing a kind of centrally driven synchronization [42,43]. It has already been questioned if neural control of muscle actions are independent of the type of voluntary contraction (concentric, isometric or eccentric) [44]. In this case, only the amount of muscle activation (IF) in relation to the load (EF) would result in the specific contraction type [44]. However, it was proposed that at least eccentric muscle actions are differently controlled compared to concentric and isometric ones (for review see [44–46]).

Although the recruitment order (size principle) of motor units seem to be similar between contraction types, the recruitment threshold was found to be higher for isometric compared to concentric or eccentric muscle actions with slow contraction velocities[1] [48,49]. Tax and colleagues (1987) even found dissimilar recruitment thresholds for different (quasi-) isometric tasks with very slow force rises (quasi isometric position task < isometric force task) [48]. Thus, IMAs might have different inputs received by motor neurons [45] and control strategies [34] in respect of the performed motor task. The possible distinction of IMAs will be addressed more in detail in chapter 1.3. Moreover, the recruitment strategies might be different even during activities of multifunctional muscles and, therefore, might be task specific [40]. This highlights important influencing factors of muscle control which are made much more complex by considering intermuscular synergies and interferences (e.g., cutaneous inputs [40]). However, these are out of the scope of the research program.

[1] The contraction velocity need to be controlled during comparisons since it highly influences motor unit recruitment as well as force thresholds [47].

The net neuromuscular output is the generated force, which is modulated by the number of recruited motor units (MU) as well as the firing rate (rate coding): the greater the MU recruitment and discharge frequency, the higher the force [40,47]. It is generally accepted that reaction forces during isokinetic eccentric actions are higher compared to isometric and concentric ones [50]. However, this was not a consistent finding as several studies did not reveal systematic differences [46]. For voluntary contractions, eccentric and isometric forces are comparable independently of the eccentric movement velocity, which was convincingly shown by the force-velocity relation (a diagram can be found ,e.g., in [51]). Moreover, if an individually optimal muscle length (joint angle) is used during isometrics, forces can even be higher than under eccentric conditions at least in the lower extremity [50]. The maximal voluntary isometric contraction (MVIC) can be used to related results of other measured forces or to normalized EMG signals [39].

To sum up, the muscle mechanics and neuromuscular control during IMA are not understood entirely. These are treated as a black box while focusing, i. a., on measurable neuromuscular force outputs. In this regard, a special but fairly unknown force is considered – the Adaptive Force (chapter 4). However, motor unit recruitment is not only influenced by force and speed of contraction but also by the availability of energy substrates and oxygen [47]. Some background of muscle metabolism blood flow is given in the following and to introduce the other central part of the research program – the oxygen and blood supply of IMAs.

1.2 Metabolism and Blood Flow of Isometric Muscle Actions

As stated in chapter 1.1, ATP is necessary to generate muscle actions by converting chemical potential energy into contractile work [31,52–54]. The need of ATP is not only limited to cross-bridging since calcium pump in sarcoplasmatic reticulum and membrane excitability also depend on it [55]. As ATP storage within muscle cells is small, it need to be refilled by other metabolic pathways to maintain homeostasis even during increased workloads [52,53]. During short intense exercises, metabolic processes can mainly run without oxygen by degradation of phosphocreatine or anaerobic glycolysis with accumulation of lactate [52]. Submaximal muscle actions over longer periods need to oxidize substrates such as carbohydrates to regenerate ATP (aerobic glycolysis) [52]. Detailed descriptions of underlying biochemical processes can be found elsewhere [53,55,56], although regulative mechanisms of metabolic homeostasis in muscles are still unknown [53].

With regard to energy turnover, the muscle fiber type plays an important role. Muscle fibers are classified according to their metabolic profile which can be specialized for slow oxidative actions (slow twitch, type I) or for fast and intense anaerobic ones (fast twitch or type IIb/x fibers) [52,57]. There is also an intermediate fiber type (fast oxidative, type IIa) [52]. Each motor unit consists of the same type of muscle fibers [52], whereby recruitment and firing rates not only depend on force and contraction velocity but also on the state of energy supply [58]. The energy turnover is about six-

times higher in fast twitch fibers compared to slow twitch ones [59]. However, this needs to be related to several other influencing factors as the performed muscle action, contraction velocity and intensity [54,60,61]. Isometric actions are less metabolically demanding than intermittent isometric actions but also less than eccentric and concentric actions (listed in ascending order) [62,63].

At low sustained voluntary isometric contractions (< 20% MVIC), slow twitch fibers mostly contribute to metabolic activity [64]. At 40% MVIC, a higher (anaerobic) ATP turnover in the soleus muscle (mainly slow twitch fibers) compared to the gastrocnemius (mainly fast twitch fibers) was found [65]. Studies with stimulated cat soleus and gastrocnemius muscles also indicated a dependence of energy pathway on the muscle fiber composition [66,67]. Additionally, differences in fiber type composition might partly explain found sex differences in metabolic responses to muscle actions [68].

Irrespective of the fiber type, the ratio of anaerobic to aerobic ATP production increases with the intensity during fatiguing isometric contractions of 10%, 25% and 40% MVIC (ratio: 0.4, 0.31 and 0.37, respectively) [69]. This is supported by findings of increased anaerobic parameters with rising intensities (~33%, ~72%,~98% MVIC) during IMA [70]. It is further stated that higher intensities or intensities above the so-called “critical force”, to be more precise, cannot be performed with a metabolic steady state [71]. This is supported by the finding that intermittent isometric contractions at maximal and at a submaximal level substantially above the critical force (~55% MVIC) have shown similar metabolic perturbations especially at exhaustion [71]. If this holds true for sustained isometric contractions with comparable intensities as well needs to be examined in future research.

Although the primary energy pathway (anaerobic or aerobic) depend on exercise intensity and duration, both are activated simultaneously at the onset of exercise [54,55]. Thus, the oxidative pathway is always active also during sustained isometric muscle actions [69]. For that, oxygen need to be transported via hemoglobin within red blood cells. It releases oxygen to muscle tissue in the smallest vessels – the capillaries.

It is commonly accepted and written in physiological textbooks, e.g. [72–75], that blood supply is reduced or even completely stopped during an IMA. However, study results are inconclusive. For instance, in an early sophisticated experiment of Barcroft and Millen (1939), temperature differences were used to draw conclusion on muscle blood flow in response to sustained IMA up to ~30% of the maximal force capacity described for plantar flexor muscles of two subjects [76]. The results were compared to dynamic contractions and IMA with externally arrested blood flow. At estimated 20% and 30% MVIC, the rate of temperature rise was nearly equal during IMAs with and without externally arrested blood flow, leading to the conclusion of a probable arrested blood flow during an IMA even if a total standstill cannot be excluded [76]. However, other experiments which examined forearm blood flow during hand-grip exercises plethysmographically found increases during maximal and submaximal IMAs (up to at least 70% of MVIC) [77–79].

Thus, the behavior of blood supply during IMAs might be muscle specific despite of methodological differences in studies. Even muscles of the same muscle group (soleus vs. gastrocnemius) have shown differences in blood flow dynamics found in voluntary activated muscles of humans [80] and electrically stimulated cat muscles [66]. Further support of possible blood flow maintenance came from several studies which found dilated blood vessels during strongly electrically stimulated gastrocnemius muscles of dogs as cited by Barcroft and Millen (1939) [76].

By use of ultrasound Doppler, a better time resolution can be achieved compared to methods used in studies mentioned before [81]. Other methods which can be used to determine muscle blood flow are reviewed previously [82,83]. During IMA (10% to 75% MVIC) of the quadriceps muscle, blood flow velocities in femoral artery were found to decrease at the onset of contraction and even reached negative values representing a retrograde flow [81]. Subsequently, velocities increased and slowly rise above resting values for longer contraction times even at intensities above 50% MVIC [81]. These results indicate a possibly maintained blood flow during IMAs although post exercise velocities increased to a much greater extent [81].

Other indirect evidence of a restricted or occluded blood flow during IMA has come from performance parameters like isometric endurance times at ~33% and ~66% MVIC [84] of the elbow flexors or isometric force decline of forearm muscles [85] by comparing results under conditions of external blood flow occlusion.

Although studies mentioned above, did not examined microcirculation directly in muscle tissue, a frequently cited approach to explain results of a probably reduced muscle blood flow during contraction is the mechanical compression of vessels due to the high intramuscular pressure. Isometrically working muscles normally do not have phases of relaxation or reduced tension. Thus, the resulting constant high intramuscular pressure is thought to compress capillaries permanently and impede oxygen transport to tissue [80,86–89]. This issue is mainly considered in the first part of research program (chapter 3). It deals with the arising question of what happens with the muscle oxygenation in microcirculation during isometrics if the blood supply is possibly restricted or occluded (publication 1). The logical follow-up question of how the results that were found can be explained is addressed in publication 2.

Before focusing on the blood and oxygen supply during an IMA of humans in vivo, it is important to define the specific isometric motor task subjects have to perform. This is relevant for all studies dealing with isometry irrespective of the considered parameter. It was proposed that there might be at least two main forms of IMA [34]. The differentiation should briefly be introduced in the following.

1.3 Two Main Modalities of Isometric Muscle Action

Concentric (shortening) muscle actions are simply used to displace a submaximal load whereas eccentric (lengthening) ones can be performed either to control its displacement or to resist a

supramaximal load [40]. Isometric contractions also vary by the specific motor task. This can be exerting (internal) force by pulling on or pushing against an immovable resistance or holding a position by adapting to an external force and resist a muscle lengthening. The former is described as “force task” [90–93], “restrained task”[94], “force control” [95,96] and pulling or pushing isometric muscle action (PIMA) [34]. Due to the attempt to overcome the external force, it was also termed as “concentrically loaded isometric contraction” [97].

Pulling on or pushing against an immovable external resistance is rarely necessary in daily activities. However, most strength training and rehabilitation regimes or strength assessments use PIMAs [2,98–102]. If a muscle or muscle group performs a PIMA, a lot of other muscles have to work in an isometric holding manner aiming to stabilize the loaded joint or to maintain posture of respective body parts. Every time a person has to hold a position he or she attempts to adapt to an external force and avoid a provoked yielding. The isometric action is “loaded eccentrically” [97]. This is also termed “position task” [90–93], “postural task”[94], “position control” [95,96] or holding isometric muscle action (HIMA) [34]. The terms HIMA and PIMA are preferred in the following dealing with a potential objective distinction.

Several research groups examined if IMAs (mainly of arm or finger muscles) can be differentiated according to the performed specific motor task [34,35,90–92,94,97,103–105]. In this regard, EMG studies revealed conflicting results. As mentioned in chapter 1.1, recruitment thresholds of the biceps brachii muscle with very slow force rises might be higher during HIMA than PIMA [48]. Between tasks, motor unit discharge characteristics and extents of motor unit synchronization of first dorsal interosseus muscle seem to be not different at very low forces (< 5%) [94]. Regarding EMG amplitudes, Garner et al. (2008) did not found a difference at 20%, 30%, 40%, and 50% of the MVIC (soleus muscle) [106].

Another research group also found no task effects of EMG activity in elbow flexors at 20% MVIC [90]. However, at the last 40% of the contraction the average EMG of flexor muscles revealed higher amplitudes for PIMA compared to HIMA [90]. The study of Buchanan and Lloyd (1995) found significant differences in EMG amplitudes between force and position control of elbow flexor and extensor muscles but also indicated a possibly subject specific neural control strategy in respect of the task [96]. Spectral analyses revealed that the normalized EMG power in a frequency band of 10 – 29 Hz was found to be significantly higher for PIMA of elbow flexor muscles compared to HIMA [91]. The same frequency band as well as the band of 8 – 15 Hz showed a reversed behavior in power of mechanotendinography (MTG) of the triceps brachii muscle [34]. In the same study and comparable to EMG amplitudes at exhaustion, the mechanomyography (MMG) amplitudes seem to be higher during PIMA, too [34].

In contrast to EMG parameters, time to task failure (TTF) revealed more consistent results. It was found to be significantly longer during PIMA at least at low intensities (15%, 20% and 30% of the

MVIC) and if performed by elbow flexor muscles in a horizontal forearm position [90,91,105,107]. In contrast, no significant differences were found between both isometric tasks with vertically positioned forearm and at intensities of 45% and 60% [90,91]. Maluf et al. (2005) also reported longer TTFs during PIMA at 20% MVIC of the first dorsal interosseus muscle but similar ones at 60% [108]. Thus, differences between HIMA and PIMA might not be present at higher intensities. However, two studies revealed significantly shorter TTFs for HIMA vs. PIMA during 80% MVIC performed with the triceps brachii muscle in vertical position [34,35]. According to these results, further research is indicated especially with higher intensities (> 50% MVIC). This will be considered in the research program of this dissertation.

Some more parameters have been analyzed. On the one hand, significant differences have been found (mean arterial blood pressure (HIMA > PIMA) [90], glucose uptake in leg muscles of young men (HIMA > PIMA) [92]. On the other hand, differences have not been different considering IMAs of elbow flexor muscles (TTF and mean heart rate relative to rest with constant loads of 30 to 96% MVIC as well as MVIC values itself [103], tissue oxygenation index (TOI) and normalized total hemoglobin index (nTHI) at 20% and 60% of the MVIC [105]. According to the presented graphs of the latter study, the TOI at 60% seemed to decrease less during HIMA compared to PIMA. It could be reasonable to prove this appearance with a statistical difference test. Furthermore, TTF might be a highly promising variable to detect hypothesized differences.

Both, the oxygenation and TTF at 60% MVIC but also the maximal force output of HIMA and PIMA are compared within the research program. It was questioned if holding and pulling IMA differ regarding muscle oxygenation and / or time to task failure (publication 3) and if the maximal force capacity during a special form of HIMA could be differentiated from a conventional MVIC determined by PIMA (publication 4). The latter question will be elaborated in chapter 4. The presented results add data to the objective distinctness or non-distinctness of HIMA and PIMA. Based on previous research, it was already proposed that both IMA are distinguishable and that HIMA requires more complex control strategies [34,35,104]. The present work follows these hypotheses even if direct conclusions on neural control are not possible due to the used research methods.

At last, it should be noticed that holding a position while resisting an external load has the potential of joint movements [96]. Thus, alternating concentric and eccentric contractions are highly probable. Strictly speaking, the muscle action cannot be really isometric but quasi-isometric if there is only a small tolerance with degrees of freedom. However, it was argued that concentric contractions during a holding task might change the quasi-isometric character from HIMA to PIMA [34]. Additionally, it was examined if clearly visible intermittent muscle contractions (voluntary twitches) have an influence on muscle oxygenation and TTF. This could be indicative of the possibility of a switch from HIMA to PIMA and concurrently if such contractions could support the oxygenation by interrupting the quasi-IMA.

2 Overview of the Research Program

As briefly introduced, muscles can be activated differently in respect of the type of contraction or specific motor task and, therefore, take different functions. Besides enabling movements, maintaining a desired position by providing stability of joints is an essential muscle function with important relevance in daily activities or sports. During any kind of movement, some body parts always need to be stabilized. For that, the holding capacity of involved muscles plays a key role. Thus, it is important to take a deeper look at the holding muscle function with an underlying IMA. This is of special interest in the research program, which consists of two parts.

The first one mainly contains a description and possible explanation for the behavior of the capillary oxygen and blood supply during an HIMA, which is not yet entirely decoded by scientists (chapter 3). Potential differences to PIMA were considered as well. The main parameters of interest are the local capillary-venous oxygen saturation (SvO_2) and relative hemoglobin amount (rHb) which is an indicator of the capillary blood filling. This research part additionally considers the time to task failure (TTF) and the influence of intermittent voluntary muscle twitches. In this regard, neuromuscular aspects are already touched.

Nevertheless, neuromuscular considerations of the holding isometric muscle function are the main content of the second part of the research program (chapter 4). For that, the measurable forces as outputs of the neuromuscular system were compared. The common MVIC was used as output during a PIMA and the relatively unknown Adaptive Force (AF) was captured during a special form of HIMA by a newly developed prototype. As a prerequisite, the reliability of the AF assessed by the new device needed to be proven.

List of Research Questions and Hypotheses

The basic question was the following:

> (1) How do the oxygen (SvO_2) and blood (rHb) supply behave in the capillary system of superficial muscle tissue during a fatiguing isometric holding action? (publication 1)

This first explorative study was not conducted to test a hypothesis since the behavior of SvO_2 and rHb should mainly be described. Subsequently, an explanation for the observed behavior, especially of the partly found increase in rHb, should be given by answering:

> (2) How can the increase in rHb be explained? (publication 2)

It was hypothesized that the SvO_2 level triggers the behavior of rHb independently of the isometric task. In the next step, holding (HIMA) and pulling (PIMA) isometric muscle actions (IMA) should be compared to investigate potential differences:

(3) Do holding and pulling IMA differ regarding muscle oxygenation and / or time to task failure (TTF)? (publication 3)

To analyze this question, four oxygenation variables and the TTF were tested according to the findings of the previous publications. It was hypothesized that PIMA reveal longer TTFs than HIMA due to a higher oxygenation. A sub-question should additionally be answered:

(3.1) Do intermittent voluntary muscle twitches during weight holding have an influence on the muscle oxygenation and time to task failure? (publication 3)

By performing twitches, a support of the capillary blood flow and consequently oxygen supply and a longer TTF during the twitching task was hypothesized. This could also be in accordance with the proposed change in neuromuscular control (switch from HIMA to PIMA) as long as PIMA reveals a longer TTF than HIMA. Despite the TTF, a probably more sensitive quantification of the neuromuscular holding muscle function (Adaptive Force, AF) was considered in the last study. For that a pneumatic device was developed to quantify the AF and assessed regarding its quality criteria first:

(4) Can the pneumatic device measure the AF reliably? (publication 4)

This was tested by reliability statistics. Subsequently, the discriminant validity of the main variable of interest, the maximal isometric AF ($AFiso_{max}$), should be proven:

(4.1) Is the $AFiso_{max}$ a specific and independent variable of muscle function in comparison to other maximal forces? (publication 4)

This was assumed and statistically tested by performing difference tests and correlations. As a last subsidiary question, it should be analyzed if the MVIC determined by PIMA can be influenced by a prior concentric phase. This specific task is understood as a counterpart to an AF-measurement which was conducted to examine the main research question in publication 4. The sub-question was:

(4.2) Does the MVIC with a prior concentric contraction (MVICpri-con) differ from the commonly determined MVIC with an underlying PIMA? (publication 4)

Here again, no hypothesis is given since this question has an explorative character which should not raise the claim to draw final conclusions.

3 Part I: Oxygen and Blood Supply during Isometric Muscle Actions

During exercise, metabolic need for oxygen increases in skeletal muscle [109]. Thus, muscular blood flow rises up to 20-fold on average to match the oxygen demand [110]. However, especially

strenuous concentric and isometric muscle actions might temporarily reduce muscular blood flow by compression of peripheral blood vessels [72].

In contrast to dynamic exercises, static ones like holding a weight, often have no relaxation phases with reduced muscle tension. Caused by constant high intramuscular pressures, muscle perfusion might be impeded over the whole IMA [72,80,86–89]. It is known that the intramuscular pressure rises proportionally to the MVIC [80,86–88,111]. The contraction intensity leading to an occlusion (occlusion threshold) is probably muscle and person-specific and ranges between 40% and 70% of MVIC [112]. Muscle fiber type composition might play a role to explain interindividual differences [89,113]. Furthermore, the occlusion threshold might also depend on individual training status [112].

Irrespective of the precise occlusion threshold, if arterial blood flow is restricted or even completely stopped due to IMAs, as stated previously [73–75,114], higher demands of oxygen and consequently blood cannot be supplied. As a consequence, local muscle fatigue might occur earlier [112] and muscle function would be impaired (reduction of motor unit recruitment) [41].

To analyze oxygen supply of muscle tissue, measurement of venous oxygen saturation is reasonable since arterial blood is nearly saturated. Barcroft and colleagues (1963) determined this by spectrophotometry of deep venous blood samples [77]. They have shown, that during an externally occluded brachial artery forearm deoxygenation was nearly complete during prolonged contractions. It decreased to ~6% (n = 4 measurements) at termination of strong contraction (maximal hand-squeezing of a bulb for one minute). A similar value has been found for moderate contractions after 4 – 5 min (n = 2: ~8%). Such values were only reached by one outlier (3%) out of ten subjects performing IMA of comparable intensity and contraction duration without external occlusion (27% and 34% on average, respectively) [77].

The reasons why isometrically working muscles with moderate to strong intensities seem not to desaturate blood completely despite theoretically compressed or occluded capillaries remain unclear [77]. A contamination of venous blood samples with highly saturated blood cannot be excluded but were thought to be unlikely [77]. As mentioned in chapter 1.2, the same experiment found an increasing blood flow with higher isometric contractions intensities but also an abrupt increase after the end of contraction [77].

All in all, the results indicate the importance of determining the oxygen saturation, preferably of microvessels. Furthermore, conclusions on oxygen supply by measuring of blood flow or intramuscular pressure are limited.

Newer studies based on non-invasive spectroscopy measurements examined microvascular oxygen saturation and hemoglobin amount (indicator of capillary blood filling) under fatiguing isometric conditions. Muscle oxygenation was found to level off into a steady state [105,115–118] or to decrease linearly [119,120]. However, none of the studies revealed a complete or nearly complete

desaturation. Further research is indicated since an entire understanding of the capillary oxygen and blood supply during IMAs is missing. The research gap should be filled by the first part of the research program regarding oxygenation and hemodynamic aspects of submaximal IMAs (60% MVIC). For that, the behavior of oxygen saturation and blood filling during HIMA of elbow flexors until exhaustion were examined in the first step (publication 1).

To measure the parameters of interest (SvO_2 and rHb), a valid and reliable light spectrophotometer (O2C, Oxygen To See; LEA© Medizintechnik GmbH, Gießen, Germany) was used [121–123]. The measuring method is comparable to the commonly utilized near infrared spectroscopy technique (NIRS). For short, white light (500 – 850 nm [124,125]) or near infrared light (700 to 900 nm [126], 650 – 1000 nm [127]) is sent to, e.g., muscle tissue [128,129] via special probes which also detect the different backscattered wavelengths. The source-detector separation determines the light penetration depth. The detected difference in wavelength mainly depends on the ratio of oxygenated and deoxygenated hemoglobin as well as myoglobin used to calculated the oxygen saturation (SvO_2). This measure can be interpreted as a kind of local mixed venous saturation before blood is reoxygenated.

However, SvO_2 has not to be confused with the systemic mixed venous oxygen saturation measured by pulmonary artery catheter. Values can be given in an absolute scale (measurement range: 0% – 100%) or in relation to the baseline value.

The amount of hemoglobin (rHb) can be determined by the amount of light absorbed by the tissue. It delivers an indication of the filling of vessels with blood. Without calibrating results with another method, e.g., quantifying milliliter per gram of tissue, only arbitrary units or ratios can be stated. It must further be noticed, that hemoglobin and myoglobin cannot be distinguished by spectrometric measurements [127]. Myoglobin is assumed to be constant during exercise and therefore, a change of total hem/myoglobin reflects a change of hemoglobin in microvessels [130]. Thus, myoglobin influences measurements during exercises less than at rest [131,132]. However, relative contributions remain controversial [127]. High amounts of hemoglobin as in arterial vessels would fully absorb the light virtually [133,134]. Thus, larger vessel have no significant influence on the recordings even arterial blood cannot be excluded completely [126,127,135–137].

The main difference between the O2C and NIRS devices is the size of included vessels during the measurement process (< 100 µm [133] vs. < 1 mm diameter [126], respectively) due to the different used wave length. It is assumed that the main signal comes from capillaries due to their largest proportion of vascular volume in muscles [127]. Detailed descriptions of the techniques as well as limitations can be found in previous studies [124,125,127,135,136].

This first explorative study generated a hypothesis to explain the found results. It was tested as an intermediate step in the second study (publication 2). Subsequently, it was investigated if the behavior depends on the isometric modality (HIMA vs. PIMA). In this regard, several oxygenation variables

and TTF were tested for a possible objective distinction (publication 3). In addition, the influence of intermittent voluntary muscle twitches during weight holding on all variables were analyzed. These twitches are little concentric contractions which interrupt the static muscular work and, therefore, might support the blood and oxygen supply.

The neuromuscular control might also be altered because the task possibly includes a switch from adapting (to an EF ≙ HIMA) to overcoming it (≙PIMA). This could influence the muscle function and might alter the TTF. Other neuromuscular aspects of HIMA are the main issue of the second part of the research program. Its background is outlined in chapter 4.

3.1 Behavior of Oxygen Saturation and Blood Filling in the Venous Capillary System of the Biceps Brachii Muscle during a Fatiguing Isometric Action.

Background:

Dealing with the holding function of muscles with an underlying IMA, it is reasonable to consider the suggested (unphysiological) specialty of permanent compressed arterial vessels. If the blood flow of arterial vessels is restricted or even completely stopped, the working muscle cannot be supplied adequately with oxygen and blood. In order to develop a better understanding of muscle oxygenation and hemodynamics in microvasculature during IMA and to verify conflicting results of previous studies, the first study questioned (publication 1):

> (1) How do the oxygen (SvO_2) and blood (rHb) supply behave in the capillary system during a fatiguing IMA?

Methods:

A fatiguing HIMA of 60% of the MVIC was performed by ten subjects (7 male and 3 female subjects) with their left biceps brachii muscle (mean age ± SD = 28.6 ± 11.68 years). For that, they had to hold a weight in a 90° elbow flexion for as long as possible in a standing position. A valid and reliable spectrophotometer (O2C; LEA Medizintechnik GmbH, Gießen, Germany) was used to calculate the local capillary-venous oxygen saturation of hemoglobin (SvO_2) in % and relative hemoglobin amount (rHb) in arbitrary units (AU) as an indicator of the local capillary-venous blood filling in superficial muscle tissue (light: 500 – 850 nm; light penetration depth: 12 mm). The measuring technique is comparable with the widely used near infrared spectroscopy (NIRS). However, parameters were only detected in the smallest vessels (> 100 µm in diameter).

Results:

Two different behaviors of SvO_2 and rHb were visible. In five of ten fatiguing measurements SvO_2 and rHb behaved nearly parallel to each other (type I). Both parameters decreased immediately after

the start of loading and leveled off into a steady state (coefficient of variation (CV): 1.19 ± 0.75%). A positive rank correlation was found, ρ = 0.725, p <.001). In five other measurements a partial inversed behavior occurred (type II). The correlation was negative (ρ = –0.522, p <.001). In these measurements, rHb increased after an initial decrease and leveled off into a steady state at about 13% above baseline value. SvO_2 also leveled off into a steady state (CV = 2.11 ± 1.59%) but on a lower level (–33.86 ±17.35 percent points (pp)) compared to type I (–10.37 ±2.59 pp). This difference was significant (p = 0.008). The durations from start of loading to leveling off as well as to end of the possible steady state were similar between both types (15.1 ± 1.6 s and 15.55 ± 3.23 s, respectively). As a consequence, the initial negative slopes (from start to leveling off into steady state) was less in type II (–3.31 ±1.26 for SvO_2 pp s^{-1} and –2.65 ±0.88 AU s^{-1} for rHb) compared to type I (–1.69 ± 0.92 pp s^{-1} and –1.83 ± 0.47 AU s^{-1}, respectively). Both behavioral types were also found in twelve MVIC trials with an underlying PIMA in a subgroup of six subjects (type I: n = 8); type II: n = 4).

Discussion:

This study was one of the first which described the behavior of oxygen saturation in conjunction with blood filling mainly of the venous capillary system in superficial muscle tissue. Based on the results of the used methods, the behavior during a submaximal HIMA and maximal PIMA can roughly be differentiated into two types. Regardless of methodological differences, the described types fit to the results of most but not all previous studies and might explain inconsistencies. In a next step, it should be explained how type I or type II emerge. The behavioral type could possibly depend on the saturation level expressed by differences in the extent of deoxygenation. It is hypothesized that a boundary level triggers the increase in blood filling, which should be examined in the next study.

According to the occurred steady states of both examined parameters in all submaximal fatiguing measurements and measurements of other research groups, a balanced need and consumption of oxygen and blood is possible during IMAs at least in the superficial muscle tissue. This fact needs further explanation since high intramuscular pressures at submaximal intensities theoretically stop blood flow in capillaries.

3.2 Muscle Oxygenation Level Might Trigger the Regulation of Capillary-venous Blood Filling during Fatiguing Isometric Muscle Actions.

Background:

In the first study (publication 1), two behaviors of oxygen saturation (SvO_2) and blood filling (rHb) in venous capillaries have been described and objectively differentiated during fatiguing HIMAs and maximal PIMAs. In type I, both parameters showed a nearly parallel behavior and by contrast, their curve progression was partly inverse in type II, i. e., rHb started to increases at a reversal point (RP_1)

while SvO_2 decreased further on. Then, both parameters leveled off into a steady state, which was maintained until stop of loading. With stop of loading, SvO_2 started to increase again, but rHb decreased until a second reversal point (RP_2) and increased together with SvO_2 towards their baseline level. The cause of this special regulation in type II is unclear. Thus, ascertaining an explanation of its occurrence was the main focus of the second study (publication 2) with the following main research question:

(2) How can the increase in rHb be explained?

For that, a hypothesized trigger mechanism by a boundary oxygenation level (threshold) was analyzed with an extended data set of the first study. Fatiguing PIMA measurements were also examined to consider both isometric forms.

Methods:

In this study, both arms of twelve subjects were analyzed. All subjects (29.75 ± 11.14 years) held a weight for as long as possible (fatiguing HIMA). In addition, a subgroup of six subjects pulled on an immovable resistance (fatiguing PIMA). All 44 fatiguing trials were performed at 60% of MVIC in a 90° elbow flexion. The above mentioned O2C device calculated SvO_2 and rHb by detecting backscattered wavelengths of priorly sent light into superficial muscle tissue. All trials were categorized visually to type I or II. As done in the first study, rank correlations between SvO_2 and rHb and maximal deoxygenation were calculated. Additionally, time to task failure (TTF) was compared between types. SvO_2-levels at the moment the two RPs in rHb, which occurred only in type II measurements, were used to examine the hypothesized boundary level. RP_1 indicates the first increase in rHb after the initial drop and RP_2 the second one after stop of loading. Additional information have been extracted: time periods in s from start until minimum of rHb before start of steady state. This variable corresponds to RP_1 in type II.

Results:

Regarding fatiguing trials, the rank correlations between SvO_2 and rHb were $\rho = 0.74 \pm 0.61$ in type I and $\rho = -0.81 \pm 0.52$ in type II. Types differed significantly in the extent of deoxygenation (type I: –12.21 ± 3.67 pp; type II: –24.45 ± 11.59 pp, $p < 0.001$, $r = 0.58$). During fatiguing HIMA, type I occurred in n = 7 and type II in n = 17 trials. During fatiguing PIMA, the allocation was similar (type I: n = 3; type II: n = 9). MVIC (PIMA) trials revealed n = 15 type I and n = 9 type II behaviors. The TTF was not significantly different between types ($p = 0.886$).

With regard to the main research question, SvO_2-level at RP_1 was 58.75 ± 2.14% in type II fatiguing IMAs. In type I, the minimal occurred oxygenation level was 59%. Similar to RP_1, SvO_2-level was at RP_2 was 58.91 ± 2.72%, $p = 0.600$. The same applies to MVIC measurements (at RP_1: 58.13 ±

1.66%; at RP_2: 57.82 ± 1.25%, p = 0.652). Time period in s from start until minimum of rHb was 11.41 ± 3.44 s in type I and 6.85 s ± 3.39 s in type II (duration until RP_1).

Discussion:

The occurrence of RPs in rHb (type II) might be explained by the oxygenation level. A threshold possibly triggers the increase. Regardless of the isometric form of muscle action (HIMA or PIMA, fatiguing or MVIC), this threshold might lie around 59% and within a transition area. Consequently, the behavioral patterns might reflect a specific regulation which depends on the oxygen saturation level. If the saturation was above the threshold, SvO_2 and rHb behaved nearly parallel, and if it was below, the behavior was inverse. The triggered increase in rHb might serve as a protective regulation to impede a further or complete deoxygenation. Local factors like nitric oxide leading to vasodilation of arterioles and enhanced blood flow in capillaries might play a role in the regulative processes behind. Hypoxia could be the stimulus in a negative feedback control system. However, the suggested threshold should to be verified in future studies examining deeper regions of the muscle as well as younger and older persons of different training status.

Regardless of the existence of a threshold, it need to be discussed, how increases in the microvascular blood content (rHb) are possible despite high intramuscular pressures. As commonly thought and stated above, IMA at higher intensities ought to stop capillary blood flow. Due to homeostatic steady states in SvO_2 and rHb, a stopped outflow (venous stasis) is highly unlikely. The location of capillaries within muscle tissue might be an approach to explain, how blood flow could be maintained. Capillaries proceed mostly parallel to the muscle fibers and lie in the endomysium where three to four muscle fibers adjoin each other. Muscle fibers increase their circumference during contraction and increased tension. Instead of compression of the capillary, the fibers might compress each other and enhance the space in between. Thus, capillaries and also nerves might be unaffected even if higher intramuscular pressures arise. Furthermore, collagenous struts, as detected by other research groups, might prevent capillaries from collapsing.

Vasodilating processes by hypoxic induced release of NO might explain the increase in rHb if the blood flow is maintained during contraction. Another factor which could support capillary blood flow might be the transversal oscillations of 10 – 15 Hz during IMA. They might serve as a kind of pump in conjunction with the anatomical considerations mentioned before. However, the mechanisms are not completely clear yet and subsequent research is indicated.

Although the explanation of the two types has been on main focus in this study, some more findings should be highlighted. The behavioral type seem to be independent of the person or gender because both types could be found within subjects as well as males and females. In addition, types are probably independent of the TTF. These were similar, even though type II deoxygenated significantly more than type I. Thus, onset of fatigue might not be related to deoxygenation. This should be

examined in future studies. Moreover, comparisons between HIMA and PIMA were not considered here and should be addressed, i.a., in the next study.

3.3 Muscle Oxygenation and Time to Task Failure of Submaximal Holding and Pulling Isometric Muscle Actions and Influence of Intermittent Voluntary Muscle Twitches.

Background:

As discussed in the previous two studies (publication 1 and 2), the oxygenation and hemodynamic response of IMAs could be roughly categorized into two types, whereby the type might mainly depend on the saturation level. The focus of the third study was to compare several oxygenation variables between HIMA and PIMA. This was rarely considered before and should bring further insights of a potential distinction of two isometric forms. In the past, time to task failure (TTF) was found to be one of the most promising distinguishing parameters. Thus, it was analyzed together with oxygenation variables. That leads to the following main research question of the third study (publication 3):

(3) Do holding and pulling IMA differ regarding muscle oxygenation and / or time to task failure?

As a sub-question, the influence of intermittent voluntary muscle twitches during weight holding (Twitch) should be answered:

(3.1) Do twitches during weight holding have an influence on the muscle oxygenation and time to task failure?

A voluntary twitch is defined as a rapid but short auxotonic contraction leading to a little motion of the limb. The muscle length and tension is changed temporarily On the one hand, twitches might serve as a pump and, therefore, supporting capillary blood flow. On the other hand, neuromuscular control of the whole task might be changed. Under isometric conditions, pure responses to EFs are associated with HIMA and, by contrast, initiated actions are associated with PIMA. If a load is exceeded, the formerly weight holding task as a kind of reaction to an external load, changes: to initiating an action and lifting up the weight minimally. It is hypothesized that twitches during a weight holding task switch the isometric character from HIMA to PIMA.

Methods:

In total, twelve subjects performed two elbow flexion tasks in a random order. Half of the group did HIMA and PIMA (HP group) and the other half HIMA and Twitch (HT group). Due to discomfort or pain, two subjects and one arm each of two others had to be excluded (n = 36 measurements, n =

9 per task). The intensity during all trials was 60% of maximal torque which should be maintained until muscle failure. Both arms were examined in a random order. SvO_2 and rHb were measured by light spectrometry. Subsequently, maximal deoxygenation (max. SvO_2 decrease), slope of initial linear SvO_2 decrease (SvO_2 slope), SvO_2 level at global minimum of rHb (SvO_2 at rHb min), which corresponds to RP_1 in type II measurements, and time to leveling off into a steady state of SvO_2 (TSS) were extracted as oxygenation variables. TTF served as performance variable.

The second study (publication 2) also indicated that the TTF might be independent of the extent of deoxygenation. Thus, Pearson's correlations coefficients were calculated between TTF and max. SvO_2 decrease over all measurements independent of the task.

Results:

None of the oxygenation variables differed significantly within subjects between HIMA and PIMA as well as not between HIMA and Twitch.

The TTF was significantly shorter during HIMA (42.63 ± 7.64 s) compared to Twitch (52.78 ± 11.61 s, $p = 0.043$). HIMA (44.80 ± 18.06 s) was also shorter compared to PIMA 50.33 ± 9.46 s but the differences did not reach statistical significance ($p = 0.394$). The result might be influenced by effects of fatigue caused by an unbalanced order of tasks (drop outs). Considering PIMA and Twitch together with a more balanced distribution of tasks the difference was significant again ($p = 0.047$).

Regardless of the type of task, TTF and maximal deoxygenation did not correlate substantially ($r = –0.13$).

According to the categorization of trials, type I ($n = 9$) and type II ($n = 27$) behaviors were nearly equally distributed between HIMA and PIMA (type I: 4 vs. 3; type II: 5 vs. 6) and identically distributed between HIMA and Twitch (type I: 1 vs. 1; type II: 8 vs. 8).

Discussion:

Most of the analyzed oxygenation variables were considered for the first time in respect of a comparison between HIMA and PIMA. Based on the results of a small sample size, microvascular oxygen and blood supply seem to be similar between both isometric forms (HIMA and PIMA). The two previously described behaviors of SvO_2 and rHb (type I and II) occurred during all tasks with a nearly equal number of trials. Thus, the type is probably independent of the performed task. This is a plausible consequence by considering that none of the oxygenation variables were statistically different. It was already hypothesized the type depends on the level of deoxygenation or more precisely, the drop below a threshold of about 59% (publication 2).

According to the occurred steady states in SvO_2 and rHb as well as increases of rHb in most measurements, the oxygen and blood supply in the capillary system might be sufficient during IMAs

(HIMA and PIMA). Twitches as performed in the presented study did not further support the supply substantially. However, TTF was found to be longer during Twitch compared to HIMA even though the weight had minimally to be overcome several times. Possibly, increases in blood flow or changed metabolic processes might play a role by activation of muscle pump and vasodilation. Because oxygenation variables were equal and TTF did not corelate substantially with the extent of deoxygenation, a changed neuromuscular control might rather serve as an explanation.

A twitch interrupts the adaptation to the weight (HIMA) by minor concentric contractions. Possibly, the muscle action could switch to a PIMA afterwards. PIMA might be closer to a concentric contraction ("concentrically loaded") and HIMA, by contrast, to an eccentric one ("eccentrically loaded"), as postulated by our research group previously. Further research need to be done in order to fully understand the mechanisms of eccentric contractions, which might have different control strategies. Furthermore, HIMA tended to reveal shorter TTFs in comparison to PIMA in the presented study.

This study adds data to the conflicting results of previous research regarding a distinction between the two isometric forms. Methodological reasons might have result in inconsistencies. Holding tasks as performed in the present study and by most of other researchers do not exclude concentric contractions for compensation of a prior yielding. Pure HIMAs are not understood to allow such minor concentric muscle actions in order to prevent a hypothesized switch into PIMA. As a consequence, other research methods are required, e.g., by measuring the Adaptive Force as reaction to increasing external loads in conjunction with control or even prevention of concentric contractions. This will be addressed in the next study.

4 Part II: Adaptive Force – a Measure of a Neuromuscular Function

In great contrast to PIMA, during HIMA, the neuromuscular system needs to adapt adequately to the EF which can be constant or varying in size. To match the EF, the muscle tension and length must be continuously adapted. The resulting force is defined as Adaptive Force, inaugurated by the research group of Prof. Frank Bittmann, University of Potsdam. It reflects a special functionality of the neuromuscular system in sense of adapting adequately to EFs [138,139]. This requires strength and sensorimotor control to prevent a provoked muscle lengthening. High demands or the the motor control centers are expectable [34,91].

Many daily activities require an adequate adaptation to EF. Examples are maintaining posture during any kind of activity while sitting or standing, supporting body weight while walking, running or biking or carrying any kind of object like shopping bags. If the adaptation to external loads is not adequate, joints might not be stabilized appropriately and musculoskeletal complaints, injuries or damages could be the consequence [138,140,141]. Prior to the evaluation of such hypotheses, basic research

regarding the assessment and objectification of the AF is necessary and, therefore, the focus of the second part of the research program.

Previous research which compared HIMA and PIMA mainly used constant EF during HIMA. It could be worthwhile to consider the adaptation to varying EF or more precisely increasing EF, too. Possibly, it is more sensitive to detect differences from a PIMA. In the following, two opportunities are described to enable an increasing EF for scientific purposes.

From a methodological point of view, the assessment of the adaptation to constant EFs is easy to realize, e.g., by holding a weight. In contrast, the adaptation to varying or increasing EFs was rarely considered, yet [4,138,139,142]. This could be explained by limited possibilities to provide such EFs on a standardized way. In the past, a pneumatic measurement system enabling a standardized increasing EF was introduced [4,138,139].

However, some methodological limitations has been described, i. e., the stick-slip effect caused by the used non-frictionless cylinder, the not individualized pressure increase to the MVIC of the participants and absent recording of the limb position. Thus, new prototypes which eliminates these problems have been constructed. For the prototype of the lower extremity, the basic construction and setting of the SeBit system was used [138,139]. The measurement setting described in Schaefer and Bittmann (2017) served as a template for the upper extremity. The developed prototype is of only interest in the following [34].

In principle, a bellows cylinder (Zitec SP-2 B04, 2-fach) driven by compressed air (compressor: JUN-AIR 700367; Condor MDR 2 EN 60947-4-1; control unit: custom build, Seifert Drucklufttechnick GmbH, Lauter-Bernsbach, Germany) pushes against a lever and generates an increasing EF. The subject, whose elbow joint was placed on a table in rotational axis of the lever (arm-trunk-angle: ~80°), has to adapt to this increasing EF by activating elbow extensor muscles (generation of IF). The reaction force between lever and subject is measured by strain gauge (LMZ 2000 N, 3006, modified by Biovision, Wehrheim, Germany). If the IF meets the EF, vertical forearm is held in position. The measured force is termed isometric Adaptive Force (AFiso) with an underlying HIMA.

The new pneumatic system for determination of the AF of elbow extensor muscles (termed as device in the following) was tested on its quality criteria (publication 4). This includes the test-retest reliability of the maximal isometric AF ($AFiso_{max}$) and its discriminant validity from the conventional MVIC force (PIMA). To evaluate the maximal holding capacity the increasing EF needs to “break” the isometry. Hence, the subject is forced from an IMA to an eccentric one. Thus, the AF can be differentiated according to the underlying muscle action. If it is still isometric, it is termed AFiso and if it is eccentric, AFecc. The $AFiso_{max}$ corresponds to the force at the moment of yielding (break off-point). The movement of the arm and lever is recorded by accelerometers (modified by

Biovision, Wehrheim, Germany). The break-off point can be determined by sophisticated algorithm[2]. It was already proven on > 800 AF-measurements of the upper and lower extremity and fits optically with an accuracy of 99.53%. To control for a potential pushback of the lever with an underlying concentric muscle action, a strict limit of ≥ 0.3° in direction of elbow extension is defined as task failure (no pure HIMA). A tolerance 2° of forearm yielding is given and still interpreted as IMA.

The $AFecc_{max}$ is the highest force during the eccentric phase which occurs always subsequently to this isometric one. Regardless of the muscle action, the highest force during an AF-measurement is termed as AF_{max}. Since isometric and eccentric muscle actions are combined during an AF-measurement, it was also described as composed muscle action [4].

4.1 Publication 4:
Assessment of the Adaptive Force of Elbow Extensors in Healthy Subjects Quantified by a Novel Pneumatically Driven Measurement System with Considerations of Its Quality Criteria.

Background:

While holding a constant weight it is difficult to perform a pure HIMA, i. e., an exclusive reaction to external loads as discussed in the third study (publication 3). The fourth study (publication 4) considers another assessment of HIMA by adapting to increasing forces instead of a constant one. Besides TTF, the neuromuscular holding function can be quantified by the Adaptive Force (AF) which might be more sensitive to detect differences from a PIMA because it not only requires strength but also sensorimotor control. AF quantifies the adaptation of the neuromuscular system to external forces with the aim to maintain a position without the influence of muscular strength endurance capacity (short measurement ~3 – 4 s).

To enable a standardized increasing external force, a pneumatic measurement system (SeBit) was refined and, in a first step, assessed regarding its quality criteria with the following research questions:

(4) Can the new pneumatic device measure the AF reliably?

Subsequently, the discriminant validity of the main variable of interest, the maximal isometric AF ($AFiso_{max}$), was analyzed by answering the question that follows:

[2] For further details and limitations, see descriptions in the original article (Publication 4).

(4.1) Is the $AFiso_{max}$ a specific and independent variable of muscle function in comparison to other maximal forces?

During AF-measurements the muscle action is first of all isometric which merges into an eccentric one. The functional counterpart could be understood as a concentric contraction merging into an IMA. The influence on the MVIC was analyzed in a sub-question:

(4.2) Does the MVIC with a prior concentric contraction (MVICpri-con) differ from the commonly determined MVIC with an underlying PIMA?

Methods:

Nine male and four female healthy subjects participated in the experiment on two days (t_1 and t_2). On both days, their dominant elbow extensors were examined by determining pre-MVIC, MVICpri-con, highest (AF_{max}) and maximal isometric AF ($AFiso_{max}$) as well as post-MVIC after all other measurements. The last measurements were conducted to examine possible effects of fatigue. Most variables correspond to the highest torque of each trial. Only $AFiso_{max}$ was determined as the torque at the moment of giving way of the forearm within a 2°-tolerance. To ensure a pure HIMA and exclude a switch into PIMA, a pushback of the lever of 0.3° resulted in an exclusion of the trial (n = 1). The maximal eccentric AF ($AFecc_{max}$) was mainly identical to AF_{max} and, therefore, excluded from statistical analysis.

Arithmetic mean (M) and maximal (Max) torques of all force types were calculated out of four trials per day. Measurement series of MVICpri-con and AF were performed in a randomized order. For reliability analysis, a liberal alpha level of 10% was chosen. Due to homoscedastic data, standard error of measurements (SEMs) and additionally intraclass correlation coefficients (ICCs (3,1)) were calculated. Comparisons between forces types as absolute values and ratios to pre-MVIC were conducted with a conventional alpha error of 5%.

Results:

Regarding test-retest reliability, AF variables were not significantly different between t_1 and t_2 ($p = 0.175 – 0.552$). Mean differences were 0.31 – 1.98 Nm (0.61% – 5.47%). SEM reached from 1.29 to 5.68 Nm (2.53% – 15.70%) and ICCs (3,1) from 0.896 to 0.996.

In comparison of force types, AF_{max} did not differ significantly from pre-MVIC ($p = 0.109 – 0.531$). In contrast, $AFiso_{max}$ was significantly lower (6.12 – 14.93 Nm) compared to AF_{max} and pre-MVIC ($p \leq 0.001 – 0.009$). Normalized to pre-MVIC, $AFiso_{max}$ was 70.01% – 76.88% and AF_{max} 94.64% – 101.55%. All differences between $\frac{AFiso_{max}}{pre-MVIC}$ and $\frac{AF_{max}}{pre-MVIC}$ (M and Max, t_1 and t_2) were significant ($p = 0.001$).

Very high correlations between AF_{max} and pre-MVIC were found (r = 0.97 – 0.98). Values were lower but still high if AF_{max} or pre-MVIC were correlated with $AFiso_{max}$ (r = 0.85 – 0.97).

$AFiso_{max}$ had higher coefficients of variation between single trials (≥ 24.92%) compared to those of pre-MVIC and AF_{max} (CVs ≤ 5.4%).

Considering the sub-question, MVICpri-con revealed significantly lower torques compared to pre-MVIC (p = 0.005 – 0.041) in exception of M torques at t_1. Post-MVIC was significantly lower than pre-MVIC on both days (p = 0.001 – 0.020).

Discussion:

By use of accelerometers for detecting movements of limb and lever, the new pneumatic device can determine $AFiso_{max}$ easier compared to its predecessor version (SeBit). A reference curve is not necessary anymore. In addition, the stick-slip effect was eliminated by using a frictionless bellows cylinder. The individualizable pressure increase is another advantage of the system.

Limitations are the slightly flattened force increases due to lever drive during the eccentric phase and the partly sudden force increase. A smooth start should be provided by a motor-controlled valve to give especially strong subjects a better chance to adapt to the external force. At last, the algorithm for the detection of $AFiso_{max}$ should be seen critically. For example, setting tolerance of 2° during yielding was necessary to deal with unavoidable slight elbow shifts. The algorithm seem to detect the breakoff point reliably. However, an influence on the variability of $AFiso_{max}$ cannot be ruled out completely.

According to the test-retest data, the refined pneumatic device can reliably quantify the AF. The measurement errors should be taken into consideration for future studies. Higher random error of $AFiso_{max}$ might be due to a higher biological variability.

AF_{max} occurred mainly during an eccentric muscle action. The yielding was very slow (2.31 ± 0.50 °/s) which might explain why AF_{max} did not exceed pre-MVIC. For assessing maximal force, both variables could be used.

In contrast, $AFiso_{max}$ could be differentiated from pre-MVIC even in healthy subjects. This finding supports the hypothesis of two isometric forms (HIMA vs. PIMA). Thus, it is suggested to assess the adaptive holding capacity separately from the pushing or pulling MVIC.

Due to high correlations to other maximal forces, $AFiso_{max}$ could be integrated into the conditional ability of strength (r^2 = 72.25 – 94.09%). It might depend on the maximal strength of a person but also the sensorimotor control in sense of adapting muscular length and tension to external forces. The higher complexity and higher neuromuscular demands within combined feedback and feedforward control mechanisms might explain why $AFiso_{max}$ was found to be lower and more variable compared to other muscular forces. Thus, a normalization to the MVIC or AF_{max} is reasonable. This might

serve as an indication of the functionality of the neuromuscular system. A high $AFiso_{max}$ might prevent muscles from an inappropriate lengthening and, therefore, injuries. Some measurements revealed that the muscle gave way before 50% of the maximal pushing isometric force (pre-MVIC) was reached. The appropriate size or relation should be investigated in future by considering subjects with musculoskeletal complaints. It is hypothesized that the holding muscle function in sense of AF is more vulnerable to inhibitory factors compared to a simple MVIC-test and might be an explanatory approach for the cause of musculoskeletal complaints.

Regarding the influence of a concentric contraction prior to an IMA, inconsistent results were found. Interpretations should be handled with care because systematic differences of MVICpri-con were found between t_1 and t_2 despite of low SEMs and high ICCs. Furthermore, mostly lower values compared to pre-MVIC might rather be explained by effects of fatigue than neuromuscular factors. If only subjects were considered who performed MVICpri-con before AF-measurements, there was no significant difference to discover. Lower post-MVIC compared to pre-MVIC torques also express possible central or peripheral fatigue after potentially exhausting eccentric muscle actions during AF-measurements. However, further examinations with a separate study design are suggested.

The objectivity is a big advantage of the pneumatic system but practical use is limited. Further research should also focus on a practical assessment of the AF which can be easily used in clinical settings. A hand-held device could be applied in daily routines during a manual muscle test (MMT) since AF can manually be assessed by an MMT.

4.2 Assessment of the Adaptive Force by Use of a Manual Muscle Test

The special holding function of a muscle or muscle group (AF) can be assessed by the previously introduced pneumatic device. The standardized external force application is independent of the rater. However, the assessment requires high expenditure of time making clinical practice unfeasible. Another possibility to assess the AF is to measure forces and movements during an MMT [143,144]. The MMT should be outlined in the following since its principle is the basis of AF-measurements.

MMTs were firstly applied by Lovett and his colleagues with patients suffering from infantile paralysis as mentioned by Wright (1912) [145]. The test result was documented by numeric but subjective scores. Based on this idea several others, e.g., Lowman [146], Daniels, Williams and Worthingham [147], Medical Research Council [148], Janda [149], refined the method of testing and rating. However, during these MMTs the patient initiates the muscle action (≙ make test, comp. PIMA) and does not react and adapt to an external force (≙ break test, comp. HIMA). Thus, the holding function of a muscle is not tested. In order to deliver a quantification instead of subjective rating, Martin and Lovett described the spring balance test [150–152]. For that, a break test was performed. The measurement accuracy depends on exact readings of the spring balance scale at the moment when the limb gives way due to the pull of the examiner.

Based on Lovett's work, Kendall and Kendall described an MMTs which also tests the holding muscle function during a break test [153–155]. The alternative to perform a break test was also marginally mentioned by Daniels, Williams and Worthingham (1947) due to its simpler and quicker application especially with children [147]. In newer editions of this book, the break test became the dominant form of muscle testing [156]. Testing the holding function needs an external force like gravity or pressure (formerly termed as "resistance") [154]. "Pressure is used to denote the outside force applied by the examiner to determine the strength of the muscle holding in test position" (Kendall & Kendall, 1949, p. 7 [155]).

According to the descriptions in the international 5th edition of their book "Muscles Testing and Function with Posture and Pain" [157], which is used as gold standard, the examiner positions the patient in a way that the tested muscle is activated as isolated as possible from synergists. The respective muscle contracts in dependance of its function and testability partially or completely. Subsequently, the adjusted position should be held against gravity or additional EF applied by the examiner. The examiner assesses the muscle activity. Holding the position against gravity is rated as "sufficient" ("fair", or a numeric equivalence) activity. This rating is the most objective one. For assessments better than "sufficient", an EF of the examiner is necessary. The force rise needs to be "gradually" to give the patient a chance to adapt to the increasing force and consequently to hold the position. Such way of testing assesses the holding function of a muscle against an increasing EF. If the muscle can resist to an adequate force level or not is judged by experiences of the examiner. For description of the whole grading see [157]. The principle of such MMT is used by different healthcare professionals, especially Applied Kinesiologists [158,159], in daily practice. However, the subjectivity might be a hindrance for scientific purposes.

Henry O. Kendall designed one of the first analog hand-held devices already in 1941 to record forces during the MMT [157]. In the following, several other hand-held dynamometers were developed and used to assess intra- and intertester reliability of the applied EF of an MMTs in sense of break test [160–163] as well as validity of the MMT [164,165].

However, not only the maximal applied force but also the force rise during an MMT needs to be reliable within and between examiners. The reproducibility of force profiles during the MMT is an essential prerequisite for valid tests results which was tested [166]. Examiners with different MMT experiences (beginner, little experienced, experienced) showed dissimilar force profiles created against a fixed limb in order to exclude the influence of the patient [166]. Intra-individually, a low reproducibility was found even for some experienced testers [166]. However, some subjects of the beginner group showed a high reproducibility. These results indicate a need of standardization and practicing of the MMT. The training of force application should be conducted without a patient at first since the motor tasks gets more complex during such interaction. A suggestion for a standardized force profile during a MMT was proposed by Bittmann et al. (2020) [166].

During a break test, force measurements alone cannot give any information if the patient is able to hold a desired position against the examiners applied external force. Thus, it is not clear if the muscle action is isometric or merges into an eccentric one. It was shown that the reaction force between subject and examiner rises during yielding (eccentric phase) [144]. To capture AF, force as well as position or movement of a tested body part must be measured. Consequently, the moment of yielding (break off point) and the respective force ($AFiso_{max}$) can be determined. This might be the key variable in assessing the holding muscle function.

A prototype has been constructed to unify force and kinematic sensors within one hand-held device for a simultaneous recording of force and position of the tested body part [166]. By use of such devices it is possible to assess the AF in clinical settings and deliver a basis for advanced diagnostics but also for integrative research approaches, e.g., in medicine, psychology, health, sport and nutritional science as previously indicated by recent articles [167–169].

5 Overall Discussion

Isometric muscle function can differ visibly in respect of the performed task. The underlying muscle actions (HIMA and PIMA) have been partly distinguished by objective parameters. The presented four original articles, i.a., added data in this field of research and confirmed the hypothesis that HIMA and PIMA are differentiable. On the one hand, TTF tended to be shorter during HIMA compared to PIMA at moderate intensities. On the other hand, maximal forces differed between an exerted special form of HIMA (AFiso) and PIMA. Another research group has found that HIMA performed at constant loads (HIMA) was not significantly different from PIMA [103]. By combining these results, it is suggested to differentiate not only between HIMA and PIMA but also between a HIMA in sense of an adaptation to constant loads and an adaptation to varying or increasing loads (AFiso). However, more studies with greater sample sizes are indicated.

The found differences in TTF (HIMA < PIMA) and maximal force (AFiso < PIMA) might primarily be attributed to neuromuscular factors. Since differences on metabolic level cannot be excluded, oxygenation might serve as an approach to explain results. Muscle function depends highly on energy supply and, therefore, oxygen delivery to muscle tissue. Thus, it is reasonable to discuss related insights first. Subsequently, the discussion focuses on neuromuscular aspects with regard to fatigue resistance and maximal generated force during different isometric muscle actions. At the end of the chapter, an outlook is given and limitations of the methods are discussed.

5.1 Recent Insights of Muscle Oxygenation under Isometry

An exclusively anaerobic energy supply is not very likely during fatiguing IMA of 60% MVIC and TTFs of about 30 s to 60 s achieved by subjects in the presented studies (publications 1 – 3).

Furthermore, anaerobic and aerobic metabolism is activated simultaneously during exercises (comp. chapter 1.2) [54,55].

The studies 1 – 3 revealed that an isometrically working biceps brachii muscle seems to be sufficiently supplied with oxygen and blood at least in the recorded superficial muscle tissue. During submaximal and even during maximal efforts, an increase in microcapillary blood content (rHb) partly occurred (type II behavior). This indicates a maintained blood supply for both submaximal and maximal IMAs. The heterogenous behavior of rHb can most likely be explained by the oxygen saturation level (publication 2). The suggested threshold of about 59% SvO_2 might trigger the blood regulation in order to prevent a further deoxygenation. Although such on-off mechanism is seldom seen in biological systems, presented data showed that this approach is comprehensible. It was further shown, that the modality of IMA probably does not play a role in the behavioral pattern (publication 3).

The findings of a sufficient oxygen and blood supply during short maximal and fatiguing submaximal IMA are partly in conflict with other opinions and studies which especially examined calf muscles. In those, blood flow was found to be decreased under conditions of isometry [76,80,113]. Regardless of methodological differences, the behavior might be specific to muscle and / or fiber type composition as already argued [77,78]. It was further stated that conflicting results between previous studies might partly be explained by differences in intramuscular pressure which is higher during shortening contractions compared to isometric ones [78]. However, the authors have been aware that it does not account for study designs including IMAs only [78].

Another approach might be that capillaries are not necessarily compressed during contraction as generally accepted (publication 2). This is in contrast to others who have argued that blood flow in muscle tissue is restricted in proportion to the intramuscular pressure [80,86–88,111]. Increasing tissue pressure is even correlated with a reduced nerve function in relation to compartment syndrome [170]. In contrast, it was suggested that nerves and capillaries might be protected from the arising intramuscular pressure by considering their geometrical configuration within muscle tissue as well as the oscillating character of muscle fibers during IMAs. The arguments are supported by histological data [171–173] and the described squeezing effect of intermittent contractions (skeletal-muscle pump) [75], with frequency of 10 – 15 Hz [32–38].

Increase of local muscular blood flow is thought to be centrally driven by higher cardiac output and redistribution of blood [174–177]. The latter is regulated by arterioles containing smoothed muscles for control. A homogenized and redistributed blood flow according to the longitudinal recruitment theory can serve as an understanding of the hemodynamic regulation of capillaries [175,177–180]. Bringing this together with the proposed 59%-threshold, SvO_2-level or – in other words – a specific level of hypoxia might lead to a release of nitric oxide. NO is thought to be the primary stimulus of

vasodilation [181]. Sophisticated research designs with multiple methods are necessary in future to test if those suggestions hold true for IMA.

5.2 Fatigue Resistance of different Isometric Muscle Actions

The influence of energy metabolism on muscle function can especially be expressed by local muscle fatigue [47,52]. It might occur earlier if demanded oxygen supply is lacking during contraction [112]. However, oxygenation does not predict muscular endurance alone. The found low correlation of time to task failure (TTF) and the extent of deoxygenation suggest a possible independence of fatigue by the muscle oxygenation level as long as it does not reach zero. This is especially reasonable by considering the occurred steady state behavior of SvO_2.

Steady states indicate a balanced oxygen demand and supply. A rapidly increased oxygen consumption at the onset of muscular work probably leads to an initial decrease in SvO_2 and might be compensated by biological system. It is even reasonable that fluctuations in SvO_2 are not counteracted immediately to prevent frequent adjustments in vascular tone (blood flow regulation) [176]. Otherwise, a delay could be explained by slow regulation processes. Nevertheless, as long as oxygen saturation in muscle tissue is not critically low, muscle fatigue (TTF) might rather depend on other factors.

Muscle fatigue is a highly debated issue without scientific consensus. It is thought to occur either centrally (impaired α-motoneuron activation [182]) or peripherally (impaired intramuscular contractile function [52]). Several factors have been related to both forms [52,182,183], which should not all be discussed in detail here.

As reviewed by Westerblad and colleagues (2010) [52], Ca^{2+}-sensitivity or -release rather explains peripheral fatigue than the occurrence of acidosis or reactive oxygen species. Isolated muscle fibers showed a decrease in cross-bridge force generation possibly depending on a decreased Ca^{2+}-release during fatiguing stimulation [52]. It is argued that such regulation prevents a critical ATP concentration (danger of permanent rigor state) as soon as metabolic exhaustion emerges or inorganic phosphate concentration is too high [52].

It is controversial if central fatigue is involved during contractions especially during moderate to high intensities [52]. However, impairment of α-motoneurons could also be triggered by the high intramuscular pressure if the supplied muscle elicits a reflex inhibition or if intrafusal signaling support is deficient [41]. Furthermore, neuromuscular fatigue is, among other measurable changes, accompanied with the force (or work) generating capacity [183]. According to the found shorter TTFs during HIMA compared PIMA in the presented third study and previous ones [34,35,90,91,105,107,108], fatiguing factors might differ or be differentially modulated.

A dissimilar neuromuscular control as potential reason was discussed as well [34], although some studies revealed no significant difference [90,91,108]. This hypothesis was based on the assumption that HIMA is closer related to eccentric muscle work and PIMA, by contrast, to concentric one [34]. The eccentric muscle action was associated with a more complex control strategy than concentric muscle actions [44–46,184]. This might explain the frequently found shorter TTF during HIMA on condition that the basic assumption is correct.

The assumption of a proximity of HIMA to eccentrics as well as of PIMA to concentrics was used regarding the sub-question on the influence of intermittent short and rapid muscle twitches during a weight holding task (Twitches) (publication 3). Pure weight holding is associated with HIMA and Twitches possibly with PIMA due to the concentric phases in between [34]. The comparison revealed a significantly longer TTF for Twitch compared to HIMA. This result would fit to a longer TTF during PIMA compared to HIMA – still under the assumption as mentioned above. It also indicates, that weight holding or position tasks might be influenced by concentric contractions. Such contractions probably occur to correct for position deviations in a freely moving system.

A reasonable criticism could be that HIMA is not a real isometric muscle action due to the quasi-static character. Thus, the termination “position hold” [48] or position task [90] is comprehensible. Sittig et al. (1987) proposed that PIMA is the (real) isometric contraction task and HIMA, by contrast, a movement task with zero velocity [185]. It could further be argued that there is no real isometry in working muscles [186], since slight oscillations with minimal shortenings and lengthenings occur [32–38]. Thus the term “homeometry” was proposed [186].

With regard to the oscillatory behavior, different MMG and EMG amplitudes at exhaustion have been discussed to explain a shorter TTF during HIMA (comp. chapter 1.3) [34]. The higher amplitudes during PIMA have been interpreted to support metabolic environment [34]. This line of arguments show that neuromuscular factors could be interrelated with metabolic ones and might suggest that there is not only one exclusive reason for longer TTFs during PIMA.

Despite little muscle oscillations as considered above, a control or prevention of switching into a significant concentric contraction during a holding task would be appropriate. Such a control was provided by use of the introduced measurement system for the detection of the Adaptive Force (publication 4). An AF measurement requires a special form of HIMA. For that, a person has to adapt to an increasing external force. This might be a more sensitive approach to detect differences between HIMA and PIMA compared to the usage of constant loads.

5.3 Isometric Voluntary Contraction vs. Isometric Adaptive Force

The measurement of isometric force endurance (e.g., by TTF) can be complemented by measuring the maximal isometric force capacity since both conditions are of relevance in daily activities. These often require an adaptation to external loads. If the maximal force capacity of a muscle is lower than

the external impact, respective joints are not stabilized adequately. Thus, not only the MVIC which is commonly accessed by PIMA, is relevant. The fourth study showed that under conditions of an externally applied force a muscle or a muscle group often starts to lengthen before the respective force level of the MVIC is reached. Thus, the load-bearing capacity during an adaptive holding ($AFiso_{max}$) might be lower compared to an initiating pushing or pulling one (MVIC). The latter does only require adjustments of tension and not of length which could be a key in the understanding of different control strategies.

Furthermore, $AFiso_{max}$ also varies much more than the MVIC. This could be fateful in only one individual case. Such considerations could possibly serve as an approach to understand, why highly trained athletes get injured even during actually harmless strains (comp. non-contact traumata). That does not mean that an injury always follows to a low $AFiso_{max}$. However, the probability might increase especially if a low $AFiso_{max}$ is a general condition.

A reduced $AFiso_{max}$ despite a normal muscle function under PIMA conditions might be associated with a higher sensitivity to afferent signals during length regulation. This might be supported by studies which examined hand muscles. In comparison to a force control task, reflex responsiveness as well as stretch evoked stiffness increased to a greater extent with increasing force in position control particularly with unstable mechanical loads [95]. Moreover, long latency reflex responses to an evoked stretch seem to be greater during a position task (whereby external force was changed) than a force task (changed position) [93]. These findings indicate that the holding muscle function (inclusive of AFiso) might have such an increased sensibility to afferences. These could be, e.g., nociceptive signals or mental strains which affect the α-motoneuron pool during the force-length comparison via involvement of supraspinal pathways [166]. Such inhibitions would result in a control error and consequently muscle instabilities.

Based on the results of the fourth study it is suggested the $AFiso_{max}$ or its ratio to the MVIC or the AF_{max} should be quantified separately to or in addition to the MVIC since it could serve as an indicator of the functionality of the neuromuscular system and subsequently in the prediction of injuries or musculoskeletal complaints. As an advantage of using a ratio as normalization of $AFiso_{max}$, no reference values are necessary.

5.4 Outlook – Clinical Assessment of the Isometric Adaptive Force

Another possibility and more practical way to assess the neuromuscular holding function ($AFiso_{max}$) is by use of an MMT in sense of a break test. During this kind of MMT, the tested person (patient) has to adapt to the varying force applied by the examiner (tester). As long as the forces of the patient and tester are equal, the muscle action is isometric. Consequently, two different isometric modalities work against each other: PIMA by the tester and HIMA by the patient.

In contrast to Daniels et al. (1947) [147], Schmidt and Rogers (1982) have argued a make test is easier to perform compared to a break test and, therefore, it is more reliable [187]. A recent study of our research group showed that in individual cases, experienced testers could reveal insufficient reliable force profiles during a MMT against a fixed limb [166].

The reproducibility of force profiles is an essential prerequisite for valid tests results. Most experienced testers (n = 6 of 9) and surprisingly some beginners (n = 2 of 12) have fulfilled strict requirements of reliability [166]. Little experienced testers (n = 8) have not reached high reproducibility between their ten force profiles. The results indicate the need of practicing the MMT especially for beginners and little experienced testers. The introduced hand-held dynamometer can easily be used to control the force profiles [166]. Even some experienced testers might benefit through training of their sensorimotor skills. The training of force application should be conducted at first without a patient since the motor tasks gets more complex during such interaction. Furthermore, different styles of testing are expectable between examiners. In order to reach a higher acceptance of the MMT as a clinical tool in medicine and science, it has to be standardized. A suggestion for a standardization has been put up for discussion based on the average curves of two experienced testers.

During a real MMT the proposed force profile can only be achieved if the patient is able to maintain a stable isometric resistance. The maximal force level during the test can hardly be equal to the maximal force of the subject. It would always be lower unless the maximal holding capacity of the patient is broken by the applied force. The test could be rated as positive, i.e., patient gives way in a binary grading system. Measuring the exact force at the moment of giving way is a far better way of quantification. However, the applied force should also be high enough to detect a potential insufficient holding function of the tested muscle. An applied force close to the patient's maximum force avoids false negative test results. In this regard, the physical constitution of the patient needs to be taken into account. This points out the complexity of a real MMT and indicates more research based on the theory of the AF.

Future examinations could further address potential influencing factors on the Adaptive Force. The pneumatic device presented in the fourth study or the discussed hand-held device in conjunction with an MMT as a practical alternative can be used. Although parallel-test reliability remains, both devices are able to quantify AFiso reliably. In this regard complex biological links between muscle function and, e.g., emotions could be analyzed. Study approaches and first data were provided recently [167–169]. It could further be questioned if the holding muscle function is trainable. According to the presented high explained variance by other forces, AFiso is suggested to be integrated in the conditional ability of strength. Thus, it might be improvable by training as well. However, inhibitory afferences can – if present – not inevitably be resolved by training. Thus, the treatment of the cause of inhibiting factors must be on focus.

Nevertheless, there are musculoskeletal disorders with unknown causes. Adolescent idiopathic scoliosis serves as an example. The holding function of suffering patients is probably abnormal since bones are not aligned as usual (3D deformation). A training regime has been developed to train the holding function of scoliosis specific muscles by use of climbing exercises [188,189]. In an ongoing randomized controlled study, it is questioned if the special training regime has a compensatory effect on the spine. Results will be presented in near future.

5.5 Limitations

The first three studies had an explorative character. According to the low sample sizes, they should be seen as pilots. In contrast, the fourth study provided a power calculation. Multiple testing in the explorative studies was accepted [190,191]. Furthermore, the possibility of an increased type 1 error could be ruled out, because none of the oxygen variables showed a significant difference.

Oxygen saturation cannot be measured by a gold standard [192]. Regarding spectrophotometric measurements, the general main limitations must be noticed [126,127,135,136,193]: Although local capillary-venous blood mainly influences the recordings, arterial blood cannot be excluded completely [126,135–137]. Skin perfusion might confound signals in response to temperature rise during exercise but the influence is discussed controversially [127]. Furthermore, skin pigmentation and adipose tissue are relevant light absorbers [127].

In specific regard to the used probes with a source-detector separation of 14.5 mm, a maximal light penetration depth of 12 mm was reached. Thus, superficial muscle tissue was examined. Probably, the exact depth had varied between subjects. Subcutaneous fat levels were not determined. However, skin fold thickness on the anterior side of the upper arm was assumed to be low in the normal weighted participants. As indicated by pre-test, obvious thick layer of subcutaneous fat would not allow the sent light to reach into muscle tissue. All findings in regard of SvO_2 and rHb need to be interpreted by considering these limitations. Especially statements of deeper regions of the muscle should be reserved, where intramuscular pressure might be higher [86,194].

Furthermore, it should be noticed that elbow angles were visually assessed by the rater. Thus, TTFs and extents of twitches might have been influenced by that limitation. Since this is assumed to be a random error, the influence was expected to be low. Unbalanced orders of measurement series (HIMA vs. PIMA; HIMA vs. Twitch) caused by drop outs from the statistical analyses might have biased the results, especially the TTF due to effects of fatigue. Furthermore, it must be noticed that the human body is highly adaptable [195]. Effects of different training status but also gender or age were not analyzed within the research program and should be considered in future.

Regarding the fourth study, the Adaptive Force was rarely measured before and there seems to be no equivalence. Adequate measurement devices are not marketed, yet. Thus, a new one was introduced. Under theoretical static conditions, the force rise is fully standardized provided by the system.

However, expansion of the bellows cylinder reduces the pressure within the system and force slope flattens as a consequence. According to the individual dynamics of each trial, force slopes slightly varied in between. This, was accepted to capture the AF which prescribes a subject controlled movement velocity by concept [138,139]. The force increase might have been too abrupt for some subjects. This issue was already solved for future measurements by interposing a motor-controlled valve. At last, the determination of $AFiso_{max}$ might have been influenced by the limit values within the algorithm.

6 Proposals for further Research

According to the mentioned limitations, the presented studies do not provide complete evidence to draw final conclusions. However, the following proposals should be offered for scientific discourse:

- The behavior of local capillary-venous oxygen saturation (SvO_2) and relative hemoglobin amount (rHb) during maximal and submaximal isometric muscle actions should be differentiated into two types (publication 1).
- The type might depend on the level of deoxygenation. A threshold of about 59% is suggested which determines the increase in blood filling (publication 2).
- In contrast, the type is probably independent of the performed isometric task (HIMA or PIMA). In this regard, oxygen saturation might not serve as an objective parameter to distinguish the hypothesized two forms of isometry (publication 3).
- Muscle actions, even performed isometrically might not inevitably compress capillaries within muscle tissue as generally assumed. Thus, blood flow could be maintained and could even increase. (publication 2)
- As a consequence, oxygen demand of superficial muscle tissue might be supplied sufficiently during maximal and submaximal IMA (HIMA and PIMA) as indicated and shown by homeostatic steady states (publications 1 – 3).
- Intermittent voluntary muscle twitches do not substantially support the oxygen and blood supply during a weight holding task. However, the time to task failure (TTF) was found to be longer compared to weight holding alone. This might be caused by a changed neuromuscular control which remains highly speculative (publication 3).
- PIMAs could possibly be maintained longer compared to HIMAs not only at low but also at moderate intensities (publication 3).

- TTF is probably independent of the extent of deoxygenation as long as this is not critically low. (publication 3)
- It is hypothesized that a prior concentric contraction to an MVIC-test does not influence its result (publication 4).
- AF measures ($AFiso_{max}$ and AF_{max}) can be assessed reliably by a pneumatic device (publication 4).
- $AFiso_{max}$ could be integrated into the conditional ability of strength. However, its biological variability is higher compared to other maximal forces (publication 4).
- In relation to AF_{max} or MVIC, the $AFiso_{max}$ could be a relevant parameter in assessing muscular function. It is understood as an indicator of the functionality of the neuromuscular system to adapt adequately to external forces (publication 4).
- If the adaptive holding capacity of a muscle is very low, related joints might be stabilized insufficiently and injuries or other musculoskeletal complaints might follow (publication 4).
- The clinical assessment of $AFiso_{max}$ by use of a hand-held device during an MMT could be a practical alternative to the introduced pneumatic device. Reproducible force rises provided by the examiner are an essential prerequisite for valid test results (overall discussion).
- It is suggested to differ not only between holding and pulling or pushing isometric muscle actions but also between an adaptation to constant loads and to varying or increasing loads (overall discussion).

7 References

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8 Scientific Publications

In the following, articles and supplementary materials are presented exactly as they have been published.

8.1 Publication 1: Behavior of Oxygen Saturation and Blood Filling in the Venous Capillary System of the Biceps Brachii Muscle during a Fatiguing Isometric Action.

Citation:

Dech, S., Bittmann, F., & Schaefer, L. (2020). Behavior of oxygen saturation and blood filling in the venous capillary system of the biceps brachii muscle during a fatiguing isometric action. *European Journal of Translational Myology*, *30*(1), 79-87. https://doi.org/10.4081/ejtm.2019.8800

Behavior of oxygen saturation and blood filling in the venous capillary system of the biceps brachii muscle during a fatiguing isometric action

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Abstract

The objective of the study was to develop a better understanding of the capillary circulation in contracting muscles. Ten subjects were measured during a submaximal fatiguing isometric muscle action by use of the O2C spectrophotometer. In all measurements the capillary-venous oxygen saturation of hemoglobin (SvO_2) decreased immediately after the start of loading and leveled off into a steady state. However, two different patterns (type I and type II) emerged. They differed in the extent of deoxygenation (–10.37 ±2.59 percent points (pp) vs. –33.86 ±17.35 pp, p = .008) and the behavior of the relative hemoglobin amount (rHb). Type I revealed a positive rank correlation of SvO_2 and rHb (ρ = 0.735, p <.001), whereas a negative rank correlation (ρ = –0.522, p <.001) occurred in type II, since rHb decreased until a reversal point, then increased averagely 13% above the baseline value and leveled off into a steady state. The results reveal that a homeostasis of oxygen delivery and consumption during isometric muscle actions is possible. A rough distinction in two types of regulation is suggested.

Key Words: muscle oxygenation, hemoglobin amount, isometric muscle action, O2C spectrophotometer

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Isometric muscle actions play an essential role in daily activities which include posture or static work. During that type of muscular activity the intramuscular pressure increases proportionally to the maximal voluntary isometric contraction (MVIC).[1-4] According to some authors, the resulted mechanical pressure might impede the blood flow within the muscle, which is essential for an adequate oxygen supply.[1-3,5] The blood flow could already be restricted at intensities of 15% MVIC.[2] The comparison of studies which examine the relationship between muscle tension and blood flow is difficult because of an extensive range of methodologies and measurement techniques. Thus, it is still unclear which relative or absolute contraction intensity possibly causes a restriction or even a complete occlusion of the capillary vessels.[6] But if the inflow is restricted or occluded the available oxygen ought to be depleted over time. As a result, the saturation might decrease to zero (complete deoxygenation).

Several studies examined the oxygen saturation of different muscles during sustained isometric contractions with various intensities and exercise durations. Most of them used the near infrared spectroscopy technique (NIRS), which primarily reflects the oxygen saturation of small veins (<1 mm diameter).[7] The principle and other limitations are described elsewhere.[7-9] Disregarding methodological inconsistencies, two different tendencies are described or shown graphically. On the one hand, the muscle oxygenation decreased and leveled off into a steady state after a certain time.[10-17] This implies that the saturation stays nearly constant over time. On the other hand, it decreased continuously or in a phasic way with different decay rates until termination of the exercise.[17,19,20-25]

According to Sadamoto and colleagues (1983)[1] a stopped outflow during isometric contractions due to a possible venous stasis should be considered, too. This could be verified by measuring the hemoglobin concentration as an indicator of the blood filling. In most cases, the total hemoglobin amount measured by the NIRS method decreased and behaved like the oxygen saturation.[10,11,21,24,25,27] However, there are also research groups which found an increase after an initial decrease,[17,20,28] or a direct increase after the start of load.[17,18,29] Inter-[19] and intra-individual differences were also found.[17]

Because of the inconsistencies mentioned above, the results should be verified by use of the diagnostic device O2C (Oxygen To See; LEA Medizintechnik GmbH, Gießen, Germany). In contrast to the NIRS technique, O2C is able to detect only very small vessels (<100 µm diameter).[30] Thus, measurements mainly represent the capillary-venous oxygen saturation of hemoglobin (SvO_2) and the relative hemoglobin amount (rHb) per local tissue volume. The device is usually used for non-invasive determinations of oxygen supply in microcirculation of blood perfused tissues and commonly applied in surgery like organ or flap transplantations, monitoring processes of diabetic foot or arterial occlusive diseases.[31,32]

This study questions how SvO_2 and rHb behave in muscle tissue during a fatiguing isometric action despite a potentially stopped blood flow.

Materials and Methods

Subjects

The left arm of seven male and three female healthy Caucasian volunteers (mean age ±SD = 28.6 ±11.68 years) were examined. They included students, colleagues of the University of Potsdam and local acquaintances. The exclusion criteria were any kinds of chronic or acute health problems. The participants weighted 70.2 ±11.8 kg on average and were 176.3 ±8.6 cm tall. Based on the BMI (22.44 ±2.19 $\frac{kg}{m^2}$) everyone was normal weighted. The study was conducted according to the declaration of Helsinki and local ethical permission was given. All subjects were informed in detail and gave their informed written consent to participate.

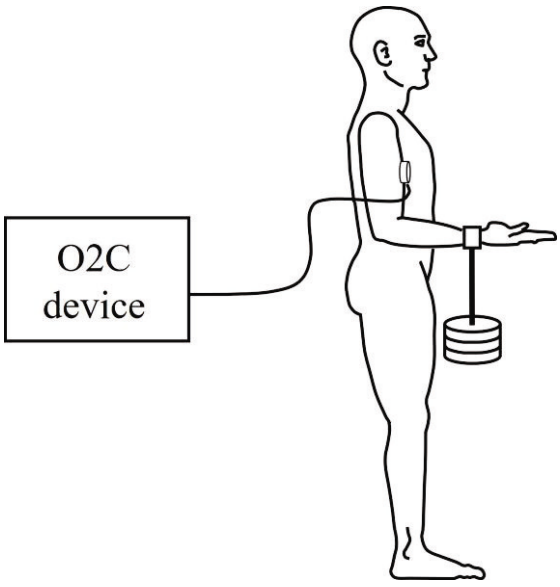

Fig. 1 *Measurement position and set up.*

Measuring technique

The non-invasive O2C device was utilized to record SvO_2 in % and rHb in arbitrary units (AU). A calibration with another method measuring e.g. milliliter per gram of tissue is missing. However, for this study the curveshape is more important than a quantitative comparison. The sampling rate was 40 Hz. Preliminary studies revealed that the device is valid, reliable,[31-33] and also applicable to muscle tissue at rest,[34] or during exercise.[35] The principle of the measurement relies on a combination of laser Doppler technique and tissue spectrophotometry (laser light: near infrared, continuous wave, power >30 mW; white light: 500-850 nm, 1 nm resolution). In this study, only the spectrometry for a detection of SvO_2 and rHb is relevant, whereby white light is sent into the tissue and the detection of different backscattered wavelengths of oxygenated and deoxygenated hemoglobin is used for their calculation. A detailed description of the techniques can be found in previous studies.[36-38] During all measurements the room light was dimmed to minimize light effects on the probe. We monitored the parameters in the muscle with a depth up to 12 mm. For this purpose, the measuring probe (LF3, separation: 16 mm) was directly stuck on the skin over the anterior side of the belly of the biceps brachii muscle and along its fibers by use of a double-sided adhesive film.

Setting and procedure

At the beginning the MVIC of each subject was determined. Six subjects pulled twice maximally on a fixed strain gauge (resting period: 2.53 ±0.33 min). These two MVIC-tests were recorded by the O2C device (sub-group analysis). The other four subjects should hold the highest possible weight for 1 s within maximal 5 steps. In both versions the arm position was identically to the subsequent fatiguing trial. For this, everyone had once to hold a weight of 60% of the MVIC until fatigue. This intensity was chosen to generate a high intramuscular pressure in order to ensure theoretically a nearly full occlusion of capillaries. Furthermore, it provides a loading duration which might be long enough for a maximal deoxygenation and short enough to minimize an early stop because of reasons of motivation.

Figure 1 illustrates the measurement position. The participant stood upright habitually. The upper arm was adducted, the forearm was supinated and positioned horizontally (90° elbow flexion). A cuff was applied 2–3 cm proximal to the wrist crease. The rater hooked the respective weight onto the cuff (hereinafter referred to as loading). Subjects were instructed to maintain the elbow angle for as long as possible. The weight was taken off as soon as the angle of the elbow exceeded 90° for more than two seconds, assessed by the rater subjectively. The measuring record started 10 s before loading and was stopped after two minutes of recovery.

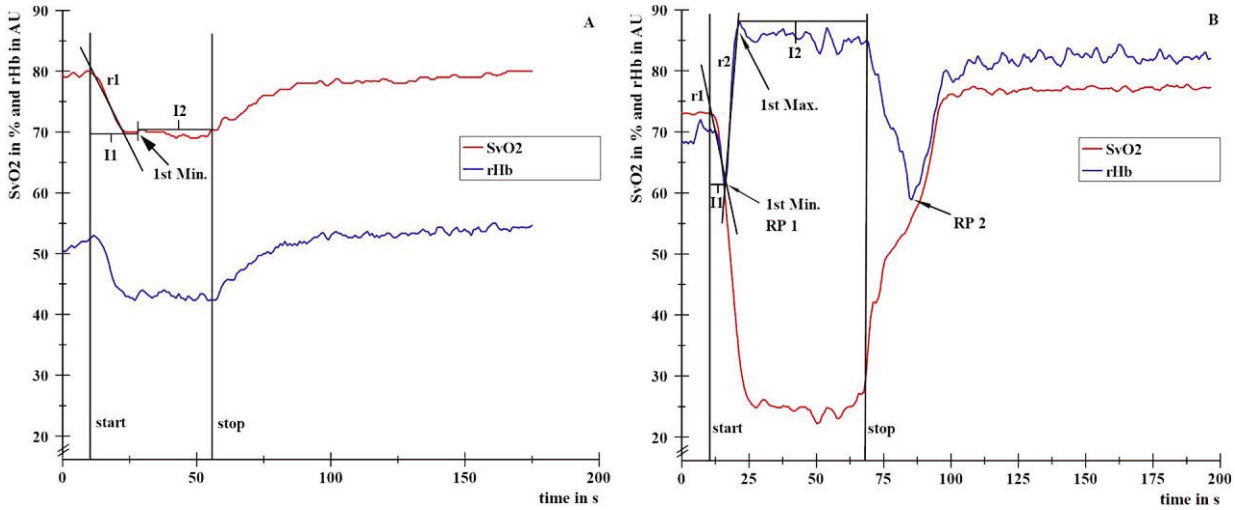

Fig 2. *Curve examples of the capillary-venous oxygen saturation of hemoglobin (SvO2) and the relative hemoglobin amount (rHb) in type I (**A**) and in type II (**B**) during a fatiguing trial of 60% of the MVIC. Start and stop of loading are indicated by vertical lines. The first (I1) and second (I2) interval, first local maximum (1st Max.) and minimum (1st Min.) or reversal points (RP1, RP2), respectively, and regression lines (r_1 and r_2) were set exemplarily in 2 curves. All curves are smoothed (moving average, maximal smoothing width: 50)*

Data processing and statistical analysis

The graphs of the raw data of the fatiguing trials and MVIC-tests were initially viewed in NI DIAdem™ 2012. For further calculations all curves were smoothed (moving average, maximal smoothing width: 50). To describe and cluster the patterns of behavior of the parameters (SvO_2, rHb) the following variables were analyzed:

i. coefficient of variations (CVs) of a possible steady state
ii. the slopes from start of loading to leveling off into a possible steady state
iii. the durations from start to the leveling off and to the end of the possible steady state
iv. extents of alteration in relation to baseline values

Firstly, two intervals were defined in each curve. The boundaries of the first interval (I1) were set from start of loading to the following first local minimum (1st Min.), Figure 2 A, left panel. The boundaries of the second interval (I2) were set in two different versions depending on curve progression. If the 1st Min. is equivalent to a reversal point (RP), i.e. a direct continuous increase follows the first interval, the start of I2 was set at the first local maximum (1st Max.) after the continuous increase (Figure 2 B, right panel). If a RP does not exist, the latter boundary of I1 (1st Min.) corresponds to the start of I2 (Figure 2 A, left panel). In both versions, I2 ends at stop of loading.

To analyze i, arithmetic mean (M) and standard deviation (SD) of all data points within I2 were calculated. Subsequently, the CVs within one subject were computed ($\frac{SD}{M} \times 100$). Furthermore, peak-to-peak amplitudes of the parameters within I2 and their calculated means and SDs were extracted.

Variable ii was quantified by least square regression line within the I1 (r_1) and additionally, between I1 and I2 if a RP exists (r_2). However, regression lines were calculated under exclusion of the leveling off phase. For this purpose, only data points according to the corresponding plateau of the first derivative were used for regression analysis.

For iii, M and SD are stated in seconds (s).

Concerning iv, baseline values were determined by averaging the initial 400 data points (10 s) in the unloaded measuring position. Alteration of parameters (extent of SvO_2 decrease (deoxygenation), extent of rHb decrease and increase, respectively) were obtained by calculating the differences from baseline values to the respective means of I2. They are presented in percent points (pp) for SvO_2, AU for rHb and additionally in % for both.

The statistical analysis was made by use of IBM SPSS Statistics, Version 22. All variables were tested for normal distribution by the Shapiro-Wilk-test. Since the data were not normally distributed, analysis of differences in curve patterns concerning the extent of deoxygenation were made by the exact Mann-Whitney-U-test. Confidence Intervals were estimated with the bias-corrected, accelerated method (BCa 95% CI). Effect sizes were expressed by Cramer's phi (φ). Correlations of the parameters of each curve pattern were determined by Spearman's rank correlation coefficients.

Results

The mean MVIC of all subjects was 279 ± 68.57 N.

Based on curve shapes, the behavior of SvO_2 and rHb during isometric actions could be differentiated into two patterns termed type I and type II. Figure 2 A and B illustrate the different types using typical examples. They differ in the curve shape of rHb and in the extent of deoxygenation. Five subjects were assigned to each type. All 3 female subjects belonged to type I. The BMI in type I was 21.89 ±2.54 $\frac{kg}{m^2}$ and 23.00 ±1.88 $\frac{kg}{m^2}$ in type II.

Type I: behavior of oxygen saturation and blood filling during fatiguing trials

SvO_2 and rHb behaved nearly parallel to each other, as illustrated in Figure 2 A. At the start of loading both parameters decreased immediately and leveled off after averagely 15.1 ±1.6 s. After the onset of recovery (after 49.72 ±12.35 s on average) both parameters approached to or increased above the baseline value, respectively.
The average CV of I2 within subjects was 1.19 ±0.75% in SvO_2 and 1.89 ±0.72% in rHb. The peak-to-peak amplitude of I2 within subjects amounted averagely 2.45 ±1.37 pp (min.–max.: 1.36–4.74) in SvO_2 and 3.39 ±1.14 AU (min.–max. 1.72–4.75) in rHb.
The slopes (ii) amounted averagely r_1 = –1.69 ±0.92 for SvO_2 and r_1 = –1.83 ±0.47 for rHb.
SvO_2 decreased by an average of –10.37 ±2.59 pp (≙ –13.38 ±2.75%) and rHb decreased averagely –11.17 ±6.3 AU (≙ –18.22 ±9.03%) below its baseline value.

Type II: behavior of oxygen saturation and blood filling during a fatiguing trial

SvO_2 and rHb showed a partial opposing behavior to each other, as illustrated in Figure 2 B. SvO_2 decreased immediately with an average slope of r_1 = –3.31 ±1.26 and leveled off after averagely 15.55 ±3.23 s. At the onset of recovery (after 41.89 ±14.10 s on average) it approached to or increased above its baseline value. On the contrary, rHb decreased immediately to a reversal point (RP) with an average slope of r_1 = –2.65 ±0.88. Directly after this turning point it increased with a slope of r_2 = 4.81 ±1.55 on average and leveled off at nearly the same time as SvO_2 did. During recovery rHb again decreased immediately to a second reversal point (RP 2) before it increased up to its baseline value or higher.
The average CV of I2 within one subject was 2.11 ±1.59% in SvO_2 and 1.41 ±0.75% in rHb. The peak-to-peak amplitude of I2 within subjects in SvO_2 and rHb amounted averagely 2.67 ±1.77 pp (min.–max.: 0.93–5.15) and 3.58 ± 1.80 AU (min.–max.: 1.75–5.44), respectively.
SvO_2 decreased averagely –30.86 ± 17.35 pp (≙ –41.46 ± 22.4%). The rHb increased 9.03 ±10.48 AU (≙ 13.28 ± 15.66 %) on average over its baseline value.

Behavior of oxygen saturation and blood filling during MVIC-tests

During the 12 recorded MVIC-tests out of a sub-group of six subjects SvO_2 generally decreased, followed by an immediate or a little delayed increase after stop of the test to the baseline value or higher, respectively. Nevertheless, the two patterns of behavior also occurred and were consistent within each subject. Figure 3 A and B show typical examples. Except for one subject, everyone was grouped in the same type as referred to the fatiguing trials.

Comparison of type I and type II

The curve shapes of SvO_2 of both types were similar to each other. However, 1. the extent of deoxygenation and 2. the behavior of rHb were different.
Concerning 1, arithmetic means and SDs of the extent of deoxygenation during loading of 60% of the MVIC are

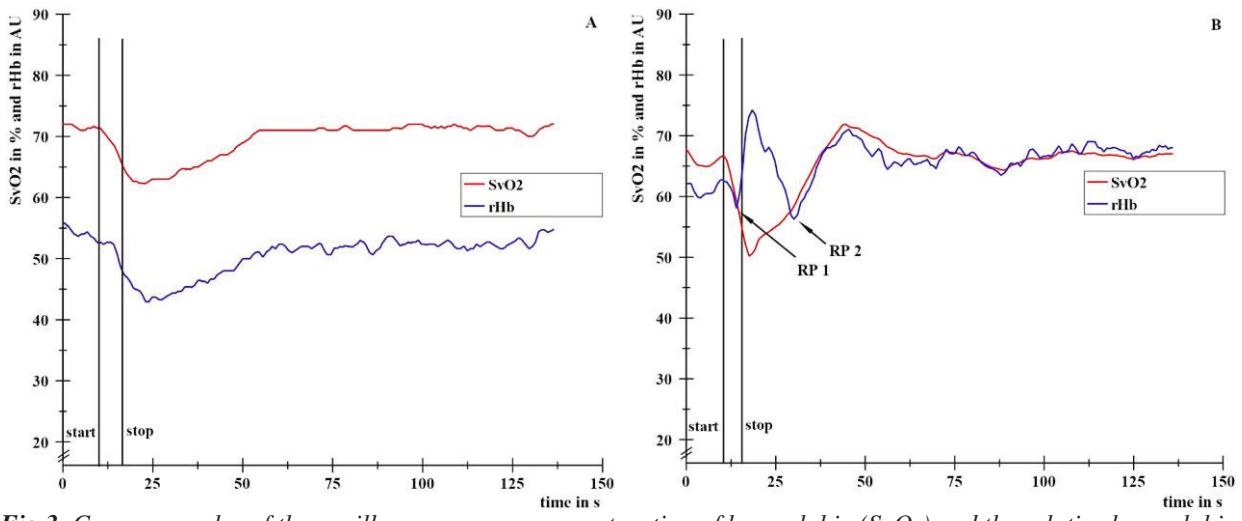

Fig 3. *Curve examples of the capillary-venous oxygen saturation of hemoglobin (SvO_2) and the relative hemoglobin amount (rHb) in **type I (A)** and in **type II (B)** during a MVIC-test. Start and stop of loading are indicated by vertical lines. All curves are smoothed (moving average, maximal smoothing width: 50)*

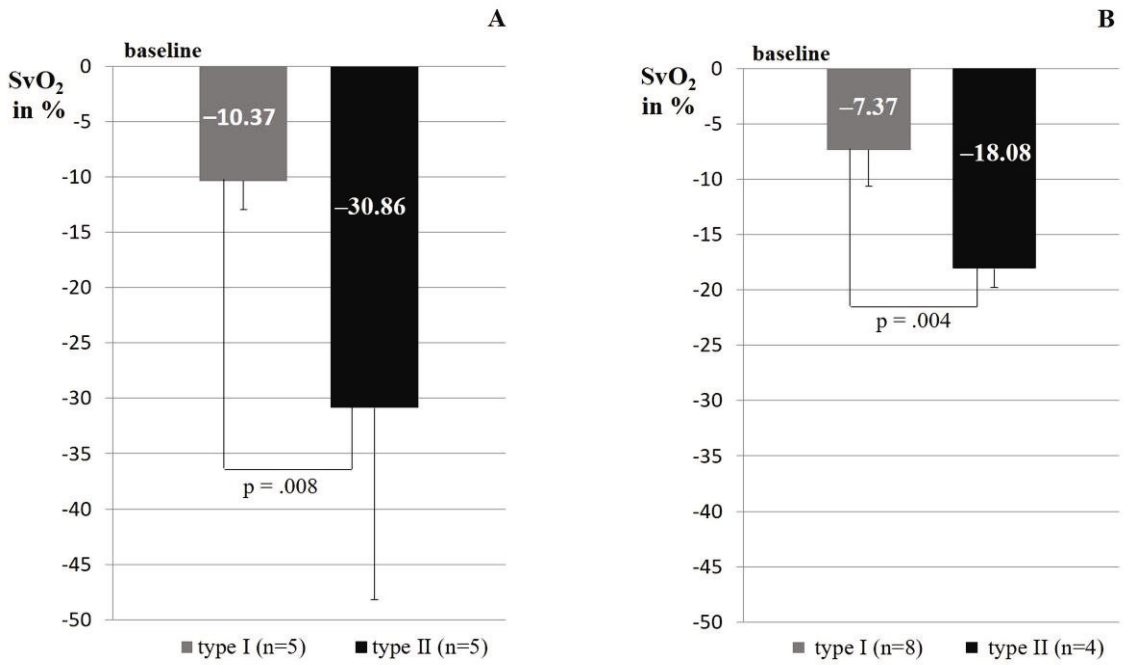

Fig. 4 *Means of the extent of deoxygenation during fatiguing trials at 60% of the maximal voluntary isometric contraction (MVIC) in type I (BCa 95%CI = –7.93 to –12.16) and type II (BCa 95%CI = –17.26 to –44.15) (**A**); and during MVIC-tests in type I (BCa 95%CI = –5.02 to –9.69) and type II (BCa 95%CI = –16.64 to –18.97) (**B**); Vertical lines express standard deviations.*

shown in Figure 4 A and during the MVIC-tests in Figure 4 B with stated BCa 95% CIs. The rank sums of extents of deoxygenation differed significantly between the types in the fatiguing trials (U = –2.61, p = .008, φ = .37) as well as in the MVIC-tests (U = –2.72, p = 0.004, φ = .79).

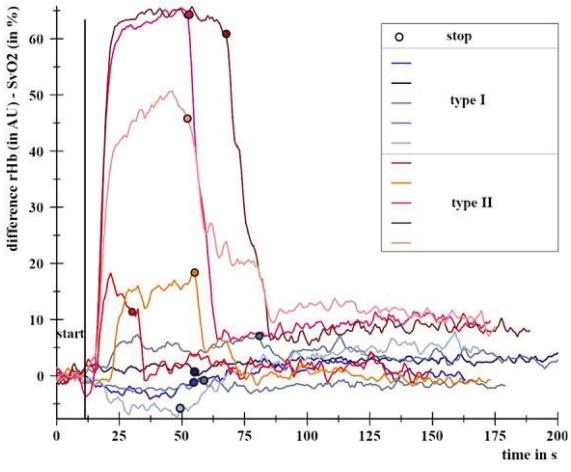

Fig 5. *Differences of the raw data between the relative hemoglobin amount (rHb) in AU and the capillary-venous oxygen saturation of hemoglobin (SvO_2) in % of the fatiguing trials (n = 10). All curves are smoothed (moving average, maximal smoothing width: 50)*

Concerning 2, type I had a positive rank correlation of SvO_2 and rHb from start until stop of loading with ρ = 0.725, p < .001 on average. In contrast, SvO_2 and rHb in type II were negative correlated (ρ = –0.522, p < .001). To illustrate the different types, Figure 5 shows the differences between rHb and SvO_2 of all measurements.

Discussion

The authors suggest a distinction of two behavioral patterns (type I and type II) of oxygen saturation and blood filling of the venous microvessels during fatiguing isometric muscle actions. The crucial difference is the nearly parallel behavior of SvO_2 and rHb in type I expressed by a positive rank correlation and in contrast, the partial opposing behavior in type II with a reversed rank correlation.

A steady state of the considered parameters is characterized as an equilibrium of demand and supply with natural fluctuations. The presented within subject CVs of SvO_2 (0.31–4.33%) and rHb (0.5–2.88%) during the defined I2 seem to be low enough for a characterization as a relative equilibrium. Hence, I2 is interpreted as a steady state behavior found in every parameter of the fatiguing trials. Moreover, the peak-to-peak amplitudes of values within I2 up to maximal 5.15 pp in SvO_2 and 5.44 AU in rHb are interpreted as biological variability. This implies, that a homeostatic

adjustment of the oxygen saturation and blood filling during isometric actions would be possible despite a high intramuscular pressure, which was detected by other research groups and inferred as a cause of flow restriction.[1,3-5]

Measuring technique

In contrast to other research groups, we used the O2C device. The system unifies laser Doppler flowmetry and white light spectrophotometry. Both techniques combined in the device meet the quality criteria.[31-33] The advantage of the O2C device is the detection of SvO_2 and rHb of only very thin venous vessels. Blood vessels with a diameter greater than 100 µm have no significant influence on the measurements. Because of the high hemoglobin amount, they would absorb the light virtually completely.[30] In contrast, caused by the greater wavelength of the released light (700 to 900 nm), the NIRS method includes the oxygen saturation of larger vessels (<1 mm diameter).[7] The comparison with the inconclusive results from other studies has to be interpreted considering this fact.

Results of oxygen saturation in comparison with other studies

In the presented study SvO_2 decreased during the MVIC-tests, particularly in type II, less than during the fatiguing trials at 60% MVIC. This could be explained by the shorter loading duration but is still speculative because of the low sample size. The MVIC-tests lasted approximately 4 s compared to more than 40 s in the fatiguing trials. During such a short loading time a maximal deoxygenation might not be possible. The SvO_2 of the MVIC-tests also showed no steady state behavior but a decrease to a reversal point and an immediate or a little delayed increase during recovery. This is comparable with findings of Maguire, Weaver and Damon (2007).[42] It might be necessary to sustain a load over a longer duration and consequently, submaximal intensities seem to be required in order to reach a steady state. Our results revealed durations between start of loading and leveling off into a steady state in both types of approximately 15 s. Studies which did not limit a loading duration and recorded muscle oxygenation until volitional fatigue are rare.[11,17,18,25] In investigations with a shorter measuring time, it is not clear whether the saturation would level off into a steady state or would decrease further on.

Fryer *et al.* (2014) observed a significantly higher extent of oxygen consumption measured by NIRS in elite climbing athletes compared to controls, intermediate and advanced groups.[25] In conclusion, the extent of deoxygenation might depend on the fitness level. However, in their study the oxygen saturation neither decreased to zero nor leveled off into a minimal physiological steady state until volitional fatigue occurred. Kell & Bhambhani (2008) also registered a continuous decrease of the muscle oxygenation albeit only after a slight increase.[18] The results of both studies mentioned above do not correspond to the findings of the presented study. We recorded an immediate decrease at the onset of loading and a leveling off into a steady state followed by an approach to or an increase above the baseline values when the loading was stopped. A steady state behavior was also found in studies with limited loading durations[10,12,16] and during fatiguing isometric muscle actions.[11,17] Irrespective of methodological differences it remains unclear, why a discrepancy relative to the two mentioned studies exists.

Felici *et al.* (2009) described a phasic decrease of the oxygen saturation of the biceps brachii muscle with two different decay rates until termination of the isometric action after 30 s of loading, regardless of the intensity (20–80% MVIC).[20] The initial phase had a fast and the second a slower decay rate, whereas the oxygen saturation in the slower phase proceeded very flat but still decreased.[20] This is comparable with the leveling off before adjusting a steady state as seen in the presented data. Because of the limited loading duration, it is unclear whether the oxygen saturation would also have been adjusted into a steady state in their study. In two of our fatiguing trials a long leveling off phase appeared. If in those trials only the first 30 s would be considered, the two different decay rates would be found, which were described by Felici and colleagues (2009).[20] That is in line with findings of Jensen *et al.* (1999), in which the oxygen saturation in paravertebral muscles remain relatively stable after 30 s during an isometric trunk extension at 20 % MVIC.[4]

Results of blood filling in comparison with other studies

Regarding the hemoglobin concentration, most studies have described and / or graphed a decrease and leveling off into a steady state, similar to to our findings in type I.[10,11,21,24,25,27] Other research groups found an increase after an initial decrease,[20,28] or a direct increase at the start of loading.[17,29] This might fit to our findings in type II in the broadest sense. The study of Pereira and colleagues (2009) revealed the possibility of different behaviors in several subjects.[19] Furthermore, Akima and Ando (2017) found different behaviors in different muscles of the same individual.[17] The two distinct types of regulation suggested in the present study do not seem to be person-specific. Due to the small sample size, we cannot give any statements about influencing factors such as gender, although all three female subjects were assigned to type I. The suggestion to categorize two behavioral patterns cannot exclude hybrid or transitional forms of regulation.

Study limitations

Like the NIRS technique, the O2C device is not able to exclude arterial blood completely.[7-9,43] The tissue penetration of the white light of 12 mm does not represent the whole muscle. A statement about deeper regions, in

which the pressure on the microvessels might be higher,[2,44] cannot be given.
Caused by the pilot character of the study, some further limitations have to be considered in the interpretation of the results. It should be noticed, that no goniometer was used for the exact determination of the elbow angle. Consequently, termination of loading was assessed by the examiner subjectively as soon as the elbow angle exceeded 90° for more than two seconds. Another one is that the thickness of skin folds were not examined. Despite of this lack, the skin fold thickness on the anterior side of the upper arm is regularly low in normal weighted adults as participated here. Hence, low subcutaneous fat levels can be assumed. Moreover, in pretests different body types were compared. In a presence of an obvious thick subcutaneous fat layer, no change in the oxygenation during load occurred, i.e. the white light did not reach muscle tissue.
Anyhow, results of the present study are worth to be replicated in both young and aged persons. The latter, may have peculiar circulatory impairments that will ask for special adaptations.

Conclusion

Based on the results of the current and previous studies, an adjustment of the oxygen saturation and relative hemoglobin amount into a homeostatic steady state during a fatiguing isometric action occurs at least in the superficial muscle layers. Maybe the blood flow in microvessels is not fully restricted due to the intramuscular pressure. The authors suggest to roughly categorize the behavior of muscle oxygenation and blood filling in two types. For a possible explanation, a triggered increase of the blood filling by a threshold of the oxygenation level as a consequence of an intramuscular regulation is hypothesized. Further studies are necessary to understand the regulation mechanism.

List of acronyms

1st Max. - first local maximum
1st Min. - first local minimum
AU - arbitrary units
BMI - body mass index
CV - coefficient of variation
I1 - first interval
I2 - second interval
MVIC - maximal voluntary isometric contraction
NI DIAdem™ – National Instruments DIAdem™
NIRS - near infrared spectroscopy technique
O2C - Oxygen To See; LEA Medizintechnik GmbH
rHb - relative hemoglobin amount
RP - reversal point
SvO_2 - capillary-venous oxygen saturation of hemoglobin

Authors contributions

LS and FB have designed the study. SD has analyzed the data, has searched references and has written the manuscript. All authors were involved in the collection and interpretation of the data, revised the manuscript critically and done the final approval. They agree to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no potential conflict of interests.

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.

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Muscle Oxygenation Level Might Trigger the Regulation of Capillary Venous Blood Filling during Fatiguing Isometric Muscle Actions

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Abstract: The regulation of oxygen and blood supply during isometric muscle actions is still unclear. Recently, two behavioral types of oxygen saturation (SvO_2) and relative hemoglobin amount (rHb) in venous microvessels were described during a fatiguing holding isometric muscle action (HIMA) (type I: nearly parallel behavior of SvO_2 and rHb; type II: partly inverse behavior). The study aimed to ascertain an explanation of these two regulative behaviors. Twelve subjects performed one fatiguing HIMA trial with each arm by weight holding at 60% of the maximal voluntary isometric contraction (MVIC) in a 90° elbow flexion. Six subjects additionally executed one fatiguing PIMA trial by pulling on an immovable resistance with 60% of the MVIC with each side and same position. Both regulative types mentioned were found during HIMA (I: $n = 7$, II: $n = 17$) and PIMA (I: $n = 3$, II: $n = 9$). During the fatiguing measurements, rHb decreased initially and started to increase in type II at an average SvO_2-level of 58.75 ± 2.14%. In type I, SvO_2 never reached that specific value during loading. This might indicate the existence of a threshold around 59% which seems to trigger the increase in rHb and could explain the two behavioral types. An approach is discussed to meet the apparent incompatibility of an increased capillary blood filling (rHb) despite high intramuscular pressures which were found by other research groups during isometric muscle actions.

Keywords: muscle oxygen saturation; hemoglobin amount; isometric muscle action; O2C spectrophotometer; capillary recruitment; blood flow; holding isometric muscle action (HIMA); pulling isometric muscle action (PIMA)

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1. Introduction

During exercise, the demand for oxygen, nutrients and, therefore, blood increases in the muscular capillary system to transfer chemical energy into mechanical energy. During isometric muscle actions (IMAs), the regulation of blood filling of the microvessels is not entirely understood. In the past, a blood flow restriction or complete stop due to high intramuscular pressure have been discussed [1–5]. If the blood flow is restricted or stopped, the muscle ought to completely deoxygenate over time, i.e., the oxygen saturation decreases to zero. However, during IMAs maintained until muscle failure ("fatiguing measurements"), this assumption was not confirmed, at least in the examined superficial muscle layer [6–13]. On the one hand, the oxygen saturation showed an immediate decrease at the onset of loading [6–10] or short increase [11], followed by a leveling off into a steady state until fatigue [6–11]. These studies revealed that a homeostasis of oxygen delivery and consumption during IMAs is basically possible. On the other hand, a continuous decrease in the oxygen saturation with [12] or without [13] a previous slight increase has been described. However, it never decreased to zero until fatigue-related termination of the exercise. Other studies have limited the duration of muscle action [14–21] and, therefore, nothing can be said about the further progress of oxygen saturation. Nevertheless, steady states were also found in studies with limited loading durations [19–21].

Recently, our research group suggested to categorize the behavior of capillary venous oxygen saturation of hemoglobin (SvO_2) and relative hemoglobin amount (rHb), as an indicator of the blood filling, roughly into two patterns (type I and type II) [6]. The crucial difference was the behavior of rHb. In type I, it ran nearly parallel to SvO_2 (it only decreased and leveled off into a steady state), whereas in type II, it increased after reaching a reversal point (RP_1). Subsequent to a leveling off into a steady state, rHb decreased in type II after termination of loading until a second reversal point (RP_2) before returning to baseline level or higher. This behavior indicates a partial opposing behavior of both parameters [6]. The main objective of the present study was to clarify why rHb increases in type II. To investigate this, a closer look was taken at the course of rHb with regard to the behavior of SvO_2 over time and in comparison of both types. A triggered regulatory mechanism by a boundary oxygenation level (threshold) was already hypothesized [6]. This should bring new insights into the regulative behavior of the microcirculation in the superficial muscle tissue during IMAs.

2. Materials and Methods

2.1. Subjects

Twelve Caucasian subjects (9 males, 3 females, mean age ± standard deviation (SD) = 29.75 ± 11.14 years) participated. Nobody had any health problems, to meet the one and only inclusion criterion. They weighed averagely 72.00 ± 11.03 kg and were 1.78 ± 0.08 m tall (BMI: 22.61 ± 1.93 $\frac{kg}{m^2}$). Except for two left-handed subjects, everybody was right-handed. The study was conducted according to the declaration of Helsinki and was approved by the ethics committee of the University of Potsdam, Germany (approval No. 28-2017, 2 February 2018). All subjects were informed in detail and gave their written consent to participate.

2.2. Measuring Technique

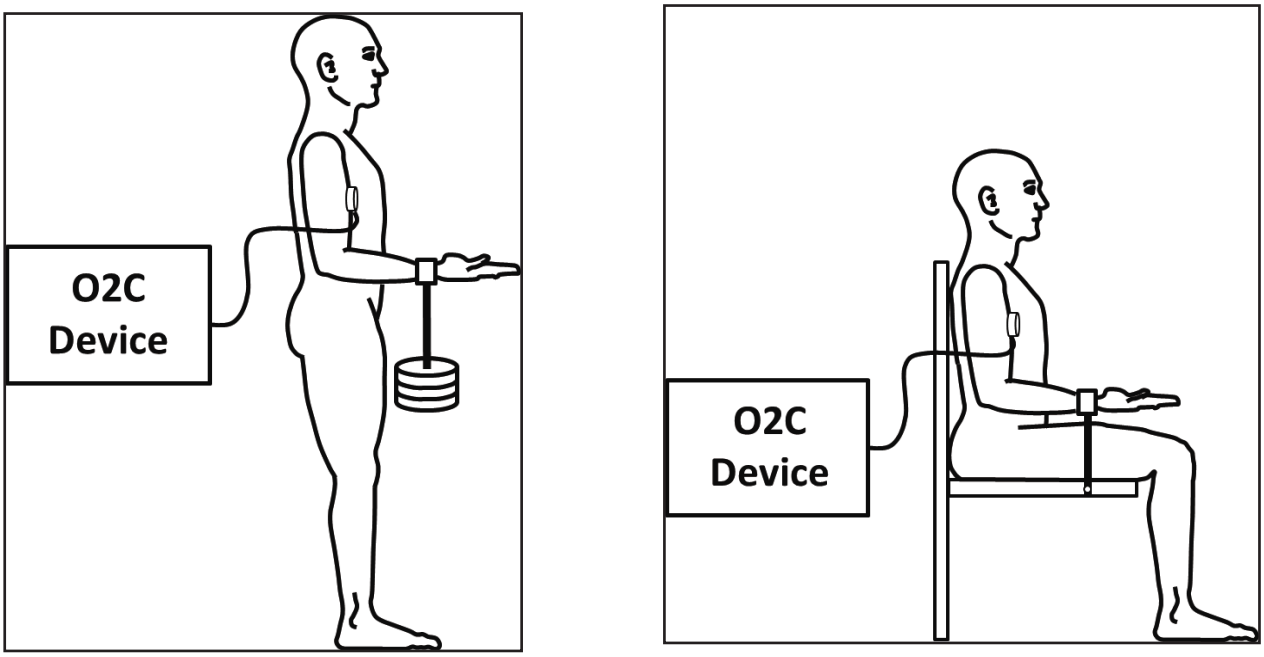
To examine SvO_2 and rHb of microvessels in the superficial muscle layers of the biceps brachii muscle, the O2C spectrophotometer was used (Oxygen To See; LEA© Medizintechnik GmbH, Gießen, Germany). The device operates with a combination of the laser Doppler technique and tissue spectrometry (laser light: near infrared, continuous wave, power > 30 mW; white light: 500–800 nm, 1 nm resolution). Previous studies have given a detailed description [22,23]. For a detection of SvO_2 and rHb, only the spectrometry is relevant. The sent white light is backscattered in different wavelengths in dependence of the ratio of oxygenated and deoxygenated hemoglobin. The detected wavelengths are used for the calculation of SvO_2 in %. The amount of light absorbed by the tissue is used for determining rHb in arbitrary units (AU). The specifications of the used flat probe (LF3, separation: 16 mm) allows for a light penetration depth of 12 mm. It was placed over the most prominent part of the biceps brachii muscle belly along its fibers. A double-sided adhesive film was used for fixation. The room light was dimmed to minimize light effects on the probe. The sampling rate was 40 Hz. The O2C device is valid and reliable [24–26] and is applicable to muscle tissue at rest [27] and during exercise [28].

2.3. Setting and Procedure

In the previous study, the differentiation of type I and type II was based on fatiguing measurements during a holding isometric muscle action of the left arm (HIMA) [6]. These measurements were also considered in the present study. The data set has been extended by measurements of the right arm of the same persons and two more subjects. Additionally, a fatiguing pulling isometric muscle action (PIMA) was performed by a subgroup (n = 6). The nomenclature of HIMA and PIMA was chosen according to Schaefer and Bittmann [29]. HIMA refers to an isometric muscle action while resisting an external force and was termed as "position task" [30–32] or "eccentrically loaded isometric contraction" [33] by other research groups. PIMA characterizes an isometric muscle action while force is developed against an immovable resistance in a pushing or pulling manner. This is also named

"force task" [30–32] or "concentrically loaded isometric contraction" [33]. Both isometric tasks were performed in the present study since there are indications that these differ in various parameters [10,29–32,34–36]. However, there are also studies which did not find a difference between HIMA and PIMA [33,37,38].

All subjects performed a fatiguing HIMA trial, once with the right arm and once with the left arm. A subgroup of $n = 6$ additionally performed a fatiguing PIMA trial with each side. The settings are illustrated in Figure 1a,b. During all measurements, a cuff was applied 2–3 cm proximal to the wrist crease. The upper arm was in contact with the thorax, the elbow joint was flexed in 90° and the forearm was maximally supinated to emphasize the activity of the biceps brachii muscle. The intensity of every fatiguing trial was 60% of the individual maximal voluntary isometric contraction (MVIC). This intensity was chosen because it might be theoretically high enough to restrict the blood flow due to the intramuscular pressure [2]. Moreover, the loading times should be long enough to test for muscular endurance [39]. During HIMA, every subject had to hold a respective weight of 60% of the MVIC for as long as possible while standing. The weight was taken off as soon as the elbow angle exceeded 90° for 2 s, assessed by the rater subjectively. During PIMA, the participants sat upright and had to pull on a strain gauge which was connected to an immovable resistance. For maintaining the target force for as long as possible, subjects had visual feedback on a monitor. As soon as the force remained below the target force for 2 s, the rater prompted the subject to stop the task. The rest between every measurement was at least 3 min. The order of the arms performing the IMA was randomized. In addition, the order of tasks (HIMA or PIMA) of the subgroup was also randomized to minimize the effect of fatigue. The parameters (SvO_2 and rHb) were recorded 10 s before every task in the measurements position and until 2 min of rest after loading.



(**a**) (**b**)

Figure 1. Measurement position and set up during a holding isometric muscle action (HIMA) (**a**), reprinted from Dech et al. (2020) [6] with permission, and during a pulling isometric muscle action (PIMA) (**b**).

To determine the MVIC, a HIMA or PIMA was performed in dependance of the fatiguing tasks (only HIMA or PIMA additionally). The arm and cuff positions were identical as already described. For the participants who only performed fatiguing HIMA trials, the MVIC was determined by the highest possible weight which could be held for 1 s in an upright standing position (Figure 1a). The weights were added progressively within

maximal five steps and sufficient rest in between. For that, the rater hooked the respective weight onto the cuff and took it off after 1 s or if the elbow angle exceeded 90°. Because of the short duration, these measurements were not recorded by the O2C device.

The participants of the subgroup, who additionally performed fatiguing PIMA trials, sat in an upright position and pulled twice as strong as possible on a fixed strain gauge to record the maximum force (Figure 1b). These subjects were introduced to increase the force within 3 s to their maximum and hold it for at least 1 s. The rest between both trials was >2 min. These MVIC-tests were recorded by the O2C device.

The highest force value measured by the strain gauge (subgroup, maximal PIMA) or highest weight which could be held for 1 s (maximal HIMA), respectively, was determined as the MVIC.

2.4. Data Processing and Statistical Analysis

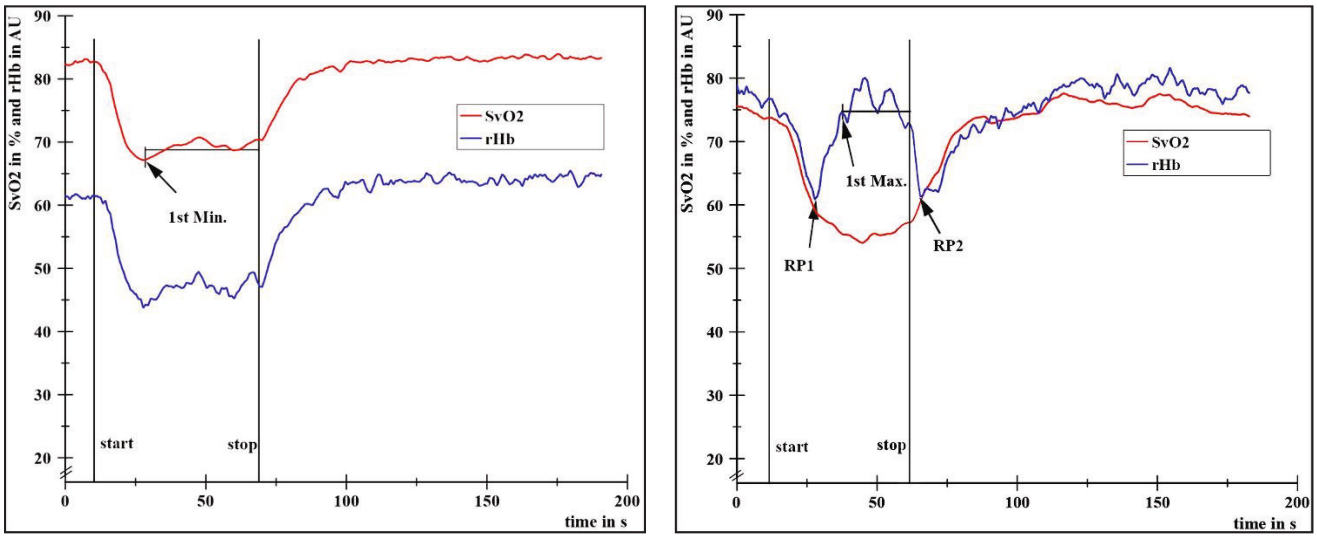
All curves were smoothed by using the software in NI DIAdem™ 2017 (moving average, maximal smoothing width on one side: 50 points). With respect to the research question, the curves were categorized visually into type I or type II as described by Dech et al. (2020) [6]: type I: parallel behavior of SvO_2 and rHb (Figure 2a); type II: partly inverse behavior of both parameters due to an increase in rHb after RP_1 and decrease after stop of loading until RP_2 (Figure 2b). The number of type I and type II measurements during fatiguing HIMA and PIMA trials as well as MVIC-tests were counted. Possible differences between HIMA and PIMA will not be considered here. This would be beyond the scope of the present study, i.e., to find a possible explanation of the two types. It will be presented within a more sophisticated study design (article in preparation). Without differentiation of HIMA and PIMA, the following variables were determined:

(1) Extent of SvO_2 decrease (deoxygenation in type I and type II), calculated by the difference of the arithmetic mean (M) of the baseline values (initial 400 data points ≙ first 10 s) to the M of the plateau between the first local minimum (1st Min., Figure 2a) and stop of the task. Values of deoxygenation are presented in percent points (pp) and additionally in % related to the respective baseline value.
(2) Time to task failure (TTF), defined as the time period in s from start to end of loading.
(3) SvO_2 levels at the moment of RP_1 and RP_2 (only in type II, Figure 2b), presented as Ms and 1.96-fold standard deviations (1.96SDs) in %.
(4) Time period in s from start until the minimum of rHb before start of its plateau (steady state). This corresponds to RP_1 in type II.

IBM SPSS Statistics 26 was used for the statistical analysis. MVICs were compared between left and right arm as well as dominant and non-dominant arm. Differences of SvO_2 baseline and deoxygenation levels (1) as well as TTFs (2) were compared between type I and type II. SvO_2 levels at the moment of RP_1 and RP_2 (3) were analyzed to collect information about the main research question (existence of a threshold). In this regard, it was tested if differences exist between RP_1 and RP_2. All data were normally distributed (Shapiro–Wilk test, $p > 0.05$), except for three variables (fatiguing measurements: SvO_2 baseline level of type I, SvO_2 deoxygenation of type II; MVIC-tests: SvO_2 level at RP_2). Regarding normal distributed variables, analyses of differences were made by parametric tests (*t*-tests, variance homogeneity). Comparisons including one of the three not normally distributed variables were made by Mann–Whitney U test (independent samples) or exact Wilcoxon signed-rank test (dependent samples). Effect sizes are given for significant results (Pearson's *r*):

$$r = \frac{Z}{\sqrt{N}} \text{ or } r = \sqrt{\frac{t^2}{t^2 + df}}. \quad (1)$$

An alpha error of 5% was chosen for all tests.



(**a**) (**b**)

Figure 2. Curve examples of the capillary venous oxygen saturation of hemoglobin (SvO_2; red) and the relative hemoglobin amount (rHb, blue) in type I (**a**) with left arm and in type II (**b**) with the right arm of the same male left-hander (26 yrs, 1.85 m, 86 kg) during two fatiguing pulling isometric muscle actions at 60% of the MVIC of the biceps brachii muscle. Start and stop of loading are indicated by vertical lines. The first local minimum (1st Min.) was set exemplarily in (**a**) and the first local maximum (1st Max.) as well as reversal points (RP_1, RP_2) in (**b**). All curves were smoothed (moving average, maximal smoothing width: 50).

Furthermore, correlations of SvO_2 and rHb from start to the end of loading were determined by Spearman's rank correlation coefficients (ρ) for every fatiguing measurement. Before calculating M ± SD for each type, Fisher's *Z*-transformation was applied:

$$Z = \frac{1}{2} \times \ln\left(\frac{1+\rho}{1-\rho}\right) \quad (2)$$

M ± SD are presented after back transformation in ρ:

$$\rho = \frac{e^{2Z} - 1}{e^{2Z} + 1} \quad (3)$$

3. Results

The averaged MVICs of all subjects did not differ significantly between the right (70.02 ± 23.83 Nm) and the left arm (69.31 ± 21.69 Nm, $t(11) = 0.80$, $p = 0.442$). This result did not change after correction for the lateral preference (dominant vs. non-dominant arm: $t(11) = 0.57$, $p = 0.581$).

3.1. Categorization of Measurements into Type I or II

Figure 2a,b illustrate the two behavioral patterns (type I and II) within the same subject during a fatiguing PIMA trial of the left and right arm. Based on the curve shapes, the visual categorization of all fatiguing measurements (HIMA and PIMA) as well as MVIC-tests (PIMA only) into type I ($n = 25$) and type II ($n = 35$) are given in Table 1. No measurement of the right arm during the fatiguing PIMA was assigned to type I. The categorization was not consistent within individuals because both types occurred in different trials in three female and three male subjects as shown exemplarily in Figure 2. During fatiguing HIMA trials of this subject, the behaviors were reversed for the left (type II) and right arm (type I).

Table 1. Number (*n*) of type I and type II behaviors of the capillary venous oxygen saturation and blood filling separated by task and arm of twelve subjects.

	HIMA		PIMA			
Task	**Fatiguing**		**Fatiguing**		**MVIC-Test**	
arm	left	right	left	right	left	right
type I (n = 25)	5	2	3	0	8	7
	7		3		15	
type II (n = 35)	7	10	3	6	4	5
	17		9		9	
total (n = 60)	12	12	6	6	12	12
	24		12		24	

3.2. Comparisons between Behavioral Types

Before the start of the fatiguing measurements, absolute SvO_2 values in type I at baseline differed significantly (M ± SD = 78.04 ± 4.50%, n = 10) from type II (73.28 ± 5.97%, n = 26; U = −2.60, p = 0.008, r = 0.43). Before MVIC-tests, the difference between type I (71.37 ± 4.92%, n = 15) and type II (68.51 ± 4.34, n = 9) baseline values was not significant ($t(22)$ = 1.44, p = 0.165).

During the fatiguing measurements of type I, SvO_2 and rHb behaved nearly parallel to each other (Figure 2a) with a positive average rank correlation of ρ = 0.74 ± 0.61 (range: 0.19–0.99), $p < 0.001$. The minimum of rHb before leveling off into a steady state was reached after 11.41 ± 3.44 s on average. Subsequently to the end of loading, SvO_2 approached to or increased above baseline value. In contrast, rHb decreased in type II until RP_1 within averagely 6.85 s ± 3.39 s and approached to or increased above baseline value before leveling off into a steady state (Figure 2b). Consequently, the average rank correlation was negative (ρ = −0.81 ± 0.52 (range: −0.97–−0.18), $p < 0.001$). During recovery, rHb decreased until RP_2 before increasing again to the baseline value or higher. In type II, the hemoglobin deoxygenated significantly more (–24.45 ± 11.59 pp ≙ –18.25 ± 9.35%, n = 26) than that of type I (–12.21 ± 3.67 pp ≙ –9.60 ± 3.09%, n = 10; U = −3.46, $p < 0.001$, r = 0.58). The TTF did not differ significantly between type I (45.88 ± 10.26 s) and type II (45.25 s ± 12.40 s); $t(34)$ = 0.15, p = 0.886. All individual values of the presented variables during the fatiguing measurements can be found in the supplementary material (Tables S1 and S2).

During the MVIC-tests, the curve progresses of SvO_2 and rHb were similar to the fatiguing measurements in respect to the regulative behavior (type I or type II). SvO_2 also decreased significantly more in type II (–16.93 ± 3.41 pp ≙ –24.58 ± 4.12%, n = 9) compared to type I (–8.59 ± 3.55 pp ≙ –11.93 ± 4.64%, n = 15; $t(22)$ = 5.66, $p < 0.001$, r = 0.77). However, SvO_2 decreased until stop of the test or somewhat further before approaching to baseline value. Thus, no steady state was seen. Individual values of the MVIC-tests can be found in the supplementary material (Tables S3 and S4).

3.3. Oxygenation Level at Reversal Points

According to the categorization of measurements, RPs of rHb exist only in type II. The SvO_2 values at RP_1 and RP_2 of all type II fatiguing measurements are shown in Figure 3. The respective Ms and 1.96SDs are given. The SvO_2 values between RP_1 and RP_2 differed not significantly ($t(25)$ = –0.53, p = 0.600), whereby RP_2 showed nearly the same Ms (58.91 ± 2.72%) as RP_1 (58.75 ± 2.14%). During the MVIC-tests, SvO_2 at RP_1 was averagely 58.13 ± 1.66 pp and 57.82 ± 1.25 pp at RP_2. Values were not significantly different (z_{exact} = −0.53, p = 0.652, n = 9). Figure 4 shows M, 1.96SDs and individual values.

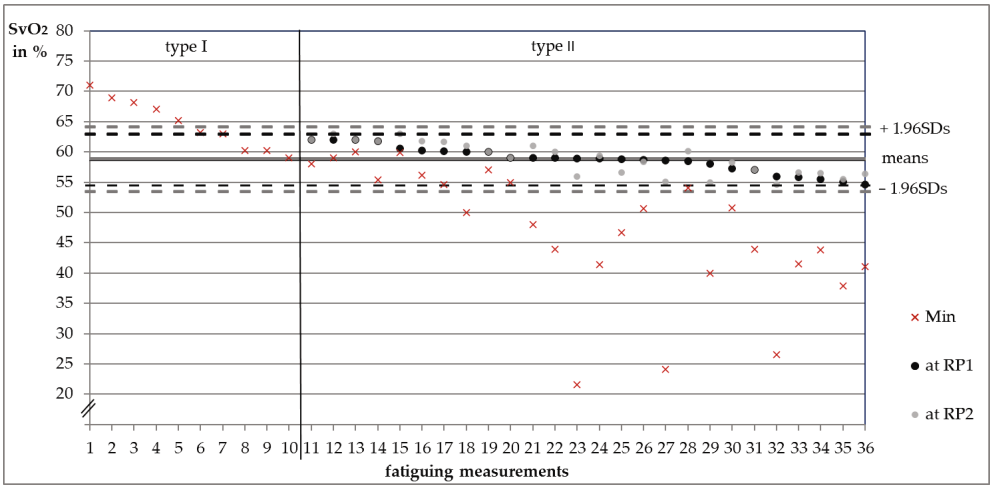


Figure 3. Capillary venous oxygen saturation of hemoglobin (SvO_2 in %) of 36 fatiguing measurements of twelve subjects. Type I minimum values (red crosses, n = 10) sorted by oxygenation level. Type II SvO_2 values at the first reversal points of the relative hemoglobin amount (RP_1, n = 26, black, sorted by oxygenation level) and respective SvO_2 values at RP_2 (grey) as well as minimum values (red crosses). In some measurements, RP_1 and RP_2 are nearly identical (only grey dots). The horizontal lines express the arithmetic means of SvO_2 values at RP_1 (black, hidden) and RP_2 (grey) of all 26 type II measurements. Dashed lines show the respective upper and lower 1.96-fold standard deviations.

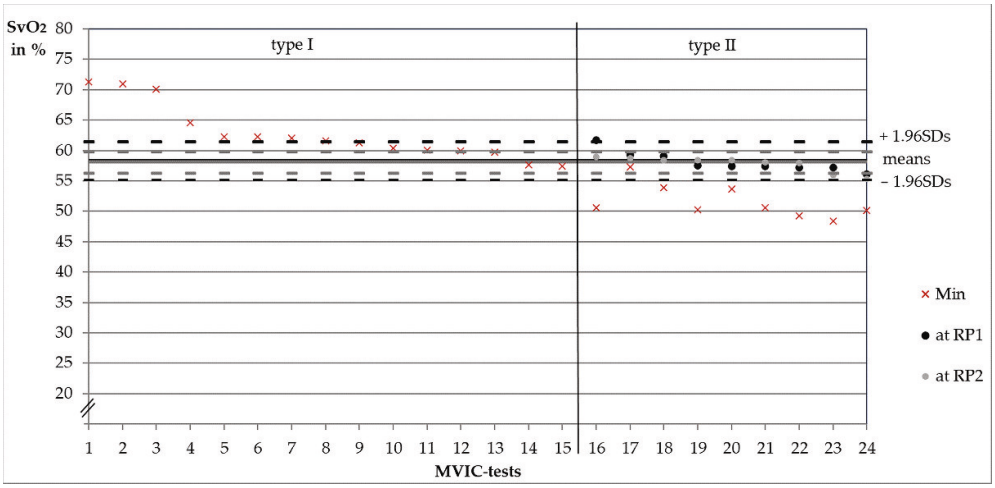


Figure 4. Capillary venous oxygen saturation of hemoglobin (SvO_2 in %) of 24 MVIC-tests of six subjects. Type I minimum values (red crosses, n = 15) sorted by oxygenation level. Type II SvO_2 values at the first reversal points of the relative hemoglobin amount (RP_1, n = 9, black, sorted by oxygenation level) and respective SvO_2 values at RP_2 (grey) as well as minimum values (red crosses). The horizontal lines express the arithmetic means of SvO_2 values at RP_1 (black) and RP_2 (grey) of all nine type II measurements. Dashed lines show the respective upper and lower 1.96-fold standard deviations.

4. Discussion

Recently, our research group reported the occurrence of two regulative behaviors of oxygen saturation and blood filling in the venous microvessels (type I and type II) during a fatiguing HIMA at 60% of the MVIC and during an MVIC-test (PIMA) [6]. Type I showed a parallel behavior between SvO_2 and rHb. In contrast, the main characteristic of the type II behavior is an increase in rHb while SvO_2 decreases further on. The measurements of the presented study could also be clearly assigned to one of each type by visual inspection.

Regarding the categorization of measurements in Table 1, type I and type II occurred during both isometric tasks. The finding that PIMA measurements of the right arm were only assigned to type II, is assumed to be due to the small sample size. This should be verified in future examinations. Furthermore, person and gender might not play a role because both types occurred within individuals and in males as well as in females.

During the fatiguing measurements at 60% of the MVIC, more type II than type I behaviors occurred. In contrast, during the MVIC-tests it was revers. The occurrence of more type I than type II behaviors in MVIC-tests might be a result of the loading duration. Our research group already argued that a maximal deoxygenation during short lasting MVIC-test (~4 s) might not be possible [6]. In fatiguing trials, the TTF was similar even though the hemoglobin in type II measurements deoxygenated more than these in type I. This result might indicate an independence of the behavioral types from the TTF during similar submaximal intensities and, therefore, possibly from the endurance capacity of the involved muscle. Thus, the onset of fatigue might not be explained by the level of deoxygenation. This is in accordance with Booghs et al. (2012) [10]. However, in the present study, the elbow angle was only controlled subjectively. Consequently, TTFs should be interpreted with care.

The main finding of the study was that during fatiguing measurements, rHb started to increase only in type II at an average SvO_2-level of 58.75 ± 2.14%. In contrast, the SvO_2 of type I measurements never reached that specific value during loading. This might be an indication of a SvO_2-threshold around 59%, which seems to trigger the increase in rHb. Thus, dropping below the proposed threshold or not could explain the behavioral type. In the following, the discussion focuses on this potentially triggered regulation of microvascular blood filling and on the possible underlying physiological mechanisms behind it. Lastly, it is discussed how an increase in blood filling might be plausible during IMA, which are generally known for impeding capillary blood flow.

4.1. Triggered Regulation of the Capillary Venous Blood Filling

The two behaviors (type I and type II) might reflect a specific kind of regulation in dependance of the oxygen saturation level. An increase in the capillary venous blood filling (rHb) started at an average SvO_2-level of 58.75%. The variation of that specific oxygenation level was very low (1.96SD = 4.16 pp), maybe indicating a specific and reproducible interpersonal threshold around 59%. A similar SvO_2 level was found at RP_2 (M = 58.91%, 1.96SD = 5.35 pp). RP_2 occurred after stop of loading which might indicate an independence of such behavior from the muscular tension. In type I measurements, SvO_2 partly reached but never decreased below 59%. Hence, the oxygenation level seems to determine the behavioral pattern (type I or type II). Reaching a SvO_2-threshold of ~59% might trigger an increase in rHb. It is suggested that this threshold lies within a transition area (±1.96SD = ~55–~63%, Figure 3) which has to be passed to cause an increase in rHb in 95% of all cases. The hypothesized trigger mechanism might impede a further or complete deoxygenation and, therefore, might play an important role in regulating the blood filling of microvessels. According to these findings, the behavior of SvO_2 and rHb might be parallel at saturation levels greater than ~59% and inverse until the saturation levels off into a steady state below that threshold. Consequently, rHb behaves parallel again but on a higher level. As SvO_2 increases again after a stop in the loading but remains below ~59%, the behavior of both parameters is inverse and changes to a parallel one after exceeding the threshold again (Figure 2).

Other research groups also described or showed the progression over time of oxygen saturation, mostly expressed as tissue oxygenation index (TOI), as well as total hemoglobin (tHb), blood volume (BV) or total hemoglobin index (THI), measured by NIRS during fatiguing IMA [7–10,12,13,16,18,40,41]. This technique is comparable with the white light spectrometry used by the O2C device. Methodological differences have been discussed previously [6]. Most importantly, the O2C device detects microvessels < 100 µm in diameter and the NIRS technique vessels < 1 mm. Other studies have focused mainly on group

level analyses [7,9,10,16,18] and/or presented only oxygenation data normalized to resting values [9,16,40,41]. This complicates a comparison with our approach, based on an analysis of rHb in relation to absolute SvO_2 values of individual measurements. Booghs et al. (2012) [10], who analyzed the normalized THI of the biceps brachii muscle during a fatiguing isometric action at 60% of the MVIC, found a return of group mean THI towards the baseline values within the first 25% of the TTF. During this time period, the TOI dropped below 60%. Because of few presented time points (25%, 50%, 75% of TTF and immediately prior to failure) of the averaged data, it is not clear at which saturation level the normalized THI started to increase. In the study of Felici et al. (2009) [16], the grand average rest value of the TOI during a fatiguing IMA at 60% of the MVIC of the biceps brachii muscle was 69.5% ± 6.3%. According to their graphs, the tHb started to increase after the TOI dropped approximately 5–10 pp [16]. Although, these are only normalized mean values of seven subjects, this result might roughly fit our suggested threshold. Akima and Ando (2017) also presented graphical data [8]. The tHb of the quadriceps femoris muscle (all parts) increased on group level after the oxygen saturation reached about 60% [8]. Jones et al. (2014) [18] reported the mean values of the tissue saturation index (TSI) of the quadriceps femoris muscle during an IMA at 50% of the MVIC. These ranged from 58.5% to 59% [18], and these were partly below our proposed threshold (59%) but within the suggested transition area (~55–~63%). It might explain why they did not find an increase in the averaged tHb since type I measurements also reached the transition area in our data. In the study of Katayama et al. (2002), the TOI of the vastus lateralis muscle also did not decrease below the 59%-threshold on average during an IMA at 60% of the MVIC [9]. Their presented mean curve of tHb did not change significantly [9]. If some of their measurements showed only a decrease (type I) and others showed an increase above baseline values (type II behavior) (data not presented), changes in the mean tHb would level out. This might explain the insignificance. In a shown representative time course of original NIRS signals, the TOI decreased below 40% without an increase in the tHb [9]. This individual example does not support the presumed threshold. Furthermore, Moalla et al. (2006) examined the vastus lateralis muscle of healthy male children during an IMA of 50% of the MVIC [7]. They did not find an average increase in the BV, despite a drop of the average oxygen saturation below 20%. The reasons for the different findings could be very diverse, including, e.g., the used measurement technique, the examined muscles, the chosen intensity, fitness level and age of the participants. Because of the partly inconclusive results of heterogeneous studies, further research is necessary to validate the suggested ~59%-threshold in different muscles, fiber types and deeper regions as well as in younger and older persons. Moreover, in the presented study, only SvO_2 and rHb and their possible dependance (trigger mechanism) were considered. Other variables such as "local increases in blood flow, temperature, carbon dioxide, acidity, adenosine, magnesium and potassium ions, and nitric oxide (NO) production" as listed by McArdle Katch and Katch (2010 [42], p. 334) could also be potential triggers in the regulation of blood filling. In addition, hydrogen ions, inorganic phosphate, prostaglandins and cytokines could be added to the list of potential substances [43]. In particular, the role of the radical NO will be addressed in the next subsection. However, the potential mediators might work synergistically instead of as one molecule alone [43].

4.2. Possible Physiological Explanation of the Regulative Response in Type II

As shown in the results and discussed before, in type II measurements, rHb initially decreased but increased after SvO_2 reached 58.75% ± 2.14% on average. How could this increase in rHb be explained? One reason might be a stopped outflow due to a venous stasis [1]. However, this does not occur directly with the start of muscle action (initial decrease in type II). Furthermore, it would not be a general phenomenon at 60% of the MVIC, because in type I measurements rHb did not increase despite the same load intensity. In addition, different studies have shown that the oxygen saturation [6–10] and blood filling [7,44] decreased with a leveling off into a steady state during fatiguing IMAs. A venous stasis is not compatible with steady states if a complete anaerobic energy supply

is excluded during fatiguing exercises. The steady states of SvO_2 and rHb found in the presented data (type I and type II of fatiguing measurements) and other research groups imply a balanced delivery and consumption of oxygen and blood. Another reason for the increase in rHb could be a rise of cardiac output [12]. That is thought to be unlikely because only a small muscle group was activated in our study (arm flexors). Furthermore, the increase in rHb would be gradual instead of sudden as seen in the presented data. Thus, the increase found in rHb in type II could rather be the consequence of a redistribution of blood or red blood cells to the active motor units and/or of the increased blood flow in microcirculation [12,45–48]. This applies at least to the superficial muscle layer, where the intramuscular pressure is the lowest [2]. An accumulation of blood could be achieved by a local capillary recruitment [49]. Two recruitment theories have been described [50]. Both mechanisms behind the theories would expand the capillary O_2-exchange area and have already been considered in analytical oxygen extraction models [50,51]. The older one hypothesized an opening of previously closed capillaries (binary recruitment) [50,52]. Despite a general acceptance in physiological and histological textbooks, the existence of precapillary sphincters as possible effectors is controversially discussed [43,48,53]. The scientific basis is limited to findings in the mesentery and could not be replicated in studies examining skeletal muscle tissue [53]. Furthermore, experimental and theoretical works challenge the hypothesis of closed capillaries during rest (for an overview see Poole et al., 2011 and 2020 [46,48]). In contrast, in the continuous or longitudinal recruitment theory a redistributed and homogenized blood flow of already perfused capillaries is hypothesized [46–48,50,54]. This approach considers the vasomotion of arterioles, the vessels with smoothed muscles, which regulate the blood flow. This stays in scientific consensus [53,54]. The arterioles also control the perfusion rate of the capillaries separately for red blood cells and plasma [43,48,54].

Thus, the increase in rHb could be the result of a vasodilation of arterioles. It is known that a vasodilation of blood vessels is initiated to maintain tissue oxygen consumption if systemic hypoxia arises [45,55–57]. In the regulation of the local vascular tone during exercise, the hypoxic induced release of NO seems to be the primary stimulus [56]. However, this concept remains controversial [55]. NO is inducted, e.g., by the neurohormone oxytocin [58], and it is regulated by β-adrenergic receptor mechanism during low-intensity exercises [56,57]. During higher intensities, vasodilation in skeletal muscle is clearly independent of this mechanism [56]. Thus, local dilatory mechanisms might be involved, but these are still not certainly identified [56,57]. In addition to systemic hypoxia, a local reduction in oxygen also stimulates vasodilation leading to a restoration of blood flow even though the compensatory response is not perfect [57]. The mechanisms behind this might be similar to systemic hypoxia [45,57]. Several pathways were suggested to explain the release of the vasodilatory NO. Adenosine or ATP release with activation of endothelial NO synthase, nitrate reduction by reaction of nitrate and deoxygenated hemoglobin as well as S-nitrosylated hemoglobin dependent bioactivity were discussed [55–57]. Further research is necessary to examine if such physiological mechanisms also apply to exercises including IMAs.

The blood filling in microvasculature might be embedded in complex regulatory processes to prevent a further deoxygenation of muscle tissue. A decreased oxygen saturation of hemoglobin is correlated with a local reduction in vascular resistance [45] and, therefore, vasodilation [59]. Thus, a SvO_2 decrease (hypoxia) during muscle actions is assumed to be the stimulus in a negative feedback control system [45]. In this regard, SvO_2 seems to be the controlled variable. The control of SvO_2 might aim to achieve a homeostasis (reference condition) expressed as SvO_2 steady states. The effector is the vascular smooth muscle in arterioles [45] which alters rHb via vasodilation or vasoconstriction. Thus, rHb would be the manipulated variable in such a loop regulation model. In contrast to the stimulus and effector, the sensor detecting SvO_2-level (hypoxia) and the signals/activators regulating the vascular tone are not clear yet [43,45]. SvO_2 or correlatives might be measured by sensors located in the endothelium, vascular smooth muscle cells, and red blood cells [56] or more

precise in the hemoglobin [45]. The suggested threshold of ∼59% might be associated with a tipping point during accumulation of activators (metabolic messengers or rather endothelia factors as NO) leading to a vasodilation. This, in turn, leads to an increase in the rHb which is associated with an increase in oxygen delivery to meet the greater oxygen demand and preventing a further decrease in SvO_2. Consequently, a steady state in SvO_2 and rHb can be provided. According to the "bang-bang-theory" or "on/off-theory", there might be an insensitive "dead-band" to the error signal (hypoxia) which enables a hysteresis of the blood filling [43]. This is necessary to prevent frequent adjustments in the vascular tone [43], and could explain the delay of blood support relative to the decrease in tissue saturation. The ∼59%-threshold could refer to the lower boundary of the "dead-band". In comparison to regulations of other homeostatic systems, such an on/off behavior is normally not seen.

During muscle actions, the role of glucose should be considered in conjunction with oxygen [43]. Thus, the delayed vasodilation or initial vasoconstriction (decrease in rHb) could also be explained by an activated anaerobic glycolysis accompanied by an increasing lactate and superoxide production by membrane NAD(P)H-oxidase (Nox) at the beginning [43]. The superoxide (O_2^-) blocks NO signals until mitochondria start their work (recycling the NADH to NAD^+ and resulting decrease in superoxide) [43]. In this regard, it could be reasonable that the start of mitochondrial activity plays a role in the variability of the suggested threshold (transition area). Regardless of the interpretation of the presented data, it remains questionable how the rHb can increase during IMA at all.

4.3. Increased Capillary Perfusion during Isometric Muscle Actions

Isometric muscle actions at 60% of the MVIC, as performed in the present study, should lead to high intramuscular pressures resulting in a blood flow restriction or complete stop [1–5]. However, the present data and other experimental data showed that the blood filling can increase (type II behavior), even during MVIC-tests [6,8,16,41,60]. Although the MVIC-test of our presented data mainly showed type I behaviors without an increase in rHb (n = 15), there were also measurements which showed an increase (type II behavior, n = 9) even during maximal intensities of muscular work. A stopped outflow (venous stasis) as an explanation for the increase in blood filling seems to be unlikely, as already discussed in the section above. Thus, capillary blood flow in superficial muscle tissue is probably maintained during IMAs even at high intensities. A vasodilatory process as discussed in the previous section could be the primary mechanism to explain the increase in microvascular blood filling. To meet the apparent incompatibility, anatomical considerations regarding the location of the capillaries in muscle tissue could be an approach. To our best knowledge, this was not considered before. Most of the capillaries proceed parallel to the muscle fibers within the endomysium [61]. In a cross-sectional view, capillaries, not to be confused with nuclei [62], are primarily located in the endomysium where three or four muscle fibers adjoin each other [63,64] (Figure 5, taken from Brelje and Sorenson [65]). If muscle fibers contract or tense during a muscle action, their circumference will increase. According to the geometrical configuration [62,64], a widening of the triangular spaces in between seems to be reasonable. Thus, the whole blood filling capacity of capillaries would be available despite a greater muscular tension. Even negative pressure differences might arise thereby. Under the described anatomical circumstances, the intramuscular pressure could be higher than the capillary pressure. Moreover, Poole and colleagues argued that muscle capillaries do not collapse easily under conditions of increased muscle or reduced intraluminal pressure. They explain this by the presence of collagen struts [46,48]. Furthermore, nerve fibers are also located in the endomysium [64,65], and they might be protected from the muscular compression due to their anatomical position, too.

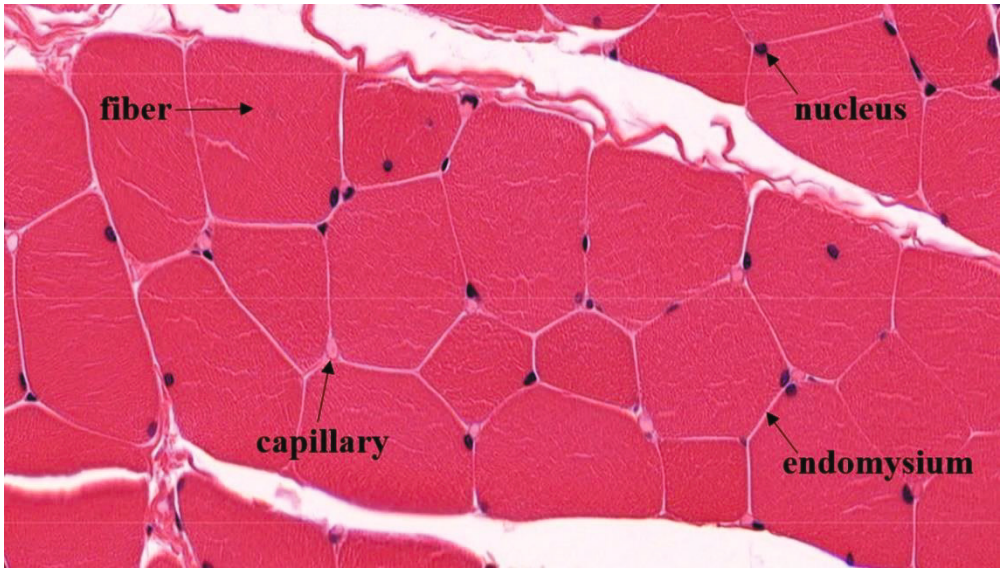


Figure 5. Cross-section of a striated human muscle. Capillaries are located in the endomysium where several muscle fibers adjoin. Cave: Nuclei (blue) are easily confused with capillaries (modified according to Sorenson and Brelje, University of Minnesota, Minneapolis, MN, USA, with kind permission [65]).

In conjunction with the anatomical considerations, the muscular blood flow during IMA might be supported by oscillations. Muscles oscillate transversally around 10–15 Hz during IMA [19,29,35,66–71]. These oscillations are an expression of the firing rate of motor units [19]. Thereby, the amplitude increases with higher intensities of muscle action [67]. Yoshitake et al. (2001) found a nearly constant group mean frequency of 10.5–11.9 Hz from start until the end of a fatiguing isometric back extension in the mechanomyographic signal (MMG) of the erector spinae muscles [19]. However, the amplitude in the MMG signal increased significantly at first and then decreased continuously until fatigue [19]. The absolute contraction intensity is not known in that study but is estimated to be 45% on average. However, the found behavior of MMG amplitude is not identical over all intensities during sustained contractions. It tends to increase at force levels between 10% and 40% of the MVIC, does not change or decreases from 50% to 80% and decreases from 90% to 100% [72]. Moreover, there are also indications of differences in the courses of MMG amplitudes between fiber types [73]. Yoshitake and colleagues (2001) discussed that the reduced amplitudes found in their examination resulted from slowed contractile elements (extension of relaxation time) and, therefore, decreased dimensional changes of the active fibers [19]. From their point of view, this would result in an increased intramuscular pressure and a restriction of the muscle blood flow, and could consequently explain the onset of fatigue. In contrast, MMG amplitude seems not to change with an increase in intramuscular pressure [74]. Moreover, due to maintenance of muscular oscillations until fatigue independently of the amplitudes, the opinion of a blood flow restriction per se might be challenged. Our research group already supposed the oscillatory behavior might serve as a pump and, therefore, could support the capillary blood flow [29]. In addition, Yoshitake et al. (2001) found steady states of the oxygenated hemoglobin amount after an initial decrease recorded together with the MMG [19]. As discussed before, a steady state implies a balanced oxygen delivery and consumption. If the blood flow is restricted while the demand increases in the exercising muscle, the available oxygen will be depleted over time. However, this has not been seen in experimental studies yet. Thus, the onset of fatigue seems not to be explained by the oxygen supply, but rather by other metabolic or neuromuscular factors.

4.4. Study Limitations

No gold standard exists for muscle oxygen saturation measurements [75]. The near infrared spectroscopy or white light spectrometry as used in the present study are recently used techniques. Limitations were described previously [6,76–78]. In brief, it should be noticed that an influence of arterial blood cannot be completely excluded in the recordings [76–79]. Regions of the muscle deeper than 12 mm with possible higher intramuscular pressures [2,80] cannot be examined by the device used in the present study. In this regard, it should be questioned if results would be different in deeper muscle layers. In a more advanced study design, the specific morphology of examined soft tissue, e.g. the individual muscle thickness, could be controlled by functional echomyography or computed tomography scans (CT-scans) in future measurements [81–83]. In this regard, the subcutaneous fat layer also plays a role and might have affected the measured parameters [84]. The skinfold thickness was not examined, but we assume low values in our normal weighted participants (BMI: 22.61 $\pm$ 1.93 $\frac{\mathbf{kg}}{\mathbf{m^2}}$) for whom the skinfold thickness above the examined biceps brachii muscle is regularly low. If the fat layer was too thick, the white light would not have reached muscle tissue and no change in the SvO_2 would be recognized. However, the thickness of the fat layer could have been different and, thus, tissue penetration depths of the white light might have been different in our subjects. Furthermore, six MVICs were determined by gold standard (strain gauge, PIMA). The other six were determined by weight holding (HIMA) and could not reach the same accuracy. The influence is expected to be small. As already mentioned, the termination of loading during the fatiguing HIMA trials was not standardized. The examiner stopped the loading as soon as the elbow exceeded 90° for more than two seconds according to visual inspection. This might have influenced the TTF. At last, the small sample size and differences in the age (min.–max.: 19–58 yrs.) of the explorative study must be mentioned. Despite all limitations and very clear findings, it could be worthwhile to examine a greater sample including participants of different ages and different fitness conditions.

5. Conclusions

Based on the method used, the presented data highlighted the obvious relation of oxygenation and blood filling of microvessels in superficial muscle tissue. It was found that the blood filling (rHb) can increase after a previous decrease during IMA at intensities of 60% and even of 100% of the MVIC. This reversal seems to be related to the amount of deoxygenation. Based on the results it is assumed that the reversal occurs if the oxygenation level decreases considerably (transition area around 59% SvO_2). It is hypothesized that this might trigger the regulation of blood filling.

The method used does not allow for direct conclusions on capillary blood flow, but indirect conclusions by regarding rHb and SvO_2 behaviors can be drawn. The increase that occurred in blood filling and steady state of oxygen saturation indicate a maintained capillary blood flow and against a venous stasis, as was discussed. On the basis of these findings, we propose to reconsider and discuss the current concept of a principally restricted or stopped capillary blood flow during IMAs. Possible theoretical explanations for the maintenance of blood flow and for an expansion of the O_2-exchange area (indicated by an increase in rHb) might be found in the special anatomical location of capillaries and the mechanical oscillations of muscle fibers during IMA. Due to those properties and features, the steady states found might have emerged. The mechanisms are not clear yet and, therefore, it is suggested to take a closer look at those anatomical and functional aspects in future studies. Further research is needed to investigate if deeper regions of muscles and different muscle fiber types show similar behavior. Furthermore, the possible influences of age, training and health status should be examined. Supposing that the findings hold true in future studies, deviations from regulative norms could potentially serve as an early diagnostic tool for metabolic disorders, myopathies or even chronic fatigue syndrome.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/diagnostics11111973/s1, Table S1: Single values of fatiguing measurements of type I behavior. Table S2: Single values of fatiguing measurements of type II behavior. Table S3: Single values of MVIC-tests of type I behaviors. Table S4: Single values of MVIC-tests of type I behaviors.

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Abbreviations

1st Max.	first local maximum
1st Min.	first local minimum
1.96SD	1.96-fold standard deviation
AU	arbitrary units
BMI	body mass index
BV	blood volume
HIMA	holding isometric muscle action
IMA	isometric muscle action
M	arithmetic mean
MMG	mechanomyography
MVIC	maximal voluntary isometric contraction
NAD^+/NADH	nicotine adenine dinucleotide (oxidized/reduced, H for hydrogen)
NAD(P)H	reduced form of nicotinamide adenine dinucleotide phosphate
Nox	NAD(P)H-oxidase
NI DIAdem™	National Instruments DIAdem™
NIRS	near infrared spectroscopy technique
NO	nitric oxide
O_2^-	superoxide anion
O2C	Oxygen To See (device, LEA Medizintechnik GmbH)
PIMA	pushing or pulling isometric muscle action
rHb	relative hemoglobin amount
RP	reversal point
SD	standard deviation
SvO_2	capillary venous oxygen saturation of hemoglobin
tHb	total hemoglobin
THI	total hemoglobin index
TTF	time to task failure

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diagnostics

MDPI

Article

Muscle oxygenation level might trigger the regulation of capillary venous blood filling during fatiguing isometric muscle actions

(Dech S, Bittmann FN and Schaefer LV)

Supplementary Materials

Table S1. Single values of fatiguing measurements of type I behavior.

IMA	subject no._arm	baseline value SvO_2 in %	baseline value rHb in AU	SvO_2 min. in %	TTF in s	SvO_2 SS mean in %	rHb SS mean in AU	extent of deoxygenation in pp (%)	extent of rHb decrease in AU (%)	time until min. of rHb before SS in s	time until SvO_2 SS in s	time until rHb SS in s	SvO_2 at RP_1 in %	SvO_2 at RP_2 in %	ρ between rHb & SvO_2
type I															
fatiguing HIMA	01_le	80.74	58.89	65.22	43.08	67.83	43.40	12.91 (10.42)	15.49 (9.12)	15.68	15.50	15.68	-	-	0.86
	06_le	67.54	48.63	60.23	70.48	61.40	47.76	6.14 (4.14)	0.87 (0.42)	9.90	17.13	9.90	-	-	0.40
	07_le	79.43	51.37	69.00	45.03	69.67	43.03	9.77 (7.76)	8.34 (4.29)	13.48	13.30	13.48	-	-	0.81
	17_le	80.40	58.75	68.15	48.93	69.09	45.36	11.30 (9.09)	13.39 (7.87)	15.93	15.93	15.93	-	-	0.99
	25_le	75.92	75.88	63.25	39.15	64.29	58.55	11.63 (8.83)	17.33 13.15)	11.70	13.68	11.70	-	-	0.57
	02_ri	81.10	66.18	63.00	37.20	63.29	43.71	17.81 (14.45)	22.47 14.87)	8.08	9.85	10.78	-	-	0.48
	07_ri	78.44	55.07	59.00	46.98	60.74	42.96	17.70 (13.89)	12.10 (6.66)	8.40	14.90	25.05	-	-	0.65
fatiguing PIMA	01_le	82.62	61.28	67.06	47.94	69.26	46.95	13.36 (11.04)	14.33 (8.78)	15.23	17.93	18.13	-	-	0.93
	06_le	73.91	53.99	60.21	48.12	61.03	47.98	12.87 (9.51)	6.01 (3.24)	8.53	14.85	8.53	-	-	0.19
	07_le	80.32	56.38	71.00	31.96	71.75	48.90	8.57 (6.88)	7.48 (4.22)	7.15	20.70	7.88	-	-	0.33
M		**78.04**	**58.64**	**64.61**	**45.88**	**65.84**	**46.86**	**12.21 (9.60)**	**11.78 (7.26)**	**11.41**	**15.38**	**13.70**	**-**	**-**	**0.74***
SD		4.50	7.84	4.13	10.26	4.13	4.68	3.67 (3.09)	6.24 (4.47)	3.44	2.91	5.22	-	-	0.61*

Abbreviations: AU = arbitrary units; IMA = isometric muscle action; HIMA = holding IMA; le = left; min. = minimum; M = arithmetic mean; MVIC = maximal voluntary isometric contraction; no. = number; PIMA = pulling IMA; pp = percent points; rHb = relative hemoglobin amount; ri = right; RP = reversal point; SD = standard deviation; SS = steady state; SvO_2 = capillary venous oxygen saturation of hemoglobin; TTF = time to task failure; ρ = Spearman's rank correlation coefficient.
* calculated by use of Fisher's Z-transformation

Table S2. Single values of fatiguing measurements of type II behavior.

IMA	subject no._arm	baseline value SvO_2 in %	baseline value rHb in AU	SvO_2 min. in %	TTF in s	SvO_2 SS mean in %	rHb SS mean in AU	extent of deoxy-genation in pp (%)	extent of rHb change in AU (%)	time until min. of rHb before SS in s	time until SvO_2 SS in s	time until rHb SS in s	SvO_2 at RP_1 in %	SvO_2 at RP_2 in %	ρ between rHb & SvO_2
							type II								
fatiguing HIMA	02_le	72.86	56.87	58.00	43.08	59.07	58.37	13.80 (10.05)	1.50 (0.88)	12.00	17.80	18.70	62.00	62.00	−0.81
	03_le	74.51	76.36	55.00	19.55	55.50	71.71	19.01 (14.16)	−4.64 (−3.33)	5.68	11.45	11.45	59.00	59.00	−0.41
	05_le	70.47	62.94	46.73	45.00	47.86	87.41	22.61 (15.94)	24.47 (21.39)	1.18	12.63	16.95	58.84	56.63	−0.74
	13_le	84.07	83.32	59.88	48.95	61.55	56.20	22.52 (18.93)	−27.12 (−15.24)	4.65	15.13	18.00	60.56	63.04	−0.91
	14_le	78.34	81.32	24.16	43.08	27.56	94.02	50.78 (39.78)	12.70 (11.94)	4.20	18.03	13.53	58.58	55.12	−0.48
	19_le	78.28	63.87	50.00	31.30	51.01	72.92	27.26 (21.34)	9.04 (6.59)	4.30	10.73	11.85	60.00	61.00	−0.91
	21_le	73.03	69.51	21.58	58.73	25.01	85.99	48.02 (35.07)	16.47 (14.17)	6.43	17.70	11.38	58.90	55.94	−0.18
	01_ri	64.01	65.92	50.72	45.03	51.98	83.97	12.03 (7.70)	18.05 (11.90)	4.83	24.93	23.13	58.70	58.36	−0.93
	03_ri	78.02	81.02	44.00	25.45	45.21	92.51	32.81 (25.60)	11.49 (10.63)	4.25	12.00	10.93	57.00	57.00	−0.83
	05_ri	62.27	75.68	37.93	39.15	42.36	106.82	19.90 (12.39)	31.14 (33.26)	6.03	11.40	14.13	55.08	55.50	−0.72
	06_ri	65.78	48.24	54.62	74.38	57.02	57.57	8.75 (5.76)	9.34 (5.37)	8.08	13.98	16.68	60.17	61.64	−0.97
	13_ri	62.38	56.58	48.00	47.00	49.92	72.61	12.46 (7.78)	16.03 (11.64)	15.55	15.13	16.75	59.00	61.00	−0.97
	14_ri	78.62	79.30	26.51	43.08	28.79	88.83	49.83 (39.18)	9.53 (8.47)	5.65	11.80	7.30	55.93	54.63	−0.46
	17_ri	72.72	57.62	55.38	41.13	56.72	65.11	16.00 (11.64)	7.49 (4.88)	7.18	13.90	13.90	61.76	61.84	−0.95
	19_ri	72.05	73.27	41.54	35.23	42.49	97.82	29.56 (21.30)	24.55 (24.01)	2.85	13.68	12.95	55.86	56.59	−0.46
	21_ri	76.89	84.91	43.80	39.13	45.69	88.80	31.20 (23.98)	3.89 (3.45)	5.65	11.63	13.43	55.56	56.51	−0.80
	24_ri	64.92	59.93	41.38	56.78	45.75	87.46	19.17 (12.44)	27.53 (24.08)	5.05	15.48	14.75	58.89	59.37	−0.97
fatiguing PIMA	02_le	80.32	56.38	59.00	47.00	59.00	64.34	21.32 (17.12)	7.96 (5.12)	4.05	13.65	12.00	62.00	63.00	−0.76
	03_le	78.08	79.23	40.00	48.93	43.38	84.29	34.70 (27.09)	5.06 (4.26)	11.83	14.83	18.45	58.00	55.00	−0.55
	05_le	74.91	73.18	50.83	29.38	51.77	82.00	23.14 (17.33)	8.83 (7.24)	6.38	8.10	8.83	57.27	58.25	−0.63
	01_ri	73.99	76.63	54.04	48.93	55.52	75.94	18.47 (13.66)	−0.68 (−0.52)	9.55	25.20	23.38	58.50	60.15	−0.71
	02_ri	69.81	55.88	60.00	58.70	60.70	58.51	9.12 (6.37)	2.62 (1.53)	6.23	16.18	23.88	62.00	62.00	−0.87
	03_ri	78.29	76.83	44.00	54.80	47.81	83.69	30.48 (23.86)	6.87 (5.75)	7.90	17.15	16.25	59.00	60.00	−0.96
	05_ri	66.90	78.99	41.09	33.28	41.64	100.89	25.25 (16.89)	21.89 (22.09)	5.98	19.55	16.63	54.60	56.40	−0.79
	06_ri	79.64	59.07	56.19	66.55	58.26	54.49	21.38 (17.03)	−4.58 (−2.50)	14.03	16.40	17.30	60.30	61.80	−0.87

	07_ri	74.25	49.51	57.00	52.85	58.03	43.18	16.22 (12.04)	−6.32 (−2.73)	8.65	14.50	9.10	60.00	60.00	−0.18
	M	**73.28**	**68.55**	**46.98**	**45.25**	**48.83**	**77.52**	**24.45 (18.25)**	**8.96 (8.24)**	**6.85**	**15.11**	**15.06**	**58.75**	**58.91**	**−0.81***
	SD	5.97	11.21	10.79	12.40	10.09	16.35	11.59 (9.35)	12.39 (10.48)	3.39	3.95	4.35	2.14	2.72	0.52*

Note: Abbreviations can be found on the first page.

Table S3. Single values of MVIC-tests of type I behaviors.

IMA	subject no._arm trial no.	baseline value SvO_2 in %	baseline value rHb in AU	SvO_2 min. in %	TTF in s	SvO_2 SS mean in %	rHb SS mean in AU	extent of deoxygenation in pp (%)	extent of rHb decrease in AU (%)	time until min. of rHb before SS in s	time until SvO_2 SS in s	time until rHb SS in s	SvO_2 at RP_1 in %	SvO_2 at RP_2 in %
type I														
MVIC-test PIMA	01_le_1	81.35	57.73	70.13	~4s	-	-	11.22 (13.79)	10.63 (18.42)	-	-	-	-	-
	01_le_2	77.14	53.64	64.6	~4s	-	-	12.54 (16.26)	12.53 (23.36)	-	-	-	-	-
	02_le_1	71.52	54.00	62.29	~4s	-	-	9.23 (12.91)	11.07 (20.50)	-	-	-	-	-
	02_le_2	64.51	54.79	61.64	~4s	-	-	2.87 (4.45)	10.15 (18.52)	-	-	-	-	-
	06_le_1	67.12	49.47	61.26	~4s	-	-	5.86 (8.73)	5.79 (11.70)	-	-	-	-	-
	06_le_2	66.18	51.65	60.36	~4s	-	-	5.82 (8.80)	6.79 (13.14)	-	-	-	-	-
	07_le_1	76.32	46.44	71.29	~4s	-	-	5.03 (6.59)	4.87 (10.49)	-	-	-	-	-
	07_le_2	77.35	48.61	71	~4s	-	-	6.35 (8.21)	6.98 (14.35)	-	-	-	-	-
	01_ri_1	69.48	64.52	57.43	~4s	-	-	12.05 (17.34)	11.68 (18.10)	-	-	-	-	-
	02_ri_1	67.91	51.31	62.29	~4s	-	-	5.62 (8.28)	5.02 (9.79)	-	-	-	-	-
	02_ri_2	70.36	54.58	62.00	~4s	-	-	8.36 (11.88)	7.94 (14.55)	-	-	-	-	-
	06_ri_1	66.66	45.19	59.76	~4s	-	-	6.90 (10.36)	5.26 (11.64)	-	-	-	-	-
	06_ri_2	68.53	48.00	60.02	~4s	-	-	8.51 (12.42)	7.50 (15.63)	-	-	-	-	-
	07_ri_1	73.95	46.93	60.00	~4s	-	-	13.95 (18.86)	12.93 (27.56)	-	-	-	-	-
	07_ri_2	72.16	46.21	57.64	~4s	-	-	14.52 (20.13)	8.92 (19.30)	-	-	-	-	-
	M	**71.37**	**51.54**	**62.78**	**-**	**-**	**-**	**8.59 (11.93)**	**8.54 (16.47)**	**-**	**-**	**-**	**-**	**-**
	SD	4.92	5.20	4.53	-	-	-	3.55 (4.64)	2.80 (5.01)	-	-	-	-	-

Note: Abbreviations can be found on the first page.

Table S4. Single values of MVIC-tests of type II behaviors.

IMA.	subject no._arm trial no.	baseline value SvO_2 in %	baseline value rHb in AU	SvO_2 min. in %	TTF in s	SvO_2 SS mean in %	rHb SS mean in AU	extent of deoxygenation in pp (%)	extent of rHb change in AU (%)	time until min. of rHb before SS in s	time until SvO_2 SS in s	time until rHb SS in s	SvO_2 at RP_1 in %	SvO_2 at RP_2 in %
type II														
MVIC-test PIMA	03_le_1	69.55	71.04	50.64	~4s	-	-	18.91 (27.19)	2.68 (3.78)	-	-	-	57.19	58.71
	03_le_2	76.22	76.14	57.29	~4s	-	-	18.93 (24.84)	−14.07 (−18.48)	-	-	-	57.46	58.07
	05_le_1	72.89	64.51	53.90	~4s	-	-	18.99 (26.05)	−1.48 (−2.29)	-	-	-	61.69	58.42
	05_le_2	65.74	61.05	50.24	~4s	-	-	15.50 (23.58)	13.10 (21.45)	-	-	-	59.32	58.43
	01_ri_2	63.09	65.87	53.63	~4s	-	-	9.46 (14.99)	9.23 (14.01)	-	-	-	59.12	58.47
	03_ri_1	70.03	67.19	50.64	~4s	-	-	19.39 (27.69)	5.48 (8.16)	-	-	-	57.21	57.93
	03_ri_2	69.67	67.33	49.29	~4s	-	-	20.38 (29.25)	9.45 (14.04)	-	-	-	57.50	58.93
	05_ri_1	64.06	70.48	48.37	~4s	-	-	15.69 (24.50)	7.43 (10.54)	-	-	-	57.48	56.02
	05_ri_2	65.32	73.07	50.19	~4s	-	-	15.13 (23.17)	3.83 (5.24)	-	-	-	56.16	55.38
M		**68.51**	**68.52**	**51.58**	**-**	**-**	**-**	**16.93 (24.58)**	**3.96 (6.27)**	**-**	**-**	**-**	**58.13**	**57.82**
SD		4.34	4.62	2.81	-	-	-	3.41 (4.12)	8.00 (11.54)	-	-	-	1.66	1.25

Note: Abbreviations can be found on the first page.

8.3 Publication 3: Muscle Oxygenation and Time to Task Failure of Submaximal Holding and Pulling Isometric Muscle Actions and Influence of Intermittent Voluntary Muscle Twitches.

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Muscle oxygenation and time to task failure of submaximal holding and pulling isometric muscle actions and influence of intermittent voluntary muscle twitches

Silas Dech*, Frank N. Bittmann and Laura V. Schaefer

Abstract

Background: Isometric muscle actions can be performed either by initiating the action, e.g., pulling on an immovable resistance (PIMA), or by reacting to an external load, e.g., holding a weight (HIMA). In the present study, it was mainly examined if these modalities could be differentiated by oxygenation variables as well as by time to task failure (TTF). Furthermore, it was analyzed if variables are changed by intermittent voluntary muscle twitches during weight holding (Twitch). It was assumed that twitches during a weight holding task change the character of the isometric muscle action from reacting (≙ HIMA) to acting (≙ PIMA).

Methods: Twelve subjects (two drop outs) randomly performed two tasks (HIMA vs. PIMA or HIMA vs. Twitch, n = 5 each) with the elbow flexors at 60% of maximal torque maintained until muscle failure with each arm. Local capillary venous oxygen saturation (SvO_2) and relative hemoglobin amount (rHb) were measured by light spectrometry.

Results: Within subjects, no significant differences were found between tasks regarding the behavior of SvO_2 and rHb, the slope and extent of deoxygenation (max. SvO_2 decrease), SvO_2 level at global rHb minimum, and time to SvO_2 steady states. The TTF was significantly longer during Twitch and PIMA (incl. Twitch) compared to HIMA ($p = 0.043$ and 0.047, respectively). There was no substantial correlation between TTF and maximal deoxygenation independently of the task ($r = -0.13$).

Conclusions: HIMA and PIMA seem to have a similar microvascular oxygen and blood supply. The supply might be sufficient, which is expressed by homeostatic steady states of SvO_2 in all trials and increases in rHb in most of the trials. Intermittent voluntary muscle twitches might not serve as a further support but extend the TTF. A changed neuromuscular control is discussed as possible explanation.

Keywords: Oxygen saturation, Microvascular blood filling, Isometric contraction, Isometric muscle action, Holding isometric muscle action, Pulling isometric muscle action, Pushing isometric muscle action, Time to task failure, Muscle twitch

Background

Isometric muscle actions can be performed during two different tasks. On the one hand, a person can apply force by pushing against or pulling on a stable resistance (e.g., common determination of the maximal voluntary isometric contraction (MVIC)). The person acts with the

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attempt to shorten the muscle but this is prevented by the stable resistance. Hence, the muscle action stays isometric [1]. This refers to a pushing or pulling isometric muscle action (PIMA) [2]. It has also been called "force task" [3–5] "restrained task" [6], or "concentrically loaded isometric contraction" [1]. On the other hand, a person can react to an external load by holding a position. The person reacts with the attempt to resist the externally provoked lengthening [1] by adapting to the applied load. The external load can be, e.g., a constant weight or increasing force for assessment of the maximal isometric Adaptive Force [7, 8]. Such muscle action refers to a "holding isometric muscle action" (HIMA) [2]. It was also termed "position task" [3–5], "postural task" [6], or "eccentrically loaded isometric contraction" [1].

In previous studies, both isometric tasks could partly be differentiated by various variables [2–5, 7, 9–11]. Most consistently, the time to task failure (TTF) was found to be significantly shorter during HIMA compared to PIMA at low intensities (15%, 20% and 30% of the MVIC) performed by arm flexor muscles in a horizontal forearm position [3, 4, 9, 11]. With a vertically positioned forearm and at intensities of 45%, 60% and 80% conflicting results have been found [2–4, 10]. Other variables which had shown differences between isometric tasks were amplitudes of electromyography (EMG) or mechanomyography (MMG) at exhaustion (PIMA > HIMA) [2, 3], normalized EMG power (PIMA > HIMA) [4] as well as MTG power (HIMA > PIMA) [2] in special frequency bands, mean arterial blood pressure (HIMA > PIMA) [3], glucose uptake in young men (HIMA > PIMA) [5] and the maximal torque (PIMA > HIMA) [7].

However, some studies did not reveal a difference between HIMA and PIMA in any of their analyzed parameters: MVIC, TTF and mean heart rate relative to rest for the biceps brachii muscle [12]; motor unit discharge characteristics and extent of motor unit synchronization at 4.4% of the MVIC (PIMA) or 3.8% of the one-repetition maximum (HIMA) for the first dorsal interosseus muscle [6] as well as EMG amplitudes at 20%, 30%, 40%, and 50% of the MVIC for the soleus muscle [1].

Regarding muscle oxygenation, Booghs et al. (2012) analyzed tissue oxygenation index (TOI) and normalized total hemoglobin index (nTHI) of the biceps brachii muscle between HIMA and PIMA at 20% and 60% of the MVIC [11]. They found similar behaviors for both tasks at both intensities. However, at 60%, the TOI seemed to decrease more during PIMA compared to HIMA. A statistical comparison was not provided.

The main objective of the present pilot study was to compare the muscle oxygenation and blood filling of microvessels between HIMA and PIMA maintained until muscle failure (fatiguing task). Previous studies have revealed that during isometric muscle actions homeostatic steady states in oxygen saturation are possible even at submaximal and maximal intensities [11, 13–17]. Thus, not only the extent and slopes of deoxygenation but also the time to leveling off into a steady state was compared between HIMA and PIMA in the present study. Our research group has differentiated two behavioral types in the regulation of local capillary venous oxygen saturation (SvO_2) and relative hemoglobin amount (rHb) in superficial muscle tissue [13]. In type I, SvO_2 and rHb generally decrease and level off into steady states. Both parameters behave nearly parallel to each other. In contrast, an increase in rHb despite a further decrease in SvO_2 is the main characteristic of type II. Thus, the behavior is partly inverse. The occurrence of type I or type II was also documented in the present study. Our research group suggested that the type depends on the oxygenation level [17]. The increase in rHb after reaching its global minimum (type II) might be triggered if SvO_2 level drops below a threshold around 59% [17]. Thus, the oxygenation level at the moment of global rHb minimum was compared between HIMA and PIMA here.

Furthermore, TTF was compared between HIMA and PIMA since it seems to be one of the most promising variables as mentioned above. The analyses should gain further data concerning the supposed distinction of two different isometric muscle actions [1–6, 12].

It must be noted that a holding task per se does not automatically prevent a muscle shortening (e.g., overcoming an applied weight). If tolerated, minimal concentric contractions are possible to compensate for a prior lengthening. At macro level this still might be interpreted as an isometric muscle action. In this regard, intermittent voluntary muscle twitches (Twitch) were performed by a another group of subjects during a weight holding task in the present study. Subjects were instructed to twitch rapidly and shortly. Caused by that kind of minor concentric contractions, the character of isometric muscle action might be changed also during the isometric phases [2]: from reacting (HIMA) to acting (PIMA). It was also questioned, if the muscle twitches have an influence on all above-mentioned variables. From a general understanding, isometric muscle actions performed at submaximal intensities were supposed to lead to a restriction of oxygen and blood supply caused by high intramuscular pressures [18–22]. Rapid but short auxotonic contractions with minimal motion of the limb (Twitch) change muscle length and tension temporarily. This might support the capillary blood flow by serving as a kind of pump. Consequently, blood and oxygen supply could be changed. The TTF might also be different because of an altered neuromuscular control.

Materials and methods

Subjects

Both biceps brachii muscles of twelve subjects were examined in this pilot study. Two of these had to be excluded due to pain or discomfort during the trials ($n = 10$; 8 males, 2 females, mean age ± standard deviation (SD) = 30.70 ± 11.67 years, 72.70 ± 11.00 kg, 1.78 ± 0.08 m, BMI: 22.84 ± 2.00 $\frac{kg}{m^2}$, two lefties).

Measuring technique

The valid and reliable O2C spectrophotometer (Oxygen To See; LEA© Medizintechnik GmbH, Gießen, Germany) mainly recorded the local capillary venous oxygen saturation (SvO_2, not to be confused with the systemic mixed venous oxygen saturation) and the relative hemoglobin amount (rHb) [23–27]. The device sent light (650–810 nm, 1 nm resolution) into the superficial muscle tissue through the measuring probe ("LF-3", source-detector separation: 14.5 mm, tissue penetration depth: ~ 12 mm). The probe was fixed above the biceps brachii muscle belly along its fibers. The amount of backscattered light and changed wavelength was used for calculating rHb in arbitrary units (AU) in dependence of the absorption rate. SvO_2 (in %, absolute measurement) was calculated as a ratio of primarily oxygenated and deoxygenated hemoglobin as well as myoglobin. The sampling rate was 40 Hz. To minimize light effects on the probe, the room light was dimmed. Even though the O2C device mainly analyze the capillary venous system, the influence of arterial blood cannot be excluded completely [28–31]. Furthermore, myoglobin also influences measurements during exercise although in a lower extent compared to rest [32, 33].

Study design and overall procedure

All subjects started with a MVIC-test with one arm randomly selected (coin toss). Two different determination methods of the MVIC were utilized according to the subsequent fatiguing tasks. The first group performed HIMA and PIMA (HP-group), the second group performed HIMA and Twitch (HT-group) (specific description see below). The authors find this acceptable since comparisons were only made within subjects. The sequence of fatiguing tasks was randomized by coin toss. The rest between fatiguing tasks was at least 3 min. Afterwards, the same procedure was applied to the other arm. An intensity of 60% of the MVIC was chosen for the fatiguing tasks according to Booghs et al. (2012) [11], and because it might lead to high intramuscular pressures to restrict the blood and oxygen supply [18]. The recording of parameters (SvO_2 and rHb) started 10 s before and lasted until two minutes after every task.

Procedures of the HP-group trials

During the MVIC-tests, the subjects of the HP-group sat on a measuring chair in an upright position. They pulled two times as strong as possible on a cuff which was connected to a fixed strain gauge (Fig. 1a). The rest between

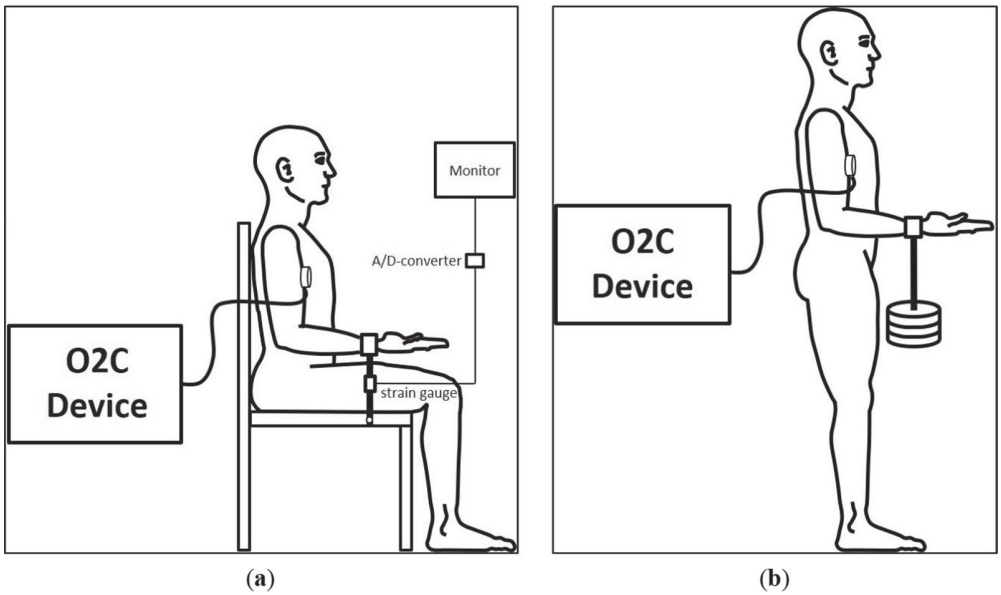

Fig. 1 Positioning and set up during the tasks, **a** pulling isometric muscle action (PIMA), **b** holding isometric muscle action (HIMA) and Twitch, reprinted from Dech et al. (2021), with permission [17]

trials was at least two minutes. The cuff was applied 2–3 cm proximal to the wrist crease of the subject whose upper arm was in contact with the thorax (anteversion–retroversion 0°, adduction–abduction 0°). The elbow joint was flexed (90°) and the forearm was maximally supinated. The highest measured force value of the two trials was determined as MVIC.

During fatiguing PIMA (Fig. 1a), the arm and sitting positions were identical to the MVIC-tests. The subjects pulled on a fixed strain gauge and maintained the target force of 60% of the MVIC for as long as possible. For that, they had visual feedback (pointer) on a monitor. As soon as the force remained below the target for 2 s, the rater prompted the subject to stop the task.

During fatiguing HIMA, the subjects had to hold the respective weight for as long as possible with the same arm position but while standing, which allows the weight to hang free (Fig. 1b). The weight was taken off as soon as the elbow angle exceeded 90° for 2 s, assessed by the rater subjectively.

Procedures of the HT-group trials

The MVIC-test of the HT-group was performed by holding a weight while standing and using the same arm and cuff position as described in the HP-group section (Fig. 1b). The weights were added progressively within maximal five steps (accuracy: ± 1 kg). The test started with an estimated appropriate first weight. The rater hooked the respective weight onto the cuff. The rest between steps had to be sufficient for the subject (30 s–2 min., depending on the load). The highest weight which could be held for 1 s was determined as MVIC. This procedure did not achieve the same accuracy as determined by strain gauge measurements but was chosen in favor of the fatiguing weight holding tasks.

The fatiguing HIMA was performed identically as described for the HP-group. The same applies for the fatiguing Twitch task except for additional intermittent voluntary contractions (muscle twitches) every 7 s. For that, an acoustic signal was given. The subjects were instructed to perform twitches rapidly but with a minimal excursion of the forearm which was visually inspected by the rater. An objective determination of the twitches was not performed (see limitations). The rater took off the weight as soon as the subject could not twitch again or if the elbow angle exceeded 90° for 2 s, visually assessed by the rater.

Data processing

All SvO_2 and rHb curves were smoothed by using the software in NI DIAdem™ 2017 (moving average, maximal smoothing width: 50). The following variables were extracted for each trial:

Variable (1.): SvO_2 baseline value (in %) was quantified by the arithmetic mean (M) of the values of the first 10 s when the arm was held in measurement position (described above).
Variable (2.): Maximal deoxygenation (max. SvO_2 decrease) was determined as the difference between the baseline and the minimum of SvO_2. Values are presented in percent points (pp) and additionally in % related to the respective baseline.
Variable (3.): Slope of initial linear SvO_2 decrease after start of loading (SvO_2 slope) was quantified by the slope of the least square regression line. According to Felici et al. (2009) [34], interval limits for calculating the slope were set respect of the start and end point of the first long negative plateau of the first derivative of the smoothed SvO_2 curve.
Variable (4.): SvO_2 level at global minimum of rHb (SvO_2 at rHb min.) corresponds to SvO_2 value at the reversal point (RP) in type II.
Variable (5.): Time to leveling off into a steady state of SvO_2 (TSS) is the time period in s from start of loading to the end of the initial linear phase (start of leveling off into a steady state).
Variable (6.): Time to task failure (TTF) was defined as the time period in s from start to end of loading.

According to Dech et al. (2020) [13], the curves were also assigned visually to type I (parallel behavior of SvO_2 and rHb, Fig. 2a) or type II (increase in rHb after the RP, Fig. 2b). The assignment and all mentioned variables (1.–6.) of each trial can be found in Additional file 1: Table S1.

Statistical analyses

IBM SPSS Statistics 26 was used for statistical analyses. Due to discomfort triggered by the cuff, the trials of two subjects and the trials of one side of two other subjects had to be excluded. Another trial (Twitch) was excluded because the participant failed to perform the twitches rapidly and shortly. In total, 36 trials of ten subjects were included for statistical analyses (HP and HT $n = 9$ trials for each task).

All mentioned variables (1.–6.) were compared between fatiguing tasks but only within subjects (HIMA vs. PIMA and HIMA vs. Twitch as well as HIMA vs. PIMA incl. Twitch). Both arms were considered together in all analyses, because MVICs of right (70.02 ± 23.83 Nm) and left arm (69.31 ± 21.69 Nm) did not differ significantly ($t(11) = 0.80$, $p = 0.442$).

All data were normally distributed (Shapiro–Wilk-test, $p > 0.05$), except for baseline values of Twitch ($p = 0.017$) and max. SvO_2 decrease of all HIMAs ($p = 0.019$). Regarding normal distributed variables, analyses of differences were made by parametric tests (t-tests for

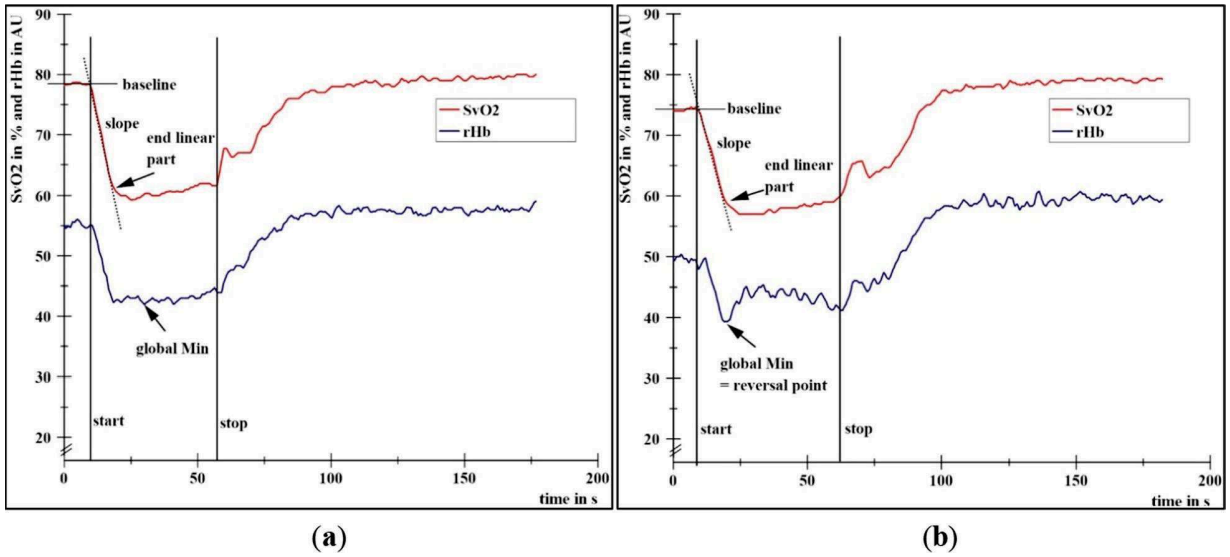

Fig. 2 Curve examples of the local capillary venous oxygen saturation of hemoglobin (SvO_2, red) and the relative hemoglobin amount (rHb, blue) during two fatiguing isometric muscle actions at 60% of the MVIC of the right biceps brachii muscle of one female (37 years, 1.60 m, 58 kg): **a** HIMA (type I) and **b** PIMA (type II). Start and stop of loading are indicated by vertical lines. Baseline, slope, end of linear slope part and the global minimum are given. The global Min in **b** refers to the reversal point. All curves were smoothed (moving average, maximal smoothing width: 50)

dependent samples). Comparisons including not normally distributed variables were made by exact Wilcoxon signed-rank test. Numbers of type I and type II behaviors per task were compared by Chi-squared test. An alpha error of 5% was chosen for all tests.

Pearson's correlation coefficients (r) were calculated between TTF (6.), max. SvO_2 decrease (2.) and SvO_2 slope (3.) of all 36 trials.

Results

Tasks did not differ significantly regarding oxygenation variables (1.–5.). In regard to TTF (6.), HIMA and PIMA did not differ significantly despite a trend in favor of PIMA. The TTF during Twitch was about 10 s longer than during HIMA ($t(8) = -2.40$, $p = 0.043$). The comparison of all HIMAs and PIMAs (incl. Twitches) also showed a significant difference ($t(17) = -2.15$, $p = 0.047$). The inference statistics of all described variables can be found in Table 1.

Figure 2 illustrates the two occurred behavioral patterns (type I and II) as described in detail by Dech et al. [13].

Based on curve shapes, Table 2 shows the categorization of all fatiguing tasks and MVIC-tests into type I (n = 9) and type II ($n = 27$). The amounts of trials assigned to type I and type II were similar between HIMA and PIMA (χ^2 (1, $n = 18$) = 0.23, $p_{exact} = 1.00$ as well as HIMA and Twitch (χ^2 (1, $n = 18$) = 0.00, $p_{exact} = 1.00$). The assignment was also similar overall trials (HIMA vs. PIMA (incl. Twitch): χ^2 (1, $n = 36$) = 0.15, $p_{exact} = 1.00$.

Regarding all 36 trials, correlation coefficients were $r = 0.31$ ($p = 0.069$) between TTF and SvO_2 slope; $r = -0.13$ ($p = 0.463$) between TTF and max. SvO_2 decrease and $r = -0.88$ ($p < 0.001$) between SvO_2 slope and max. SvO_2 decrease.

Discussion

Muscle oxygenation during different muscle actions

In respect of a possible objective distinction of two isometric modalities, oxygenation variables were compared between HIMA and PIMA. No significant differences were found regarding the maximal deoxygenation, saturation slopes, saturation level at global minimum of rHb and time to leveling off into a saturation steady state. This indicates HIMA and PIMA cannot be discriminated by these variables on the basis of the small sample size investigated here. Regarding the saturation slopes, the result is in accordance with Booghs et al. [11]. They utilized the near infrared spectroscopy technique (NIRS), which is comparable with our used light spectrometry [13, 17]. To our best knowledge, the remaining oxygenation variables were considered for the first time regarding the comparison of HIMA and PIMA.

As generally accepted, isometric muscle actions should restrict the capillary blood flow due to the high intramuscular pressure already at low intensities [19, 20]. However, the occlusion threshold might

Table 1 Inference statistics of within-subject comparisons between tasks

Variable	Group	Fatiguing task	Mean ± SD	t-values (df)/z-values	Significance level
(1.) Baseline value in %	HP	HIMA	73.78 ± 6.63	$t(8) = -1.53$	$p = 0.164$
		PIMA	77.44 ± 4.06		
	HT	HIMA	74.61 ± 6.98	$z = -0.30$, $n = 9$	$p_{exact} = 0.820$
		Twitch	74.00 ± 5.01		
	Both	HIMA	74.19 ± 6.62	$z = -1.15$, $n = 18$	$p_{exact} = 0.265$
		PIMA & Twitch	75.72 ± 4.77		
(2.) max. SvO_2 decrease in pp (% to baseline)	HP	HIMA	16.02 ± 7.75 (21.71 ± 10.50)	$t(8) = -1.73$	$p = 0.121$
		PIMA	20.61 ± 10.16 (26.61 ± 13.12)		
	HT	HIMA	30.33 ± 14.60 (40.65 ± 19.57)	$t(8) = -0.12$	$p = 0.909$
		Twitch	30.65 ± 16.76 (41.42 ± 22.65)		
	Both	HIMA	23.17 ± 13.52 (31.23 ± 18.22)	$z = -0.81$, $n = 18$	$p_{exact} = 0.442$
		PIMA & Twitch	25.63 ± 14.40 (33.85 ± 19.02)		
(3.) SvO_2 slope in pp s^{-1}	HP	HIMA	− 2.21 ± 1.51	$t(8) = 0.55$	$p = 0.598$
		PIMA	− 2.41 ± 1.59		
	HT	HIMA	− 3.63 ± 1.56	$t(8) = -0.94$	$p = 0.373$
		Twitch	− 3.11 ± 1.31		
	Both	HIMA	− 2.79 ± 1.60	$t(17) = -0.11$	$p = 0.913$
		PIMA & Twitch	− 2.76 ± 1.46		
(4.) SvO_2 at rHb min. in %	HP	HIMA	61.96 ± 3.87	$t(8) = -0.90$	$p = 0.392$
		PIMA	62.42 ± 4.56		
	HT	HIMA	58.66 ± 2.61	$t(8) = -0.31$	$p = 0.768$
		Twitch	58.81 ± 3.04		
	Both	HIMA	60.31 ± 3.63	$t(17) = -0.89$	$p = 0.388$
		PIMA & Twitch	60.62 ± 4.20		
(5.) TSS in s	HP	HIMA	7.72 ± 3.01	$t(8) = -0.5$	$p = 0.630$
		PIMA	8.45 ± 2.72		
	HT	HIMA	7.61 ± 2.61	$t(8) = -1.01$	$p = 0.344$
		Twitch	8.78 ± 2.92		
	Both	HIMA	7.67 ± 2.74	$t(17) = -1.05$	$p = 0.309$
		PIMA & Twitch	8.62 ± 2.74		
(6.) TTF in s	HP	HIMA	44.80 ± 18.06	$t(8) = -0.90$	$p = 0.394$
		PIMA	50.33 ± 9.46		
	HT	HIMA	42.63 ± 7.64	$t(8) = -2.40$	**$p = 0.043$**
		Twitch	52.78 ± 11.61		
	Both	HIMA	43.72 ± 13.50	$t(17) = -2.15$	**$p = 0.047$**
		PIMA & Twitch	51.55 ± 10.35		

HIMA, holding isometric muscle action; max. SvO_2 decrease, maximal deoxygenation; PIMA, pulling isometric muscle action; rHb, relative hemoglobin amount; SvO_2, local capillary oxygen saturation; SvO_2 at rHb min., SvO_2 level at global minimum of rHb; SvO_2 slope, slope of initial linear SvO_2 decrease; TTF, time to task failure; TSS, time to leveling off into a steady state of SvO_2

Significant differences are in bold

vary between individuals and muscles [35]. In contrast, auxotonic contractions possibly support oxygen and blood supply due to the reduced muscle tension during the lowering phase. Comparisons between HIMA and Twitch did not show any significant differences in the analyzed variables of the present study. Thus, the curve characteristics of SvO_2 and rHb seem not to be influenced by twitches. Otherwise, the minimal

Table 2 Number (n) of type I and type II behaviors of the local capillary venous oxygen saturation and blood filling during the tasks separated by groups and overall trials of ten subjects

Task	HP-group		HT-group		Overall trials	
	HIMA	PIMA	HIMA	Twitch	HIMA	PIMA (incl. Twitch)
Type I (n = 9)	4	3	1	1	5	4
Type II (n = 27)	5	6	8	8	13	14
n = 36	9	9	9	9	18	18

HIMA, holding isometric muscle action; PIMA, pulling isometric muscle action

motion of the limb caused by rapid voluntary muscle contractions might not be enough to change the muscle oxygenation and blood filling of microvessels significantly.

Previous studies revealed that increases in capillary blood filling (rHb) [13, 15, 34, 36–38] and homeostatic steady states in the oxygen saturation [11, 13–16] are possible already during isometric muscle actions without twitches. These data suggest a probable maintenance of capillary blood flow. Recently, it was discussed that this could be achieved by the anatomical placement of capillaries within muscle tissue and the oscillatory behavior of muscle fibers during isometric muscle actions [17].

The behavior of oxygen saturation and blood filling can be differentiated by two types [13]; indicated by the SvO_2 level at global minimum of rHb [17]. We have suggested a threshold of around 59% whereby values above this threshold are associated with type I (parallel behavior of SvO_2 and rHb) [17]. In contrast, if the saturation decreases below that threshold, rHb starts to increase which is related to type II. Such behavior might reflect a protective measure to impede a further deoxygenation as discussed previously [17]. The distribution of type I and type II assigned measurements reflects a qualitative behavior of the measured parameters SvO_2 and rHb. In the presented study, extents of deoxygenation and SvO_2 levels at global minimum of rHb did not differ significantly between HIMA and PIMA as well as not between HIMA and Twitch. The amount of type I and type II assigned measurements are, as a consequence, not significantly different (Table 2). Thus, the occurrence of type I and type II seems to be independent of the isometric task.

At last, a high and significant negative correlation ($r = -0.88$) between SvO_2 decrease and SvO_2 slope was found over all measurements: the greater the deoxygenation, the steeper the drop. This is plausible by considering the similar TSSs found across trials.

Time to task failure during different muscle actions

The TTF was the performance variable in the presented study. It appeared to be longer during PIMA compared to HIMA. However, the difference (5.51 ± 18.37 s) was not significant (methodological limitations see below). This is in line with the results of other studies which also examined the TTF of the biceps brachii muscle [11] or elbow flexor muscles [3] with similar settings for HIMA and PIMA at the same intensity (60% of the MVIC) and same forearm position (horizontal). However, during lower efforts ($\leq 30\%$ of the MVIC) of the elbow flexor muscles, the TTF of HIMA seems to be significantly shorter than the TTF of PIMA [3, 4, 9, 11]. If the isometric muscle action is, by contrast, performed in a vertical forearm position or during muscle activities at 45% and 60% of the MVIC, the TTF was found to be similar between tasks [3, 4]. This indicates that both, the intensity and forearm position, influences the performance of elbow flexor muscles. Regarding the first dorsal interosseous muscle, Maluf et al. (2005) found differences in the TTF between HIMA and PIMA at 20% of MVIC (TTF HIMA < TTF PIMA) but not at 60% [39].

However, the order of tasks in the presented study might have influenced the TTF in favor of HIMA. In case HIMA was performed at first (in 6 of 9 cases), the relation of PIMA/HIMA amounted to $\sim 1.17 \pm 0.68$; in case PIMA was performed at first (3 of 9 cases) the relation PIMA/HIMA was $\sim 1.61 \pm 0.53$.

Additionally, it should be mentioned again that holding tasks as performed in the present and the other mentioned studies does not imply a pure isometric muscle action. In general, muscles show slight oscillations during isometric muscle actions [2, 10, 40–44]. Thus, minor muscle shortenings and lengthenings are present. In case of weight holding, slight motions around the given joint angle have been accepted. The tolerance in different studies ranged from 2° to 10°. This also includes minor concentric contractions to lift the weight back to the starting angle position. Such muscle actions interrupt a pure

HIMA and it was hypothesized that the muscle action could be switched to a PIMA, thereby [2]. In the present study, little concentric contractions were documented during four of nine HIMAs in the HP group. This also might have biased the result and might explain why the trend of a longer TTF during PIMA did not reveal statistical significance. Different experimental procedures were applied by Schaefer and Bittmann (2017, 2021) examining elbow extensors. The methods might repeal the above-mentioned problem for HIMA during weight holding [2, 10]. In the first study, a pneumatically driven measurement system was used to realize HIMA and PIMA [2]; in the second one, an interaction between two subjects comparable with arm wrestling [10]. The former study controlled for a concentric contraction (failure criterion) and the latter one facilitates the adherence to tasks (acting part: PIMA and reacting part: HIMA). The reacting (holding) subject just had to adapt to the input of the acting (pushing) partner. In both studies, the forearm was positioned vertically and significant differences regarding the TTF of elbow extensors at 80% of the MVIC (TTF HIMA < TTF PIMA) were found. Thus, not only the intensity of muscle activity and positioning but also the examined muscle and experimental procedure might play a role.

In this regard, the present study revealed that intermittent voluntary muscle twitches during a holding task extended the TTF significantly (~ 10 s). It was assumed that twitches induce a switch of the muscle action from reacting (HIMA) to acting (PIMA) during the isometric phases. Considering PIMA and Twitch together and comparing theses to all HIMA trials, the TTF still differs significantly. As discussed above, the behavior of SvO_2 and rHb in conjunction with variables 1.–5. were similar between tasks. Thus, the longer TTF during PIMA (incl. Twitch) seems not to be derived from a different oxygen or blood supply. This is further supported by the analyzed correlations. Independently of the isometric task, very low to low, non-significant correlations between TTF and SvO_2 decrease as well as TTF and SvO_2 slopes ($r = -0.13$ and 0.31, respectively) were found. These results indicate a reasonable independence of the TTF from the deoxygenation as long as SvO_2 levels off into a homeostatic steady state. Booghs et al. (2012) also conclude that the decrease in muscle oxygenation is not a significant predictor of the TTF although they did not rule out its contribution to muscle fatigue [11]. Moreover, an enhancement of muscle oxygenation (oxygen half time recovery) as revealed in rock climbers during fatiguing forearm muscle contractions at 60% of the MVIC by New Zealand blackcurrant extract did not affect the TTF [45]. Consequently, there must be other factors why TTF was found to be extended during Twitch. An increased blood flow and altered muscle metabolism might play a role. In this regard, a contribution of muscle pump and vasodilation starting immediately after onset of dynamic and even single contractions has been discussed [46–49]. However, the indirectly related parameters measured in the presented study did not change subsequently to a single twitch. This could possibly be explained by the missing relaxation phase since the examined muscle had to act isometrically afterwards. Thus, we rather assume neuromuscular factors than metabolic ones.

It was previously suggested that the neuromuscular control could play a decisive role in the distinction of HIMA and PIMA [2]. This was based on the assumption that PIMA is closer to the motor control processes of a concentric contraction [2]. In contrast, HIMA might show a proximity to eccentric muscle action [2]. Eccentric muscle actions involve more complex control strategies compared to concentric ones possibly resulting in a greater central fatigue [2, 50–54]. Thus, the more complex control processes suggested for HIMA might be one reason for the often found shorter TTF compared to PIMA [2–4, 9–11]. The significantly longer TTF during Twitch in the present study, could support the assumption of a switch from HIMA to PIMA.

Because our findings should be assessed as preliminary, future investigations with larger samples are indicated to verify the results and examine other parameters in different muscles for an explanation of the potential longer TTF during PIMA. Further covariates like training status have not been considered yet and could also influence the result of TTF.

Study limitations

Limitations regarding the used measurement technique, not examined skinfold thickness in relation to the penetration depth of the light and different determinations methods of the MVIC have been addressed previously [13, 17].

Some more limitations need to be emphasized especially regarding the TTF. During HIMA and Twitch, the loading was stopped as soon as the elbow angles exceeded 90° for more than 2 s and if twitches were not visible anymore. No objective instrument (e.g., goniometer) was used to reach highest control accuracy. The measurement error could have influenced individual trials but on group level the random error ought to be leveled out. However, the amplitude and velocity of twitches might have varied between trials. TTFs could also be influenced by the measurement position, as discussed before. Subjects used a horizontal forearm position in all measurements but changed from standing to sitting position between HIMA and PIMA. Thus, activation of trunk stabilizing and postural muscles were different between

tasks with an expected higher activity during HIMA (standing). However, the biceps brachii muscle had to be equally activated with 60% of the MVIC within the muscle chain to maintain a 90° elbow flexion. If the trunk stabilizing muscles were not strong enough, the whole body would be bend forward. This was prevented by the counter bearing between the upper arm and thorax. Furthermore, due to the exclusion of measurements (see statistical analysis) the sequence of tasks of HP-group were not balanced anymore (n = 6 HIMA first; n = 3 PIMA first). Thus, effects of fatigue might have influenced the results as discussed above. In contrast, the order was still nearly balanced in HT group (n = 4 HIMA first, n = 5 Twitch first).

Conclusions

Muscle oxygenation seem to be similar during HIMA and PIMA (especially the max. deoxygenation and oxygenation level at global minimum of blood filling of the venous capillary system). As a consequence, the behavioral pattern of the parameters SvO_2 and rHb (type I: parallel or type II: partly inverse) occurred independently of the isometric task. In addition, intermittent voluntary muscle twitches might not alter their behavior. Possibly, oxygen and blood supply is already sufficient during isometric muscle actions without twitches. This could also explain why the TTF did not substantially correlate with the maximal deoxygenation independently of the isometric task.

In respect of the TTF, the study adds data regarding a possible objective distinction between two types of isometric contractions. The TTF tend to be shorter during HIMA compared to PIMA of the elbow flexors performed in a horizontal forearm position at 60% of the MVIC. Considering Twitch, the trend reveals statistical significance. More research is necessary in that field, especially at higher intensities (≥ 60% MVIC), different muscles and positioning.

Due to the mentioned study limitations, pilot character of the study and scarce literature on that topic, the conclusions should be seen as preliminary.

Abbreviations

AU: Arbitrary units; BMI: Body mass index; EMG: Electromyography; HIMA: Holding isometric muscle action; HP: HIMA vs. PIMA group; HT: HIMA vs. Twitch group; M: Arithmetic mean; max. SvO_2 decrease: Maximal deoxygenation; MVIC: Maximal voluntary isometric contraction; NI DIAdem™: National Instruments DIAdem™; NIRS: Near infrared spectroscopy technique; O2C: Oxygen To See; LEA Medizintechnik GmbH; PIMA: Pushing or pulling isometric muscle action; rHb: Relative hemoglobin amount; RP: Reversal point; SD: Standard deviation; SvO_2: Local capillary venous oxygen saturation of hemoglobin; SvO_2 at rHb min.: SvO_2 level at global minimum of rHb; SvO_2 slope: Slopes of initial linear SvO_2 decrease; TTF: Time to task failure; TSS: Time to leveling off into a steady state of SvO_2; Twitch: Intermittent voluntary muscle twitch.

Supplementary Information

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Additional file 1: Table S1. Extracted data from smoothed curves (moving average, maximal smoothing width: 50).

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Author contributions

SD: data analysis, writing original draft of manuscript. FB and LVS: study design. All authors: data collection and interpretation, revision. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and supplementary material, respectively.

Declarations

Ethics approval and informed consent to participate

The study was conducted according to the declaration of Helsinki and was approved by the ethics committee of the University of Potsdam, Germany (approval No. 28-2017). All subjects gave their written informed consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Article

Muscle oxygenation and time to task failure of submaximal holding and pulling isometric muscle actions and influence of intermittent voluntary muscle twitches

(Dech S, Bittmann FN, Schaefer LV)

Table S1. Extracted data from smoothed curves (moving average, maximal smoothing width: 50).

subject no._arm_task	baseline value SvO_2 in %	max. SvO_2 decrease in pp	SvO_2 slope in pp s^{-1}	SvO_2 at rHb min. in %	TSS in s	TTF in s	MVIC in Nm	behavioral type of SvO_2 and rHb
HP group								
01_ri_H	64.01	13.29	-1.00	58.70	6.93	45.03	-	II
01_le_H	80.74	15.52	-1.87	66.28	10.75	43.08	-	I
02_ri_H	81.10	18.10	-3.11	64.00	4.50	37.20	-	I
02_le_H	72.86	14.86	-1.77	62.00	9.70	43.08	-	II
03_ri_H	78.02	34.02	-5.26	57.00	4.28	25.45	-	II
03_le_H	74.51	19.51	-3.70	59.00	3.33	19.55	-	II
05_ri_H	-	-	-	-	-	-	-	-
05_le_H	-	-	-	-	-	-	-	-
06_ri_H	65.78	11.16	-1.19	60.17	10.45	74.38	-	II
06_le_H	67.54	7.31	-0.90	61.50	8.95	70.48	-	I
07_le_H	-	-	-	-	-	-	-	-
07_le_H	79.43	10.43	-1.09	69.00	10.63	45.03	-	I
01_ri_P	73.99	19.95	-1.42	58.50	13.43	48.93	65.66	II
01_le_P	82.62	15.56	-1.70	67.23	11.65	47.94	63.12	I
02_ri_P	69.81	9.81	-0.80	62.00	10.35	58.70	93.38	II
02_le_P	80.32	21.32	-2.79	62.00	5.50	47.00	89.28	II
03_ri_P	78.29	34.29	-5.14	59.00	7.23	54.80	100.45	II
03_le_P	78.08	38.08	-4.85	58.00	7.60	48.93	98.98	II
05_ri_P	-	-	-	-	-	-	-	-
05_le_P	-	-	-	-	-	-	-	-
06_ri_P	79.64	23.45	-2.33	60.30	7.38	66.55	30.89	II
06_le_P	73.91	13.70	-1.77	62.76	6.87	48.12	33.54	I
07_ri_P	-	-	-	-	-	-	-	-
07_le_P	80.32	9.32	-0.90	72.00	6.05	31.96	44.63	I
M	**75.61**	**18.32**	**-2.31**	**62.19**	**8.09**	**47.57**	**68.88**	**-**
SD	**5.66**	**9.05**	**1.51**	**4.11**	**2.81**	**14.27**	**27.93**	**-**
HT group								
01_ri_H	62.38	14.38	-1.51	59.00	7.70	47.00	60.00	II
01_le_H	84.07	24.19	-3.26	60.56	9.70	48.95	62.50	II
02_ri_H	78.62	52.11	-6.36	55.93	5.48	43.08	72.00	II
02_le_H	78.34	54.18	-4.69	58.58	9.68	43.08	74.40	II
05_ri_H	-	-	-	-	-	-	-	-
05_le_H	-	-	-	-	-	-	-	-
07_ri_H	72.05	30.51	-2.71	55.86	8.28	35.23	100.80	II
07_le_H	78.28	28.28	-3.64	60.00	2.40	31.30	96.00	II
09_ri_H	76.89	33.09	-4.17	55.56	6.15	39.13	84.00	II
11_ri_H	64.92	23.54	-2.27	58.89	10.98	56.78	70.31	II
11_le_H	75.92	12.67	-1.66	63.58	8.13	39.15	66.38	I
01_ri_T	62.38	7.38	-1.49	59.00	5.18	48.95	-	II
01_le_T	75.27	17.74	-1.96	60.82	7.50	66.58	-	II
02_ri_T	76.21	50.69	-4.73	55.62	10.58	58.73	-	II
02_le_T	79.85	53.04	-5.11	55.36	9.70	37.18	-	II
07_ri_T	74.73	25.44	-3.41	57.64	5.13	31.33	-	II
07_le_T	75.81	24.81	-3.00	60.00	7.98	60.03	-	II
09_ri_T	70.21	42.68	-3.95	56.60	10.53	60.68	-	II
09_le_T	-	-	-	-	-	-	-	-
11_ri_T	75.17	41.30	-2.71	59.11	14.43	54.80	-	II
11_le_T	76.33	12.74	-1.65	65.15	7.98	56.78	-	I
M	**74.30**	**30.49**	**-3.24**	**58.74**	**8.20**	**47.71**	**76.27**	-
SD	**5.90**	**15.26**	**1.40**	**2.75**	**2.75**	**10.87**	**14.41**	**-**

Abbreviations: H, holding; le, left; min., minimum; M, arithmetic mean; MVIC, maximal voluntary isometric contraction; no., number; P, pulling; pp, percent points; rHb, relative hemoglobin amount; ri, right; SD, standard deviation; SvO_2, local capillary venous oxygen saturation; T, intermittent voluntary muscle twitch; TSS, time to leveling off into a steady state of SvO_2; TTF, time to task failure.

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Assessment of the Adaptive Force of Elbow Extensors in Healthy Subjects Quantified by a Novel Pneumatically Driven Measurement System with Considerations of Its Quality Criteria

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Abstract: Adaptive Force (AF) reflects the capability of the neuromuscular system to adapt adequately to external forces with the intention of maintaining a position or motion. One specific approach to assessing AF is to measure force and limb position during a pneumatically applied increasing external force. Through this method, the highest (AF_{max}), the maximal isometric ($AFiso_{max}$) and the maximal eccentric Adaptive Force ($AFecc_{max}$) can be determined. The main question of the study was whether the $AFiso_{max}$ is a specific and independent parameter of muscle function compared to other maximal forces. In 13 healthy subjects (9 male and 4 female), the maximal voluntary isometric contraction (pre- and post-MVIC), the three AF parameters and the MVIC with a prior concentric contraction (MVICpri-con) of the elbow extensors were measured 4 times on two days. Arithmetic mean (M) and maximal (Max) torques of all force types were analyzed. Regarding the reliability of the AF parameters between days, the mean changes were 0.31–1.98 Nm (0.61%–5.47%, p = 0.175–0.552), the standard errors of measurements (SEM) were 1.29–5.68 Nm (2.53%–15.70%) and the ICCs(3,1) = 0.896–0.996. M and Max of $AFiso_{max}$, AF_{max} and pre-MVIC correlated highly (r = 0.85–0.98). The M and Max of $AFiso_{max}$ were significantly lower (6.12–14.93 Nm; $p \leq$ 0.001–0.009) and more variable between trials (coefficient of variation (CVs) $\geq$ 21.95%) compared to those of pre-MVIC and AF_{max} (CVs $\leq$ 5.4%). The results suggest the novel measuring procedure is suitable to reliably quantify the AF, whereby the presented measurement errors should be taken into consideration. The $AFiso_{max}$ seems to reflect its own strength capacity and should be detected separately. It is suggested its normalization to the MVIC or AF_{max} could serve as an indicator of a neuromuscular function.

Keywords: adaptive force; neuromuscular functionality; sensorimotor control; isometric muscle action; eccentric muscle action; maximal voluntary contraction; adaptive holding capacity; reliability; validity

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1. Introduction

Forces which are generated by human muscles are generally related to the strength of a person, e.g., maximal strength, strength endurance or power [1]. In addition to such common measures, Adaptive Force (AF) was introduced recently [2–5]. AF not only requires muscle strength but also sensorimotor control. It reflects the neuromuscular functionality of adapting adequately to external forces with the intention of maintaining a desired position or movement. Thereby, the external force can be constant or vary in size. The adaptation to constant loads can be measured by holding a defined weight or resisting an applied constant force isometrically in a specific joint angle. This is termed "position task" [6,7], or "eccentrically loaded isometric contraction" [8], with an underlying "holding isometric muscle action" (HIMA) [9].

However, in daily activities and sports, persons have to deal mainly with external forces which vary in size. The specific task of adapting to varying external forces has been rarely considered in sports or movement science yet [2–5]. Such adaptation implies an

evident relevance of avoiding an inappropriate lengthening of muscles, accompanied by a destabilization of joints despite an external force impact. This plays an important role, especially during an increasing force when a position, object or the moving body should be held or decelerated (e.g., during landing phases while running, descending stairs or side cutting maneuvers; resisting a tackle). An inadequate adaptation to increasing forces might result in impaired joint stability. As a possible consequence, injuries or damages of muscles, tendons and joints might occur [2,4,10,11]. For this reason, assessing AF could be a novel approach to understand the mechanisms behind it and to derive preventive strategies.

To measure adaptation to varying or increasing forces, no common measurement procedure is currently available. Although isokinetic devices can apply varying forces, these serve generally to keep the desired movement velocity constant. Thereby, the isokinetic device adapts to the generated force of the person. However, in capturing the AF to varying or increasing forces, it is crucial that the tested person responds to the applied force. This could be enabled by an isokinetic device if loads would be gradually applied, as performed by Oranchuk et al. (2021) recently [12]. However, different slopes of the force–time curve were suggested in determining the AF during a manual muscle test. These include an exponential phase in the beginning [4]. Another approach is to use pneumatics. A prototype of a pneumatic AF-measuring system (SeBit) has already been constructed and evaluated [3]. During an AF-measurement with the SeBit, a pneumatically driven lever pushes against the limb of the participant. The participant's task is to resist and hold the given start position for as long as possible. Due to the continuous external force increase, two phases of muscle actions generally occur: firstly, an isometric, and secondly, an eccentric one. During the isometric phase, the participant holds the limb position isometrically by adapting adequately to the increasing external force. Thereby, the maximal isometric AF ($AFiso_{max}$) is determined as the force value at the moment when the tested limb starts to give way. From this moment on, the person is no longer able to hold the starting position isometrically, i.e., its maximal holding capacity is exceeded. Despite this, the external force increases further on, and the participant should still try to adapt to this force increase by decelerating the pneumatically driven lever as strongly as possible (eccentric phase). The highest force value during this eccentric muscle action is referred to as $AFecc_{max}$ [3]. That eccentric maximum normally corresponds to the highest force value of the total AF-measurement (AF_{max}). However, AF_{max} can also be achieved during isometric conditions if no eccentric phase exists (voluntary stop of the subject), or if more than one isometric phase occurs.

In measuring the AF, the SeBit showed some methodological limitations (see discussion for further details). Hence, the system was refined and new prototypes for the detection of the AF of the elbow and knee extensors, as well as flexors, were constructed. In this study, only the prototype for the elbow extensors was considered. Thereby, the maximal isometric holding capacity ($AFiso_{max}$) as an expression of the sensorimotor control during the adaptation to increasing external forces was of special interest. Such a force parameter was not measured by other research groups. The main objective was to examine whether or not the $AFiso_{max}$ is a specific and independent parameter of muscle function. To do this, the discriminant validity of the $AFiso_{max}$ was analyzed in comparison to other maximal forces measured by the same system. As a condition of validity, the different forces measured by the new pneumatic device need to be reliable, which was tested in a first step. Subsequently, $AFiso_{max}$, AF_{max} and maximal voluntary isometric contraction (MVIC) were compared and correlated with each other.

As a side question, the influence of a concentric phase prior to an MVIC was analyzed (MVICpri-con vs. MVIC). This specific task of running into an isometric action from a preliminary concentric one could be understood as a functional counterpart of an AF-measurement, which starts with isometry merging into eccentrics. An AF-measurement, as well as the stretch–shortening cycle, were described as a composed muscle action (isometric–eccentric and eccentric–concentric, respectively) [5]. From this point of view, the MVICpri-con could be another variant of a composed muscle action (concentric–isometric).

At last, the MVICs before and after the AF and MVICpri-con measurements were compared (pre-MVIC vs. post-MVIC). A difference might be present because the participants had to perform 12 maximal muscle actions during the whole data collection on one day.

2. Materials and Methods

2.1. Subjects

To determine the sample size a priori, G-Power (v 3.1.9.3, Düsseldorf, Germany) and a web-based sample size calculator for reliability studies [13], which uses the formula of Bonett [14], were utilized. According to previous studies, very high intraclass correlation coefficients (ICC = 0.920–0.974) were found for MVIC tests (test–retest data of elbow extensors) and AF-measurements (interrater reliability data of knee extensors) [3,15]. Thus, the expected ICC were set at 0.920 for the test–retest design of two sessions in the present study. A minimal sample size of $n = 11$ was calculated to reveal a desired 95% confidence interval (95%CI) of ±0.1 [13,14]. For comparative analyses between force types, a two-tailed *t*-test of differences between two dependent means was chosen in G-power. The α and $1–\beta$ were conventionally set at 0.05 and 0.8, respectively. A minimum of 12 subjects was calculated to detect a substantial effect size of Cohen's $d_z = 0.9$, corresponding to a mean difference which is slightly lower than the standard deviation.

In total, 13 healthy Caucasians participated (nine males: 29.38 ± 6.35 yrs., 178.56 ± 4.19 cm, 75.39 ± 9.70 kg and four females: 32 ± 2.94 yrs., 166.75 ± 4.57 cm, 57.00 ± 1.41 kg). The exclusion criteria were any complaints of the upper extremity, spine or head within the last six months. Only the dominant arm was examined. All subjects were right-handed except for two male left-handers. The study was conducted according to the declaration of Helsinki [16], and local ethical permission of the University of Potsdam, approval no. 33/2015, was given. All subjects provided their written informed consent to participate in this study.

2.2. Pneumatically Driven Measuring System

The new measurement system for the assessment of the AF of the elbow extensor muscles is based on the main idea of SeBit [3]. Figure 1 illustrates all components of the new prototype. It enables the subject to adapt to a continuously increasing external force. Newly, the resulting forces and movements of the subject's arm and the lever I of the device are directly recordable. The generated force of the subject is transmitted to lever I through an interface, which is connected to a strain gauge (force recording, LMZ 2000N 3006, modified by Biovision, Wehrheim, Germany). The interface is lined with cushion to make the force transmission more comfortable. Two accelerometers (modified by Biovision, Wehrheim, Germany) record the movements of the lever I (ACC I) and the forearm (ACC II). The pressure is recorded by a sensor of the control unit. A laptop with the software DIAdem 12.0, National instruments (NI, Austin, TX, USA), receives and saves the amplified signals via an analog to digital converter (ADC) with a sampling rate of 1000 Hz. Table 1 summarizes the main components, the measuring equipment and technical data.

Figure 1 shows the measurement position. The subject's elbow joint was placed in line with the rotational axis of lever I. The angle between the upper arm and trunk was ∼80° to avoid a full contact of extensor muscles with the table. A strap stabilized the shoulder from dorsal. The ulnar side of the distal part of the forearm had contact with the cushioned interface. The interface was in sagittal plane of the shoulder joint (adduction–abduction 0°, internal–external rotation 0°). It was adjusted so that the subject's forearm was in a vertical position when the lever I was set perpendicular to the table surface (90°). Each subject came for two measuring sessions (t_1 and t_2) separated by 7 days. All measurements were performed by following a standardized protocol and the same procedure each day. The procedure was controlled by the same two researchers (first one: operation of the control unit and software; second one: adjustment and supervision of the measurement position). Neither visual feedback nor knowledge of result were given to the subject. For an exact documentation, all measurements were recorded by a video camera.

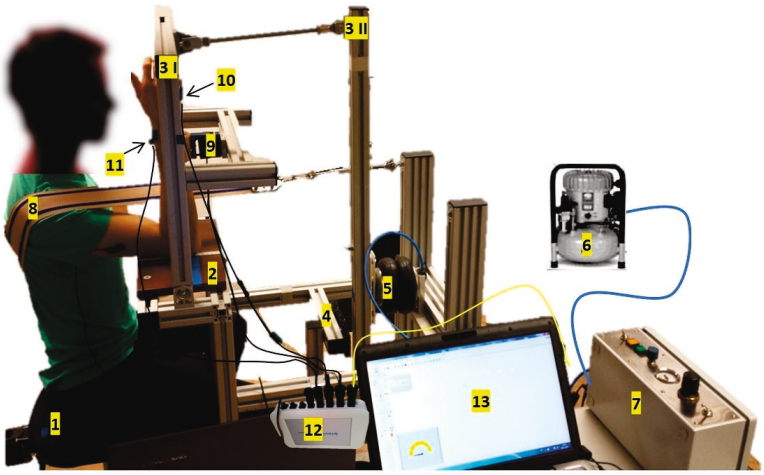


Figure 1. Pneumatic system for the quantification of the AF of the elbow extensors: (**1**) chair, (**2**) table, (**3**) pivoted and connected levers (I and II), (**4**) mechanical security stop, (**5**) frictionless bellows cylinder, (**6**) compressor, (**7**) pressure control unit, (**8**) strap for a dorsal stabilization of the shoulder, (**9**) interface with strain gauge, (**10**) accelerometer I (of lever I), (**11**) accelerometer II (forearm), (**12**) analog to digital converter, (**13**) laptop.

Table 1. Components, measuring equipment and technical specifications of the pneumatic AF system.

Section	Components	Technical Specifications
Basic construction	pivoted and connected levers	range: flexion/extension: 80°–107°
Pressure system	compressor (JUN-AIR 700367; Condor MDR2 EN 60947-4-1)	max. system pressure: 8 bar
	pressure control unit (custom build, Seifert Drucklufttechnik GmbH, Lauter-Bernsbach, Germany)	pressure reduction to max. 2 bar
	bellows cylinder (Zitec SP−2 B04, 2−fach)	Ø 165 mm force: max. 9 kN stroke length: 1–110 m (adjustable) rise time: 0.1–30 s (continuously)
Measuring equipment	1 strain gauge (LMZ 2000N 3006 + amplifier, modified by Biovision, Wehrheim, Germany)	linearly 1 V = 124.74 N
	2 accelerometers + amplifier (modified by Biovision, Wehrheim, Germany)	sensitivity 312 mV/g (range ± 2 g) cosinusoidal between 70°–110° approx. linear linearity: ± 0.2%
	1 pressure sensor (Seifert Drucklufttechnik GmbH, Lauter-Bernsbach, Germany)	linear 1 V = 1.05 bar
	analog to digital converter (National Instruments, modified by Biovision, Wehrheim, Germany)	14-bit range:−5 to 5 V
	software: NI DIAdem	Version 2012
Additional measuring equipment	hydrogoniometer (MT.DOK; Desimed GmbH & Co. KG, Müllheim, Germany)	range: 360° with 2°-intervals

2.3. Setting and Procedure

For a warm up, each subject extended the elbow 20 times against the resistance of an elastic band (Thera-band®, level 1 or 2, in dependence of the estimated strength of the subject). Then, four measurement series (a)–(d) were conducted. Prior to each series of (a)–(c), one submaximal trial was executed, so that the subject was able to acclimatize to the referring setting and task. The resting periods were 60 s after series (a) and (b), and

120 s after series (c). Series (b) and (c) took place in a randomized order (coin toss) but the order was identical at t_1 and t_2.

(a) Pre-MVIC series

To measure the MVIC, the pneumatic system was inactive, while the subject pushed against the fixed lever I as strongly as possible (pushing isometric muscle action = PIMA). For that, lever I was adjusted to 90°. Every subject was instructed to increase the force up to their maximum within 3 s and sustain this for 1 s. Four trials with resting periods of 60 s were performed.

(b) MVICpri-con series (performed at first in $n = 7$)

Here, again, the pneumatic system was inactive but lever I was not fixed. The subject pushed against the interface while the pressure system was closed. Thereby, lever I slightly gave way in the beginning, with rising resistance due to the increasing air compression, until a steady state was reached at the maximum. Hence, the elbow extensors were firstly activated concentrically and then isometrically. The starting position of lever I (99.58° ± 2.79°) was adapted to the pre-MVIC, so that a steady state was reached at ~90° (mean = 89.80 ± 2.76°). The instructions were identical as in (a). Four trials with resting periods of 60 s were performed.

(c) AF series (performed at first in $n = 6$)

For measuring AF, the pneumatic system was active. Thereby, the pneumatically driven lever II connected to lever I pushed against the subject's forearm. Lever I was adjusted to 85° in the starting position. In contrast to (a), 5° less elbow flexion was granted to meet the adjustments of the arm in the beginning, which were seen in pre-tests. In the starting position, the subject had a slight contact with the interface (0.62 ± 0.88 Nm ≙ 1.22 ± 1.74% of the pre-MVIC at t_1). The arm position should be maintained for as long as possible, while the pressure in the system increased over time. For that, the subject had to adapt permanently to the increasing external force in an isometrically holding manner. As soon as the forearm started to give way (isometric muscle actions merged into eccentrics), the subject should still try to decelerate lever I as strongly as possible, until it reached a mechanical security stop at 107° (greatest elbow flexion) or voluntary fatigue. The standardized pressure increase was adjusted manually by a throttle valve in relation to the pre-MVIC, i.e., 70% were reached after 2.5 s (norm under stable conditions). Four trials with resting periods of 120 s were performed.

(d) Post-MVIC series

This measurement series was performed analogous to (a), with only two trials.

2.4. Data Processing

Data processing was made by the use of the Software NI DIAdem 12.0. The raw data were filtered (lowpass Butterworth, filter order 10, cutoff frequency 3 Hz for force and pressure signals and 1 Hz for ACC signals, respectively, since this provided the most accurate filtering results).

2.4.1. Determination of the Maximal Voluntary Isometric Contractions and the Maximal Adaptive Force

Regarding the measured forces, the maximal values in volts of the pre-MVIC, MVICpri-con, AF_{max} and post-MVIC were determined by the highest value of each trial.

2.4.2. Determination of the Maximal Isometric Adaptive Force

The determination of $AFiso_{max}$ needs a more sophisticated approach. $AFiso_{max}$ corresponds to the highest force value at the moment when the forearm starts to give way for the first time. A standardized algorithm was utilized to identify this timepoint (Figure 2). For that, the recorded volt signals of the ACC sensors were converted into angles (ACC I for the lever angles and ACC II for the forearm angles). It should be noticed, that the

"angles of the forearm" do not reflect the elbow angle. Due to adjustments of the arm position in the beginning of the trial, intermittent deviations of $\leq 2^\circ$ of the forearm angles were tolerated and still interpreted as isometric muscle actions.

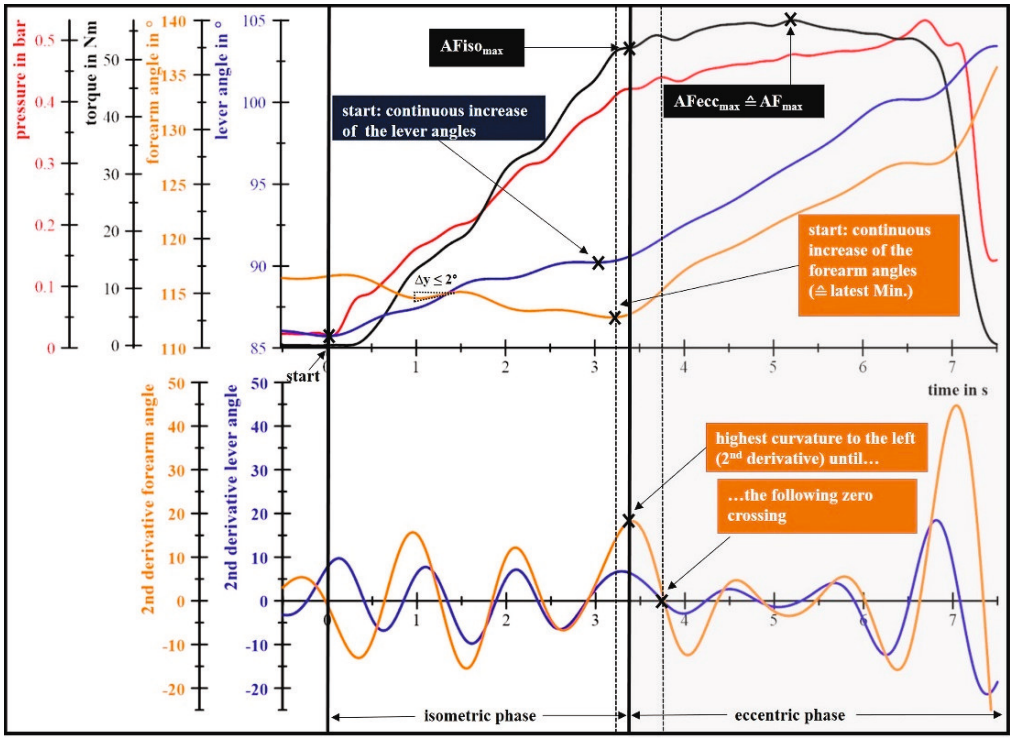


Figure 2. Exemplary AF-measurement of a male person (23 yrs, 1.81 m, 73 kg) to illustrate the algorithm of determining the maximal isometric Adaptive Force (AFiso$_{max}$), with all identified points (x) in filtered curves (lowpass Butterworth, filter order 10, cutoff frequency 3 Hz for torque (black) and pressure (red), or 1 Hz for lever angle (blue) and forearm angle (orange)).

The start of giving way was not always as clear as in Figure 2 and could not be determined easily as the start of a continuous increase in one of the angle curves (latest minimum within the determined 2°-tolerance). That is because, in some measurements, only a very slight increase was present before a considerable "break-off" (steep increase) appeared. Thus, the second derivative of the angle curves was calculated to use information about their curvatures. Referring to the considerable break-off, the start of giving way was defined as the timepoint of the highest curvature to the left, directly after the latest minimum of the time–angle curves (start of the continuous increase of forearm or lever I) and before the following zero crossing in the second derivative. In dependence of the latest minimum (angle curve of forearm or lever I), the respective second derivative was used. Differences between the forearm and lever I angle curves appeared due to filtering effects and shifts of the elbow, especially to the posterior, which could not be avoided completely by the dorsal shoulder strap. Furthermore, the back-shift can partly explain the initial decrease in the forearm angles of about 4° in Figure 2. In contrast, the lever I angles increased initially (~5°), since lever I was driven by the subject who had only a slight contact with the cushion of the interface, which was therefore crumpled. Due to this crumple zone, a decrease in forearm angles was also seen in MVIC measurements.

An AFiso$_{max}$ during a pushback of the lever I of $\geq 0.3^\circ$ was defined as task failure (pushing the lever backwards instead of holding it in position). It resulted in an exclusion, since the subject then switched into a PIMA [9]. That concerned 1 out of 104 AF-measurements in the present study. The strict limit of 0.3° was chosen according to pre-tests with PIMAs.

The described algorithm was proven on > 800 AF-measurements (elbow and knee extension, as well as flexion). The determined $AFiso_{max}$ values correspond optically to the break-off point in 99.53%.

2.4.3. Determination of the Maximal Eccentric Adaptive Force

The $AFecc_{max}$ was determined as the highest force value during the eccentric phase, which started usually after $AFiso_{max}$. It was ended as soon as lever I hit the mechanical security stop (termination of the measurement) or, if present, during the start of another isometric phase. $AFecc_{max}$ was excluded from statistical analyses because it was identical to AF_{max} in 98 of 104 measurements. In 3 measurements $AFecc_{max}$ could not be determined because $AFiso_{max} = AF_{max}$, whereby $AFecc_{max}$ could not be detected (no eccentric phase due to a voluntary stop of the subject). The 3 remaining $AFecc_{max}$ values were only slightly different from AF_{max} (mean difference = 0.41 ± 0.59 Nm).

2.4.4. Calculation of Mean and Maximal Torques and Elapsed Times

All force values (V) were converted into N (conversion factor: 124.74 $\frac{N}{V}$). For comparability, torques in Nm were calculated (T = F × r), whereby F was the force in N and r was the individual distance of the rotational axis and the middle of the interface in dependance of the forearm length. The arithmetic mean (M) and maximal (Max) torques out of the single trials of each measurement series were determined as the main variables of interest. The minimal, maximal and mean elapsed times (±standard deviation (SD)) from start to $AFiso_{max}$ and AF_{max} were calculated for all trials and subjects.

2.5. Statistical Analyses

For the statistical analyses, IBM SPSS Statistics 26 was used. The M and Max torques of pre-MVIC, post-MVIC, MVICpri-con, $AFiso_{max}$ and AF_{max} were considered. All M and Max torques of the total sample (n = 13) were normally distributed (Shapiro–Wilk test, $p > 0.05$). Thus, parametric tests were used. Due to deviations from normal distribution, differences between males (n = 9) and females (n = 4) were tested by the Mann–Whitney U test.

For all tests regarding reliability, a liberal significance level of $p = 0.10$ was used, recommended by Weir et al. (2005) [17]. In regard of all other analyses, the conventional $p = 0.05$ was chosen. For significant results of parametric tests, effect sizes were calculated by Cohen's d_z:

$$d_z = \frac{|MD|}{SD_{MD}}, \quad (1)$$

whereby MD is the mean difference between t_1 and t_2 and SD_{MD} its standard deviation. According to Cohen [18], the effect sizes were interpreted as small, moderate or large (<0.50, 0.50–0.80, ≥0.80, respectively). In non-parametric tests, the effects sizes were calculated by Pearson's r:

$$r = \sqrt{\frac{Z}{N}} \quad (2)$$

It was interpreted as being small (r = 0.1–0.3), moderate (r = 0.3–0.5) or large ($r \geq 0.5$) [18].

2.5.1. Reliability

A reliability analysis was performed mainly according to the suggestions of Atkinson and Nevill (1998) [19]. In a first step, the presence of a systematic change between t_1 and t_2 was tested by a paired t-test. The 90% confidence intervals (90%-CI) are presented.

To decide between an absolute or relative quantification of the measurement error, the scedasticity of M and Max torques was evaluated in two ways: graphically by scatter plots (absolute difference between t_1 and t_2 against the individual measurement mean) and statistically by the Breusch–Pagan test for heteroscedasticity of the standardized residuals in a linear regression (t_1 vs. t_2). Deviating from that in one exception, the

White test was used for the M of $AFiso_{max}$ because the standardized residuals in the regression analysis differed from normal distribution (Shapiro–Wilk test, $p > 0.05$). The standardized residuals of all other variables were normally distributed. According to the statistical analysis, every variable should be interpreted to be homoscedastic, since the variances of the standardized residuals were equal across the whole continuum of torques (p = 0.061–0.985, the complete statistics of the tests for heteroscedasticity can be found in Figures S1 and S2 in the supplementary material.) Thus, absolute reliability was quantified by the standard error of measurements between t_1 and t_2 (SEM), which is also known as the within-subject variation [20]. It is expressed by using the generalizability approach [21]:

$$\text{SEM} = \sqrt{\sigma_e{}^2}, \tag{3}$$

whereby $\sigma_e{}^2$ is the variance of the random error extracted from the residual variance of the repeated measures ANOVA [22,23]. For the practical relevance of individual measurements, the minimal detectable change, which is also known as the smallest detectable difference, was calculated by [17,21,22,24,25]:

$$\text{MDC95\%} = 1.96 \times SEM \times \sqrt{2}. \tag{4}$$

However, homoscedastic data are very uncommon in ratio scales as strength measures [26]. Furthermore the scatter plots partly show increasing absolute differences between days by increasing means (= positive heteroscedasticity) (see Figures S1 and S2 in the supplementary material). A logarithmic transformation of those data, as suggested by some authors [26,27], would not result in sufficient homogenization. Thus, random errors (SEM) were also presented in relation to the respective group mean of t_1 and t_2 (M_{t_1,t_2}) (percentage error) to take the positive heteroscedasticity into account [19]:

$$\text{SEM\%} = \frac{SEM}{M_{t_1,t_2}} \times 100. \tag{5}$$

Similar to the MDC95%, the SEM95% was given and expressed as the SEM% multiplied with the z-score of 1.96 [19].

The relative reliability of M and Max torques between t_1 and t_2 was quantified by the intraclass correlation coefficient (ICC(3,1) (two-way mixed, absolute agreement, single values), which is unbiased for any sample size [20]. Additionally, 95%-CI were calculated for the ICCs.

2.5.2. Discriminant Validity of the Maximal Isometric Adaptive Force

The $AFiso_{max}$, AF_{max} and pre-MVIC (M and Max torques) were compared with each other by a paired t-test. To analyze relations between the two AF parameters and the pre-MVIC, Pearson's correlation coefficients were calculated.

The AF parameters of all single trials were normalized to the M and Max of the pre-MVIC. The normalized data were presented as M ± SD in % and were compared by Wilcoxon signed-rank test because the normalized values were not normally distributed. In addition to the normalization to the pre-MVIC, the $AFiso_{max}$ of each single trial was normalized to the respective AF_{max}.

The variability between the 4 trials of a measurement series was expressed as M ± SD of individual coefficients of variation (CV) for each day.

2.5.3. Analyses Regarding the MVIC with a Prior Concentric Contraction and the Post-MVIC

For the last two analyses, paired t-tests were used. To analyze the influence of a concentric phase prior to the MVIC, M and Max of MVICpri-con were compared with the respective ones of pre-MVIC. At last, the M and Max torques were compared between the pre- and post-MVIC.

3. Results

3.1. Gender Comparison

M and Max (± SD) torques of all measurement series at both days are presented in Table 2. Males revealed significantly higher torques of the same force type than females, on average (z = −2.777–−2.623, p = 0.005–0.009, r = 0.45–0.46). Torques of all single trials and force types can be found in Table S1 in the supplementary material.

Table 2. Group arithmetic means (M) ± standard deviations (SD) of each force type (mean and maximal toques out of 4 measurements) at both days (t_1 and t_2) of the total sample of male and female subjects.

	Type of Force	Total Sample M ± SD *n* = 13		Male M ± SD *n* = 9		Female M ± SD *n* = 4	
		t_1	t_2	t_1	t_2	t_1	t_2
mean torques	pre-MVIC	50.70 ± 22.65	50.13 ± 22.50	63.03 ± 14.30	61.89 ± 15.78	22.95 ± 4.89	23.66 ± 3.51
	post-MVIC	46.38 [b] ± 21.25	46.91 [b] ± 20.76	56.94 ± 16.16	56.80 ± 16.91	22.62 ± 4.80	24.68 ± 2.86
	MVICpri-con	**48.02** [a] ± 20.50	**46.58** [a,b] ± 18.98	58.07 ± 16.09	56.10 ± 14.38	25.41 ± 2.51	25.17 ± 2.58
	$AFiso_{max}$	37.17 [b] ± 17.39	35.20 [b] ± 17.77	45.61 ± 13.40	42.23 ± 16.53	18.19 ± 6.05	19.36 ± 7.12
	AF_{max}	49.49 ± 21.01	48.35 ± 21.66	60.40 ± 14.93	58.79 ± 17.17	24.95 ± 3.35	24.87 ± 5.29
	$AFecc_{max}$	49.39 ± 21.04	48.35 ± 21.66	60.36 ± 14.86	58.79 ± 17.17	24.72 ± 3.15	24.88 ± 5.30
maximal torques	pre-MVIC	**53.67** [a] ± 24.83	**51.72** [a] ± 22.83	66.70 ± 17.13	63.41 ± 16.68	24.34 ± 5.24	25.43 ± 3.61
	post-MVIC	47.47 [b] ± 21.89	47.68 [b] ± 21.07	58.19 ± 16.97	57.69 ± 17.22	23.34 ± 5.22	25.18 ± 3.11
	MVICpri-con	**49.61** [a,b] ± 21.48	**47.92** [a,b] ± 19.94	59.86 ± 17.47	57.71 ± 15.58	26.56 ± 2.79	25.88 ± 2.86
	$AFiso_{max}$	45.09 [b] ± 19.89	43.31 [b] ± 20.01	55.76 ± 12.83	52.58 ± 16.35	21.08 ± 5.79	22.47 ± 7.22
	AF_{max}	51.20 ± 21.99	50.90 ± 21.93	62.29 ± 16.42	61.53 ± 17.31	26.26 ± 4.03	26.97 ± 4.64
	$AFecc_{max}$	51.10 ± 22.10	50.90 ± 21.93	62.29 ± 16.42	61.53 ± 17.31	25.93 ± 3.73	26.97 ± 4.64

[a] significant difference (p < 0.10) between t_1 and t_2 in the total sample (in bold); [b] significant difference (p < 0.05) to pre-MVIC of the same day of the total sample; males and females differed significantly in all variables (p < 0.01); note: due to its similarity to AF_{max}, $AFecc_{max}$ was excluded from statistical analyses.

3.2. Description of AF-Measurements

Figure 2 exemplifies the typical curves of one AF-measurement. During their adaptation to the pressure increase (red), a subject's generated torque (black) increased over time. Due to the compression of the cushion between the subject's forearm and the interface, as well as little back-shifts of the elbow, an increase in lever angle (blue) and a decrease in forearm angle (orange) occur initially. A deceleration of the lever and further decrease of the forearm angles interrupted by slight oscillations within the 2°-tolerance indicate that the forearm was held in position. As soon as the forearm starts to give way, the $AFiso_{max}$ is exceeded and the eccentric muscle work begins. Thereby, the pressure and torque curves increase further on with a flatter slope, until the highest torque is reached (AF_{max} = $AFecc_{max}$).

The mean elapsed time until $AFiso_{max}$ over all measurements was 2.78 ± 0.94 s (Min.–Max.: 0–4.50 s). AF_{max} was reached after 4.57 ± 0.79 s (Min.–Max.: 3.21–6.87 s).

3.3. Test–Retest Reliability

Figure 3 illustrates the group mean ("×") and individual differences (dots) between t_1 and t_2 for M, as well as Max torques of all force types. The Max of pre-MVIC (p = 0.099), as well as the M (p = 0.068) and Max (p = 0.044) of MVICpri-con, differed significantly between t_1 and t_2. Thereby, the torques at t_2 were consistently lower than those at t_1. The effect sizes were d_z = 0.52, 0.56 and 0.62, respectively. All other between-days comparisons differed insignificantly (p = 0.175–0.869). The complete inference statistics, SEMs, MDC95%s, SEM%s, SEM95%s and ICCs(3,1) with 95%-CIs are given in Table 3. The highest occurred mean difference amounted to 1.98 ± 8.03 Nm (M $AFiso_{max}$). The SEMs, MDC95%s, SEM%s and SEM95% ranged from 1.29 to 5.68 Nm, 2.53 to 15.70 Nm and 2.53 to 15.70%, respectively, where the highest values occurred in $AFiso_{max}$. All ICCs were greater than 0.89 (Table 3).

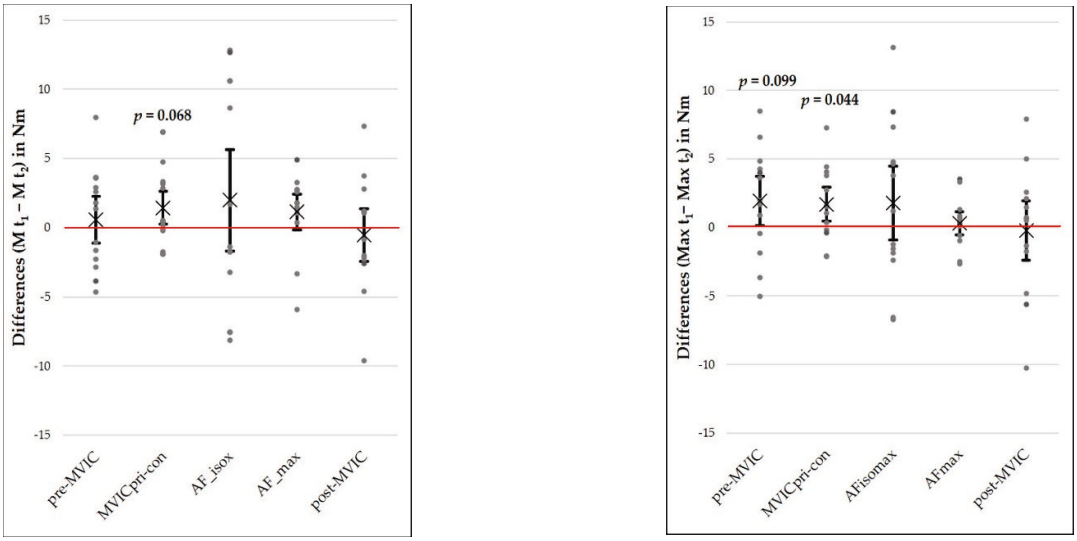


Figure 3. Differences between day 1 (t_1) and day 2 (t_2) for mean (M) (**a**) and maximal (Max) torques (**b**) out of 4 measurements of all measurement series. Dots illustrate single values. The mean difference is marked by "×". Error bars express 90% confidence intervals.

Table 3. Inference statistics of mean differences between days (MD $t_1 - t_2$), standard deviations of mean differences (SD_{MD}), 90% confidence intervals (90%–CI), *t*-values, degrees of freedom (df), *p*-values, Cohen's d_z for significant results, standard error of measurements (SEM), minimal important differences (MDC95%), SEM%, SEM95% and intraclass correlation coefficients (ICC(3,1) [95%–CI] of the mean and maximal torques of each force type.

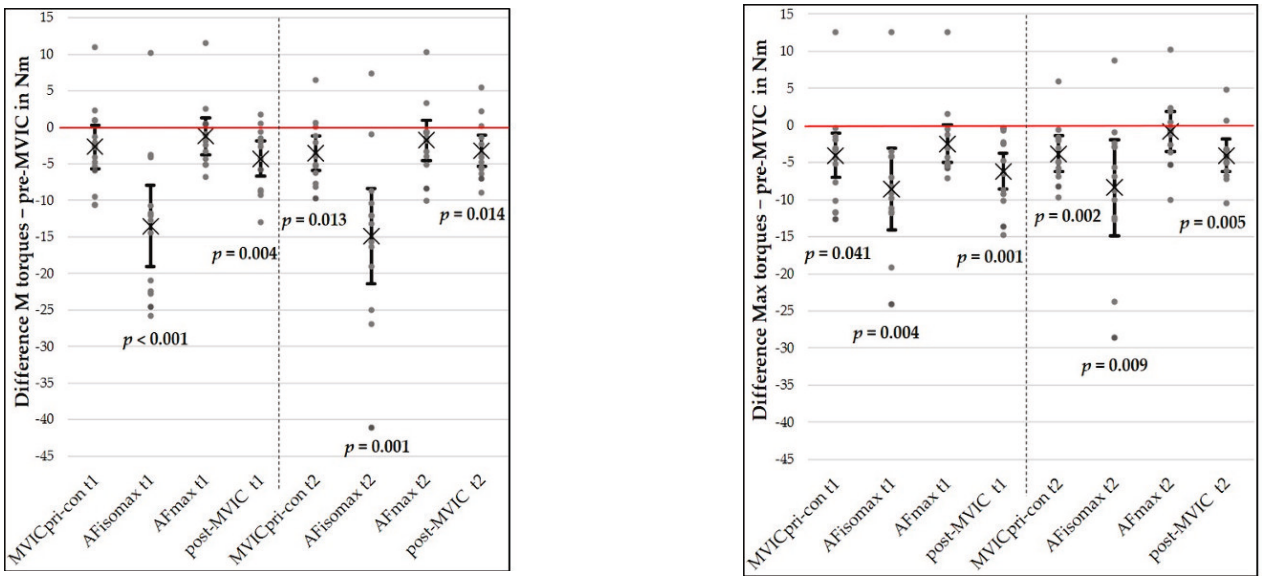
	Type of Force	MD ($t_1 - t_2$) (Nm)	SD_{MD} (Nm)	90%–CI (Nm)	*t*	*df*	*p*	d_z	SEM (Nm)	MDC 95% (Nm)	SEM% (%)	SEM 95% (%)	ICC(3,1) [95%–CI]
mean torques	pre-MVIC	0.57	3.65	−1.23–2.38	0.57	12	0.582	-	2.58	7.15	5.12	10.03	0.987 [0.958–0.996]
	post-MVIC	−0.54	4.19	−2.61–1.53	−0.46	12	0.652	-	2.96	8.20	6.35	12.44	0.980 [0.936–0.994]
	MVICpri-con	1.44	2.59	0.16–2.71	2.01	12	**0.068**	0.56	1.82	5.04	3.67	7.19	0.991 [0.972–0.997]
	$AFiso_{max}$	1.98	8.03	−1.99–5.95	0.89	12	0.392	-	5.68	15.74	15.70	30.77	0.896 [0.694–0.967]
	AF_{max}	1.14	2.85	−0.27–2.55	1.44	12	0.175	-	2.01	5.57	4.11	8.05	0.991 [0.971–0.997]
maximal torques	pre-MVIC	1.95	3.94	0.003–3.90	1.79	12	**0.099**	0.50	2.79	7.73	5.29	10.38	0.986 [0.956–0.996]
	post-MVIC	−0.22	4.70	−2.54–2.11	−0.17	12	0.869	-	3.16	8.76	6.64	13.02	0.976 [0.924–0.993]
	MVICpri-con	1.69	2.71	0.35–3.03	2.25	12	**0.044**	0.62	1.92	5.32	3.76	7.36	0.991 [0.972–0.997]
	$AFiso_{max}$	1.77	5.90	−1.15–4.69	1.08	12	0.300	-	4.17	11.56	9.43	18.49	0.956 [0.863–0.986]
	AF_{max}	0.31	1.82	−0.50–1.21	0.61	12	0.552	-	1.29	3.58	2.53	4.95	0.996 [0.986–0.999]

Note: A significant difference (p < 0.10) between t_1 and t_2 is in bold.

3.4. Comparisons of Force Types

3.4.1. Comparison between AF-Parameters and the Maximal Voluntary Isometric Contraction

Figure 4 shows the mean and individual differences for M and Max torques between the pre-MVIC and all other force types, as well as between AF_{max} and $AFiso_{max}$ on both days. No significant differences were found between AF_{max} and pre-MVIC neither at t_1 nor at t_2 (M and Max: $p = 0.109$–0.531). The complete inference statistics can be found in Table 4. M and Max torques of $AFiso_{max}$ were significantly lower than those of the pre-MVIC, as well as those of AF_{max} on both days ($p \leq 0.001$–0.009 and $p \leq 0.001$–0.002, respectively) (see Table 4).



(**a**) (**b**)

Figure 4. Comparisons of the pre-MVIC and all other measured force types on day 1 and day 2 (t_1 and t_2). Mean (M) (**a**) and maximal (Max) torques (**b**) of the pre-MVIC are subtracted from the respective value of other force types). Dots illustrate single values. The mean difference is marked by "×". Error bars express 95% confidence intervals.

The correlations between $AFiso_{max}$, AF_{max} and pre-MVIC at t_1 and t_2 ranged from $r = 0.85$ to 0.98. All correlations were significant ($p \leq 0.001$). Correlations which involved the $AFiso_{max}$ were lower ($r = 0.85$–0.97) than those between AF_{max} and pre-MVIC ($r = 0.97$–0.98).

The averages of the normalized $AFiso_{max}$ and AF_{max} are presented in Figure 5 (normalized to the M pre-MVIC (a) and to the Max pre-MVIC (b)). The normalized $AFiso_{max}$ was significantly lower than the normalized AF_{max} on both days (each $z = -3.18$, each $p = 0.001$, each $r = 0.5$). The $AFiso_{max}$ normalized to the AF_{max} amounted to $74.64 \pm 14.51\%$ at t_1 and $72.92 \pm 15.72\%$ at t_2.

The CVs between single trials of $AFiso_{max}$ were substantially greater (t_1: $28.65 \pm 21.95\%$, t_2: $24.92 \pm 18.89\%$) compared to those of pre-MVIC (t_1: $5.32 \pm 3.04\%$, t_2: $4.16 \pm 3.01\%$), AF_{max} (t_1: $3.25 \pm 1.72\%$, t_2: $5.40 \pm 2.92\%$) and MVICpri-con (t_1: $2.99 \pm 1.94\%$, t_2: $3.32 \pm 2.21\%$).

Table 4. Inference statistics of mean differences (MD) between force types for mean and maximal torques on both days (t_1 and t_2), standard deviations of mean differences (SD_{MD}), 95% confidence intervals (CI), *t*-values, degrees of freedom (df), *p*-values, Cohen's d_z for significant results.

Comparison			MD (Nm)	SD_{MD} (Nm)	95% CI (Nm)	*t*	*df*	*p*	d_z
mean torques	t_1	$AFiso_{max}$ − pre-MVIC	−13.52	10.23	−19.70–−7.34	−4.77	12	**<0.001**	1.32
		AF_{max} − pre-MVIC	−1.21	4.66	−1.61–4.02	−0.93	12	0.369	-
		$AFiso_{max}$ − AF_{max}	−12.32	8.10	−17.21–−7.42	−5.48	12	**<0.001**	1.52
		MVICpri-con − pre-MVIC	−2.68	5.47	−0.63–5.98	−1.77	12	0.103	-
		post-MVIC − pre-MVIC	−4.32	4.44	−7.00–1.64	−3.51	12	**0.004**	0.97
	t_2	$AFiso_{max}$ − pre-MVIC	−14.93	11.96	−22.16–−7.70	−4.50	12	**0.001**	1.23
		AF_{max} − pre-MVIC	−1.77	5.06	−1.28–4.83	−1.26	12	0.230	-
		$AFiso_{max}$ − AF_{max}	−13.16	8.83	−18.49–−7.82	−5.37	12	**<0.001**	1.49
		MVICpri-con − pre-MVIC	−3.54	4.37	−6.18–0.91	−2.93	12	**0.013**	0.81
		post-MVIC − pre-MVIC	−3.21	4.01	−5.63–0.79	−2.89	12	**0.014**	0.80
maximal torques	t_1	$AFiso_{max}$ − pre-MVIC	−8.59	8.65	−13.81–−3.36	−3.58	12	**0.004**	0.99
		AF_{max} − pre-MVIC	−2.47	5.14	−0.64–5.57	−1.73	12	0.109	-
		$AFiso_{max}$ − AF_{max}	−6.12	5.75	−9.59–−2.64	−3.84	12	**0.002**	1.06
		MVICpri-con − pre-MVIC	−4.06	6.38	−7.92–0.21	−2.30	12	**0.041**	0.64
		post-MVIC − pre-MVIC	−6.20	4.91	−9.17–3.24	−4.56	12	**0.001**	1.26
	t_2	$AFiso_{max}$ − pre-MVIC	−8.41	9.73	−14.29–−2.53	−3.12	12	**0.009**	0.86
		AF_{max} − pre-MVIC	−0.83	4.62	−1.96–3.62	−0.65	12	0.531	-
		$AFiso_{max}$ − AF_{max}	−7.58	6.28	−11.38–−3.79	−4.36	12	**0.001**	1.21
		MVICpri-con − pre-MVIC	−3.80	4.03	−6.24–1.37	−3.4	12	**0.005**	0.94
		post-MVIC − pre-MVIC	−4.04	3.74	−6.30–1.77	−3.89	12	**0.02**	1.08

Note: A significant difference ($p < 0.05$) is in bold.

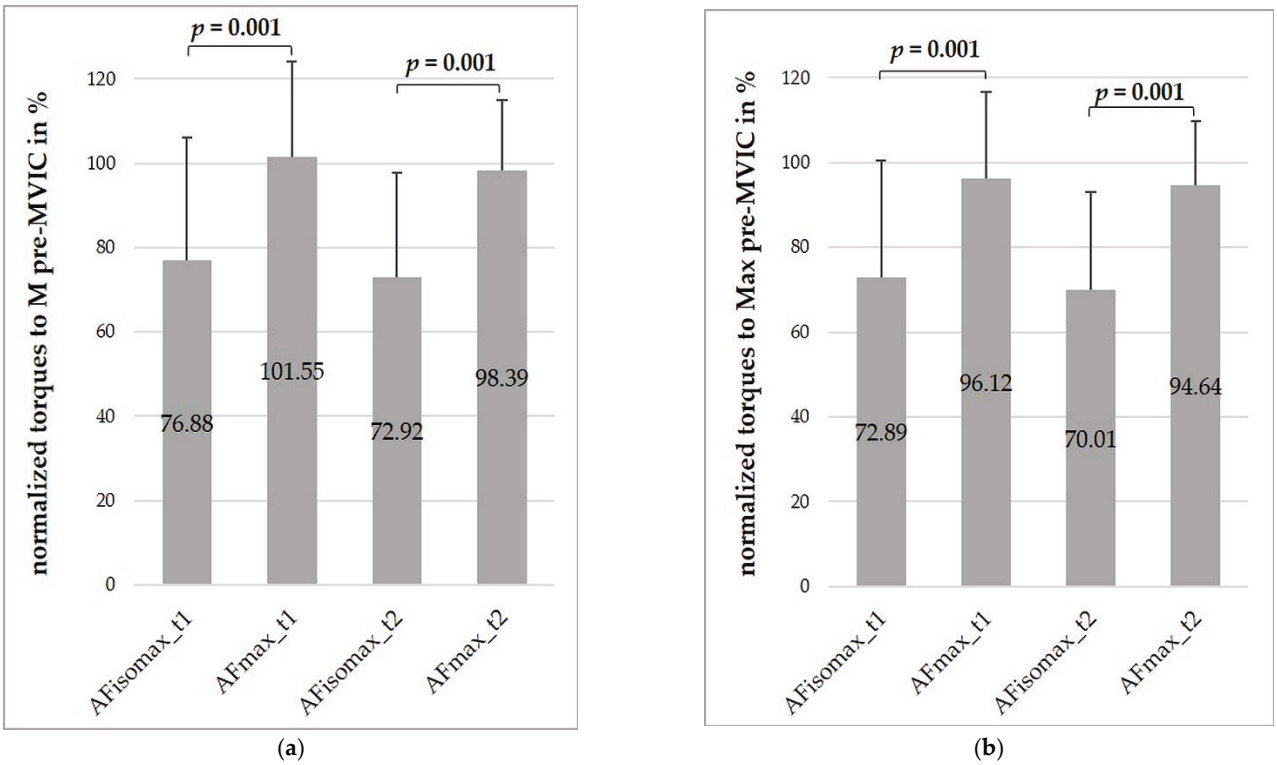


Figure 5. Comparisons of the average maximal isometric Adaptive Force ($AFiso_{max}$) and average maximal Adaptive Force (AF_{max}), normalized to the mean (M) (**a**) and maximal (Max) torques (**b**) of the pre-MVIC on both days (t_1 and t_2). Error bars express between-subject standard deviations.

3.4.2. Comparisons between Measurement Series Including a Maximal Voluntary Isometric Contraction

In regard to the comparisons of pre-MVIC and MVICpri-con, M torques at t_2, as well as Max torques at t_1 and t_2, differed significantly (p = 0.013, 0.041 and 0.005, respectively, Table 4). Thereby, MVICpri-con showed lower torques. Effect sizes were 0.81, 0.64 and 0.94, respectively. No significant differences were found between M torques at t_1 (p = 0.103).

M and Max torques of post-MVIC were significantly lower than those of pre-MVIC at both sessions, (p = 0.001–0.014, d_z = 0.80–1.26, Table 4).

4. Discussion

In the first step, the methodological quality of the new measurement procedure will be considered as a prerequisite for the following discussion. That also includes the advantages over SeBit and its limitations. Subsequently, the influence of a concentric contraction prior to MVIC, as well as possible fatiguing effects, will be discussed. The integration of the AF into current concepts of human strength and the specialty of the $AFiso_{max}$ will be our focus at last.

4.1. Reliability of the Measured Forces

The comparison of M and Max torques between days revealed no significant differences in most force types. Thus, a systematic change between days in $AFiso_{max}$, AF_{max} and post-MVIC is not assumed. In contrast, the Max of pre-MVIC, as well as M and Max of the MVICpri-con, differed significantly between t_1 and t_2 ($p < 0.1$, liberal α-level). Thereby, the torques were always lower on average at t_2, whereby moderate effect sizes occurred (d_z = 0.50–0.62). An unlikely effect of insufficient regeneration after 7 days of rest cannot be ruled out completely. However, that would raise the question why it was not seen in the other force variables. Several authors suggested adapting the measurement protocol and examining the reliability again if systematic changes are evident [17,19]. This might be considered, especially for the unconventional MVICpri-con measurements. The MVIC of elbow extensors measured by strain gauge had already proven to be reliable [15]. Furthermore, the difference between t_1 and t_2 of the Max pre-MVIC was very close to insignificance (p = 0.099). However, results of paired t-tests as sole reliability statistics are not recommended because the detection of systematic changes depends highly on random errors [19]. A significant result in a t-test could be explained by two approaches. Either the true variance is very high or the random error is very small. Inversely, an insignificant result can be explained by a high random error.

The random errors between t_1 and t_2, which cover 65% of all measurements, are provided as SEMs in the unit of interest (Nm) and as a percentage (SEM%) (Table 3). The latter is a type of within-subject coefficient of variation (CV) but calculated from the mean square error term in a repeated-measures ANOVA model, as suggested by Atkinson and Nevill (1998) [19]. CVs of ≤10–15% are conventionally rated as being reliable in sport science [28–30]. However, those thresholds are also criticized [19]. Independently of the proposed threshold (≤10% or ≤15%), only the means of $AFiso_{max}$ would exceed it (15.70%). All other force variables revealed lower CVs between days (2.53–9.43%), whereby the Max of $AFiso_{max}$ showed the highest. The higher random errors between days (variability) in $AFiso_{max}$ might be explained by the specialty of this force type, which will be discussed in a later subsection.

Rather than rating the results as reliable or not according to a CV, it is more important to consider the presented random errors for the interpretation of future interventional studies. In dependence of the assumed scedasticity, the SEMs or CVs could be used for prospective group comparisons. In contrast, to compare changes of an average individual, MDC95%s or CV95%s should be used, at least because these would cover 95% of the repeated measurements [19]. That means exemplary for Max torques of $AFiso_{max}$, group changes ≤4.17 Nm (SEM) and individual changes ≤11.56 Nm (MDC95%) are within the area of measurement error and should not be declared as relevant, despite possi-

ble significant differences. Absolute errors (SEM and MDC95%) are used because, in the presented study, Max $AFiso_{max}$ data are rated as homoscedastic (Figure S2 in the supplementary material).

To the authors' best knowledge, the study provided first data of MVICpri-con, $AFiso_{max}$ and AF_{max} of the elbow extensor muscles. Thus, the random errors cannot be compared with other studies. Concerning the MVIC, Meldrum et al. (2003) presented SDs of the mean differences (Max values out of two trials) of the elbow extensors captured by a strain gauge [15]. In experienced raters, the SD_{MD} amounted to ±1.46 kg (≙a SEM of $\frac{1.46\ kg}{\sqrt{2}}$ = 1.03 kg) for the left and ±1.58 kg (≙ SEM of 1.12 kg) for the right arm. The formula for the calculation of the SEM is similar to the one we used [17]. These SEMs are close to our presented SEMs of Max torques (converted to kg ≈ 1.15). This comparison should be interpreted with care because of methodological differences between the studies. The point of force application was also proximal of the wrist, but the measurement position differed compared to our study (supine vs. seated).

Relative reliability is commonly interpreted by the ICC [31]. It reflects reliability in relation to a measured sample. According to Koo and Li [32], the presented ICCs were good to excellent. The lowest, but still in good agreement, was found for mean values of $AFiso_{max}$ (ICC = 0.896), whereas Max $AFiso_{max}$ achieved an excellent ICC of 0.956. The ICCs of all other variables were also excellent (0.976–0.996). Regarding the MVIC, Meldrum et al. (2003) also reported excellent ICCs (0.92–0.95) of M and Max values for the left and right elbow extensors [15].

In summary, all measured force types in the presented study, and especially the introduced AF parameters, are interpreted as revealing sufficient reliability.

4.2. Advantages and Limitations of the New AF-Measurement Procedure

The introduced AF device for the elbow extensors is a refinement of the SeBit. Both devices can measure the MVIC, the MVICpri-con and the AF parameters [3]. The SeBit only provided pressure signals. In contrast, the new device uses a strain gauge to record force and ACCs to detect the movements of the limb and lever. As a consequence, AF_{max} is always detectable and $AFiso_{max}$ is easier to identify without an analysis of the deviation from a reference curve, as was done before [3]. Moreover, the frictionless bellows cylinder eliminated the stick–slip effect which occurred in the former used cylinder, including a push rod [3]. Another advantage over the SeBit is the individualized pressure increase based on the MVIC of a subject. Due to these advances, the assessment and determination of the $AFiso_{max}$ is more standardized and accurate with regard to a subjects' properties.

However, some limitations of the new system have to be pointed out. For individualization, the pressure increase was adjusted so that the external force would reach 70% of the MVIC after 2.5 s. The actual duration was 2.90 ± 0.84 s. The pressure increase depends not only on the incoming air but also on the extension of the bellows cylinder. If the cylinder expands, the pressure, and consequently the force increase, will flatten, i.e., the pressure course would only be fully standardized if the subject holds the lever in a completely stable position. That depends on the subject's ability to hold the lever in position. However, even in measurements with a high $AFiso_{max,}$ a lever drive occurred, as described before. Consequently, slightly different pressure increases occurred. However, the elapsed time until AF_{max} was 4.57 ± 0.79 s. From our point of view, this duration is reasonable, but the optimal pressure increase for capturing the AF needs to be discussed and examined in future studies [4].

Another limitation is related to the characteristics of the initial pressure course. A sudden increase was evident, especially in subjects with high MVICs. The pressure increase, according to the standardization of reaching 70% of the MVIC after 2.5 s, was relatively steep for those subjects, and the start might have been abrupt. Independent of the MVIC, a general smooth start through a motor-controlled valve will solve this problem in the next generation of the system.

As a further limitation, the determination of $AFiso_{max}$ has to be considered. In the described algorithm, the start of giving way of the forearm up to a boundary of 2° was tolerated and interpreted as an isometric holding phase (quasi-isometric muscle action). Setting a boundary was necessary because complete isometrics in a nearly freely oscillating system is not possible, and because of a slight elbow shift, which occurred in all subjects at the beginning of the AF-measurements. It reflects an initial adjustment of the subject and a compression in the respective joints during the isometric phase. It could not be avoided, although the fixation of the subject's arm and shoulder was already strong. A complete fixation is not possible. However, higher or lower boundaries (instead of 2°) would change the $AFiso_{max}$. This especially plays a role in measurements with two or more isometric phases, which occurred in 7 of 104 measurements. The current algorithm considers only the first isometric phase. Furthermore, flat slopes in lever angles (slowly giving way) were not included in the isometric phase (31 measurements). Both a second isometric phase and flat slopes characterize a different quality of resisting an external force compared to a steep incline in angles. An influence of the determination method on reliability statistics cannot be excluded completely. However, based on the high agreement (99.53%), with the break-off point in > 800 measurements, the algorithm already seems to be quite sophisticated.

4.3. Influence of a Concentric Muscle Action Prior to a Maximal Voluntary Isometric Contraction

The MVICpri-con firstly includes a concentric muscle action which merges into an isometric one [3]. Thereby, the force maximum is always reached during isometrics.

In the presented study, the comparison of MVICpri-con and pre-MVIC revealed inconsistent results. No significant difference of the M torques at t_1 was found. In contrast, M torques at t_2 and Max torques at both days were significantly lower than the respective pre-MVICs torques, with moderate to large effect sizes (0.64–0.94). In both measurement series, the force values were reached at similar lever angles (90° vs. ≈ 89°). Thus, differences in muscle length can be excluded as a reason for the lower force in MVICpri-con. The duration until reaching the MVICpri-con values lasted 0.5 s longer than reaching the pre-MVICs (4.57 ± 0.92 s vs. 4.07 ± 0.83 s), which could serve as an explanation. However, the lower force could rather be explained by the order of measurements. Six subjects performed the MVICpri-con series after the AF series. If only the other seven subjects who performed the MVICpri-con series first had been considered, no significant differences would have been found (p = 0.175–0.602). Due to the lower sample size, this should be interpreted with caution. Possible underlying fatiguing effects are discussed in the next section.

The results suggest a prior concentric phase might not have a clear influence on the MVIC, but more research is necessary for a final conclusion. Moreover, the potential systematic biases of MVICpri-con measurements are already mentioned in the reliability section above. Future studies could adapt the measurement protocol by examining only these two forces in a randomized order.

4.4. Comparison of MVICs at the Beginning and at the End of Each Measurement Session

The M and Max torques of post-MVIC (performed after 12 other maximal muscle actions) were significantly lower than the respective pre-MVIC at both days, with large effect sizes (d_z = 0.80–1.26). This could be an indication of potential central and/or peripheral fatiguing effects. On the one hand, the neuromuscular system could have been already neurologically and/or structurally exhausted, especially because of the usually involved eccentric loading during the AF-measurement [33–35]. In this regard, a reflectory inhibition of motoneurons might also play a role. Other reasons could be mental fatigue or a lack of motivation. The motivation to activate the muscles maximally might have declined towards the end of the session. In future, fewer measurements and/or measurement series might eliminate possible fatiguing and/or motivational effects.

4.5. Integration of the Adaptive Force in Current Concepts of Strength

The determination of MVIC is the gold standard for investigating maximal isometric strength, which is one central parameter in strength diagnostics [36–40]. Comparisons and correlations of the pre-MVIC with the recently introduced AF parameters were made to provide information concerning their discriminant validity. All respective variables (M and Max torques) revealed a sufficient reliability (see subsection about reliability).

In respect of the comparison of pre-MVIC and AF_{max}, the M and Max torques did not differ significantly. Nearly all AF_{max} values occurred during the eccentric phase. Only in three measurements, the $AFecc_{max}$ was somewhat lower than AF_{max} (mean difference = 0.41 ± 0.59 Nm). In the past, significantly higher forces were found during eccentric muscle actions compared to isometric ones [33,41–43]. However, it seems that it is not a general phenomenon [44–46]. Fitness level [47], examined musculature [48], joint angle or angular velocity [5,44,48,49] are discussed as influencing factors. For example, other research groups which used isokinetic devices reported higher maximal eccentric forces, with higher angular velocities in well-trained subjects [47,50]. Compared to isokinetic measurements, an AF-measurement, as conducted in the presented study, is a completely different approach to measure eccentric forces. It includes quasi-isometric and, afterwards, very slow eccentric muscle work. Thereby, the angular velocity depends on a subject's ability to decelerate the movement of the lever, which cannot be—and should not be—standardized. The average angular velocity of lever I during all eccentric phases was 2.31 ± 0.50 °/s. The highest value in one single trial was 5.93 °/s. These slow and subject controlled eccentric movements could be an explanatory approach as to why the $AFecc_{max}$ or AF_{max} did not exceed pre-MVIC. In regard to the specific measurement procedure, it is suggested the AF_{max} could be used to assess the maximal force capacity comparable to the MVIC. However, using a more explosive pressure increase and, therefore, higher angular velocity would probably change the result. This was shown in a previous study, whereby higher explosive AF_{max} values measured by the SeBit were found compared to the MVIC [5].

In contrast to AF_{max}, the M and Max torques of $AFiso_{max}$ differed significantly ($p \leq 0.001$–0.009) from those of pre-MVIC at both days, with large effect sizes ($d_z = 0.86$–1.32). Thereby, $AFiso_{max}$ ranged from 70.01% to 76.88% of the pre-MVIC (SD = ±23.00 − 29.24%). Furthermore, the $AFiso_{max}$ normalized to the pre-MVIC was significantly lower (70.01–76.88% than the normalized AF_{max} (96.12–101.55%, $p = 0.001$). The effect sizes were interpreted as large ($r = 0.5$).

Our research group already suggested considering the $AFiso_{max}$ as a measure of a special neuromuscular function [2,3]. It reflects maximal holding capacity while adapting to increasing external forces, whereas the MVIC declares the maximal isometric contraction in a pushing manner. $AFiso_{max}$ (adaptive HIMA) seems to reveal substantially lower forces than MVIC (PIMA), i.e., the forearm started to give way (muscle lengthening) before the individual MVIC was reached. This confirms the hypothesis of a differentiation between isometric muscle actions in at least two modes (HIMA vs. PIMA) [9]. A difference between HIMA and PIMA was identified concerning, e.g., the time to task failure [9,51]. However, another research group could only confirm this finding in part [6,7]. A HIMA always includes an adaptational component of muscle function. It is suggested that an adaptation to increasing or varying forces is more sensitive to detect differences from a PIMA compared to an adaptation to constant forces. This suggestion is supported by the results of the presented study, revealing a significant difference between $AFiso_{max}$ and pre-MVIC. $AFiso_{max}$ reflects a HIMA, since the subject has to adapt to an increasing force in an isometric holding manner. The MVIC, in turn, characterizes a PIMA, as the subject has to push isometrically against a stable resistance. The cause for the found difference might lie in the higher adaptational component during AFiso compared to the MVIC. As mentioned above, previous studies only found a difference in the time to task failure of PIMA and HIMA with constant forces [6,7,9,51]. The adaptational component was not considered. This emphasizes the importance of determining $AFiso_{max}$ as a special and

individual force capability (see below). The investigation could be performed by using the presented measurement system or, in a more practical way, by using a handheld device in combination with a manual muscle test, whereby reproduceable force applications are necessary [4].

Despite partial significant differences, high to very high relationships between the $AFiso_{max}$, AF_{max} and pre-MVIC were found in the present study (r = 0.85–0.98). This indicates the AF can be integrated in the conditional ability of strength in healthy subjects. Different research groups found that several force measurements or strength tests correlate with each other, and confirm the hypothesis of generality [52–54]. However, the determination coefficients (r^2) are often lower than 0.5, i.e., <50% of the variances are explained by each other. Such findings question the interpretation of generalization [55]. In the presented study, the determination coefficients between AF_{max} and pre-MVIC were very high (r^2 = 94.09–96.04%). In contrast, the coefficients regarding $AFiso_{max}$ were lower (r^2 = 72.25–94.09%). That means the $AFiso_{max}$ cannot be explained by the other two force types as well as they can explain each other.

All of the results regarding the $AFiso_{max}$ indicate that it could be discriminated from the MVIC and AF_{max}. Thus, it should be detected separately and could reflect an independent force capability. It is assumed that $AFiso_{max}$ depends not only on the maximal strength of a person. Due to the adaptive component, the influence of a proper functioning of sensorimotor control might play a decisive factor in defining $AFiso_{max}$.

4.6. Specialty of the Maximal Isometric Adaptive Force

Adaptation to external forces in an isometric holding manner is a rarely considered motor task. Commonly used strength tests are not able to capture this function. As stated before, the maximal adaptive holding capacity of a muscle can be quantified during an AF-measurement ($AFiso_{max}$). An intact holding isometric muscle function during adaptation to external forces (high $AFiso_{max}$) might prevent an inappropriate muscle lengthening up to considerably high intensities close to its maximal capacity. In the past, animal models indicate that an externally induced lengthening of a tensioned muscle (eccentric muscle action) is the primary injury mechanism of muscle strains [56]. In high speed treadmill and overground running of humans, a muscle strain most likely occurs during the late swing phase, which is accompanied by an eccentric [56], or, from a newer point of view, an isomeric muscle action [57]. According to van Hooren and Bosch (2017) [57], the presence of an inefficient eccentric muscle action in the late swing phase is caused by the inability of the muscle fascicles to act isometrically. Consequently, the muscle is more vulnerable to injury [57]. Moreover, an unwanted muscle lengthening could also lead to an exceeded joint movement in a specific direction, which might cause a traumatic injury, e.g., regarding the anterior cruciate ligament [58], ankle sprains [59] or shoulder dislocations [60]. High susceptibility to injuries during the lengthening of muscles emphasizes the importance of an adequate isometric holding function during adaptation to external forces. In this regard, high isometric holding capacities of muscles (high $AFiso_{max}$) might prevent or at least delay the moment of their lengthening, and consequently stabilize joints up to a higher force level. This is essential, especially in powerful movements or high impacting loads. As one single moment of the muscle's inability to remain acting isometrically could be harmful, not only the highest $AFiso_{max}$ of several trials but also the minimal value and its variation might be of diagnostic interest.

The present study showed that, even in subjects without health complaints, the forearm started to give way before the maximal isometric pushing force (Max pre-MVIC) was reached. There was only one subject whose $AFiso_{max}$ was greater than the Max pre-MVIC in all trials (+7.88–74.39%). In 11 other trials of six different subjects, $AFiso_{max}$ was greater than 90% of Max pre-MVIC. This demonstrates a high relative $AFiso_{max}$ is possible. Such a high $AFiso_{max}$ is considered as perfect adaptation, as long as the Max pre-MVIC is rated as sufficiently high. Regarding the average of all measurements, the $AFiso_{max}$ amounted to about 70% of the Max pre-MVIC. That percentage was reached

by 11 of 13 subjects in at least one single trial (57 in total). However, two subjects never reached that value. Furthermore, in 21 trials of nine different subjects, the $AFiso_{max}$ was even lower than 50% of the Max pre-MVIC. This, in turn, emphasizes the need for an individual analyzation. It also means that lower and higher $AFiso_{max}$ values can occur in different trials of the same subject. This is exemplified by Figure 6. In the blue curve, the start of giving way was at a substantially lower torque (4.02 Nm) compared to the red curve (16.68 Nm). Even if the arm movement could be decelerated up to 22 Nm (blue curve), the determined 2°-tolerance in angles was exceeded. Thus, the muscle action was no longer rated as isometric. Different $AFiso_{max}$ levels in the same subject result in a higher variation between single trials and between days. As described before, $AFiso_{max}$ revealed higher SEMs (M: 5.68 Nm; Max: 4.17 Nm) compared to other maximal forces (SEM = 1.29–3.16 Nm). The variation between single trials was also higher (CVs $\geq$ 24.29% vs. $\leq$ 5.40%). The greater within- and between-days variations imply a suspected lower reliability of $AFiso_{max}$ compared to other force types. Although the already mentioned limitations in the determination method of $AFiso_{max}$ might play a role (inter alia, strict 2° boundary), these results could be explained from another point of view: We suggest $AFiso_{max}$ has a higher biological variability compared to other maximal forces. It could possibly be present due to a required higher complexity of sensorimotor control during the adaptation of muscular tension and length to varying external forces compared to pushing actions, such as the MVIC test.

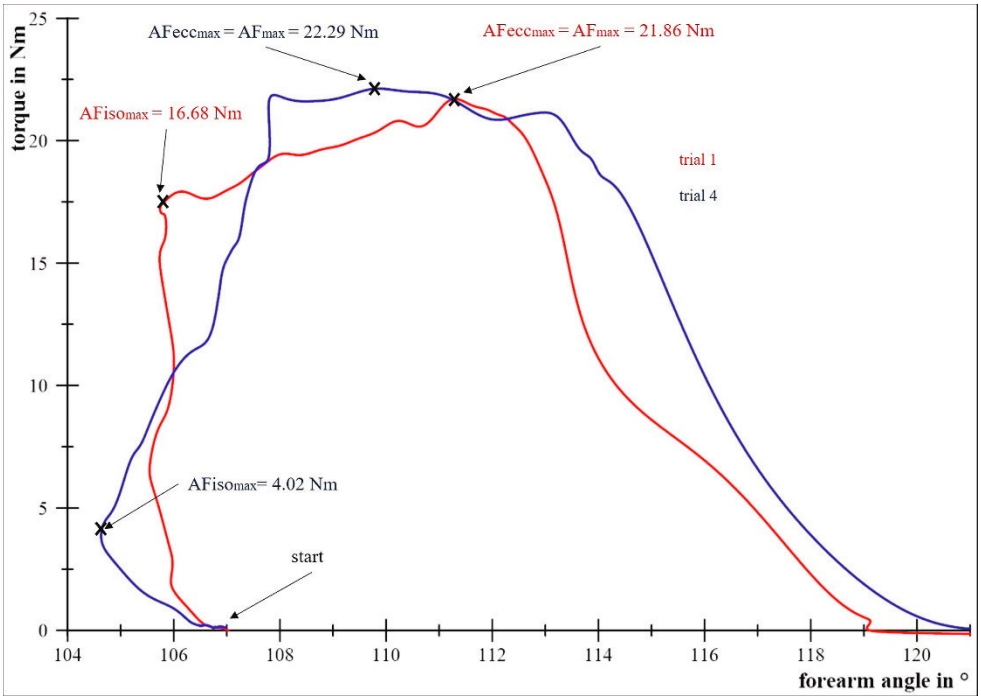


Figure 6. Angle-force plot of two exemplary AF-measurements of the same subject (female, 32 yrs, 1.68 m, 58 kg). In trial 1 (red curve), the arm angle does not change meaningfully until the maximal isometric Adaptive Force ($AFiso_{max}$ = 16.68 Nm) is reached. In trial 4 (blue curve), the forearm starts to give way at a lower force level (lower $AFiso_{max}$ = 4.02 Nm). The maximal Adaptive Forces (AF_{max}), which are reached during the eccentric phases (= $AFecc_{max}$), are similar in both trials (22.29 Nm and 21.86 Nm). These two trials illustrate the variability of $AFiso_{max}$.

The adaptation during a holding action requires an adjustment of the muscular tension, together with the muscular length. The change in muscle length is sensed by muscle spindles and the change in tension by Golgi tendon receptors [61]. The kinesthetic afferences are sent to spinal and supraspinal areas, where they are integrated and processed before an adequate response is performed. These complex feedback control mechanisms for

adjusting tension and length have to function properly during an AF-measurement [62,63]. To hold a position over time, the muscular tension and length have to be adjusted immediately after a reference error of the position has been detected. That procedure has to be repeated consecutively during the whole measurement process. However, feedback control mechanisms alone cannot be responsible for maintaining the position because the external force increases over time and a compensatory response to it would always be delayed. Additionally, to deal with this time problem, an adequate feedforward control is required, whereby the force increase must be anticipated [4]. The anticipation must be continuously adjusted on the basis of proprioceptive inputs. This results in further neurophysiological demands, leading to an approximated control of the position which anticipates the forthcoming increase in the external force. Thereby, marginal lengthenings and shortenings of the muscle fibers occur. As the resulting oscillations of the limb are stationary, the muscle action can still be considered as isometric or, more precisely, "quasi-isometric".

In contrast, by performing an MVIC test (pushing isometric task), the subject must only be proactive and change muscular tension without the need to respond to an external varying force or control the length. Thus, neuromuscular demands ought to be lower compared to an AF-measurement, and might explain why the pre-MVIC was higher and less variable than the $AFiso_{max}$. Compared to a pushing isometric mode, it was already assumed that a holding isometric mode has more complex neural control strategies [9].

Control strategies of higher complexity could be more vulnerable to disturbing influences. Thus, the $AFiso_{max}$ relative to the maximal strength capacity of a muscle could have the potential to differentiate between a functionally disturbed neuromuscular system and an intact one. An undisturbed, functionally intact neuromuscular system might be able to reach a high $AFiso_{max}$ in relation to the MVIC. As the pre-MVIC and AF_{max} differed insignificantly, AF_{max} could serve as a reference. Cases in which the limb started to give way immediately at the beginning of an AF-measurement (n = 3 in the present study), or in which the $AFiso_{max}$ was relatively low (e.g., < 50% of the Max pre-MVIC), the neuromuscular system did not respond adequately to the externally applied force. These inadequate responses could possibly be attributed to inhibitory signals to fusimotor-, skeletomotor- or interneurons within the complex response loops (spinal and supraspinal pathways) [62]. A time delay in the activation of extrafusal muscle fibers is also conceivable. As previously discussed [4], regions involved in the complex motor control are not only the motor cortex itself, but also the thalamus, basal ganglia cerebellum, inferior olivary nucleus, cingulate cortex and the red nucleus. All of these areas process several inputs and can alter motor control. Causes of disturbed control could be highly diverse, including, e.g., nociceptive signals or even emotions [64–67]. However, the assumptions of neurophysiological influences have to be taken with caution because, in the presented study, an absence of the subject's attention or bias in the measurement process cannot be ruled out completely (see limitations).

Independently of its cause, a low $AFiso_{max}$ in relation to MVIC or AF_{max} might be a theoretical explanatory approach of the genesis of musculoskeletal complaints and injuries. According to this concept, a low relative $AFiso_{max}$ as an indicator of a disturbed neuromuscular system might be present prior to complaints or injuries. If that holds true in future studies, the detection of $AFiso_{max}$ and its improvement could also play a key role in preventive strategies. Furthermore, an impairment of muscular function is discussed for chronic fatigue syndromes [68], COVID-19 [69], cancer [70] and hormonal dysfunction [71,72]. Currently, e.g., no-load resistance training [73,74] and power training [75] are being investigated, with the aim of improving functional muscle capacity. However, the parameters of Adaptive Force (especially $AFiso_{max}$) might be reduced, too. In this case, improving the $AFiso_{max}$ would be of relevance. We propose that treatments of the possible causes that might impair the $AFiso_{max}$ (see above) might help improve it, rather than training programs alone.

5. Conclusions

The presented pneumatic system, as a refinement of the SeBit, is able to measure the MVIC, the MVICpri-con and especially the AF. Conclusions about the MVICpri-con need further examination by use of separate study designs. However, the device is suitable for generating reliable data and can be used to determine the different parameters of Adaptive Force ($AFiso_{max}$, $AFecc_{max}$ and AF_{max}). Besides an evaluation of the new device, the study revealed further insights about maximal holding capacity during adaptation to external forces ($AFiso_{max}$). Despite high correlations, it could be discriminated from other maximal forces. Thus, it can be interpreted as a specific and independent parameter of muscle function. The $AFiso_{max}$ should be determined separately and its normalization to the MVIC or AF_{max} might be a meaningful variable in the evaluation of the functionality of the neuromuscular system. Future research can examine whether there is relationship between a low relative $AFiso_{max}$ and the occurrence of injuries or any other complaints. If a relationship is found, the following question arises: How can the $AFiso_{max}$ be improved, especially if the MVIC and/or AF_{max} are interpreted as appropriate, e.g., by a special training program or treatment? It is hypothesized that the holding isometric Adaptive Force is related to complex control processes of the neuromuscular system, and depends on the functional condition of the system itself. This would mean a deficient $AFiso_{max}$ might be treatable by eliminating the causes affecting of this dysfunction.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/diagnostics11060923/s1, Figure S1. Scatter plots of the pre- and post-MVIC (maximal voluntary isometric contraction) and MVICpri-con (MVIC with a prior concentric contraction). Figure S2. Scatter plots of $AFiso_{max}$ (maximal isometric Adaptive Force) and AF_{max} (maximal Adaptive Force). Table S1. Torques in Nm of all force types and trials (M1–4) at each day (t_1 and t_2).

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

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Abbreviations

AF	Adaptive Force
$AFecc_{max}$	maximal eccentric AF
$AFiso_{max}$	maximal isometric AF
AF_{max}	maximal AF
CV	coefficient of variation
HIMA	holding isometric muscle action
M	mean
Max	maximum
MD	mean difference
MDC95%	minimal detectable change covering 95% of repeated measurements
MVIC	maximal voluntary isometric contraction
pre-MVIC	MVIC at the beginning of the measurement series
post-MVIC	MVIC at the end of the measurement series
MVICpri-con	MVIC with a prior concentric contraction
NI	National Instruments
PIMA	pushing isometric muscle action
SD	standard deviation
SD_{MD}	standard deviation of mean differences
SEM	standard error of measurements (random error)
SEM%	random percentage error
SEM95%	random percentage error covering 95% of repeated measurements
t_1	measuring session at day 1
t_2	measuring session at day 2

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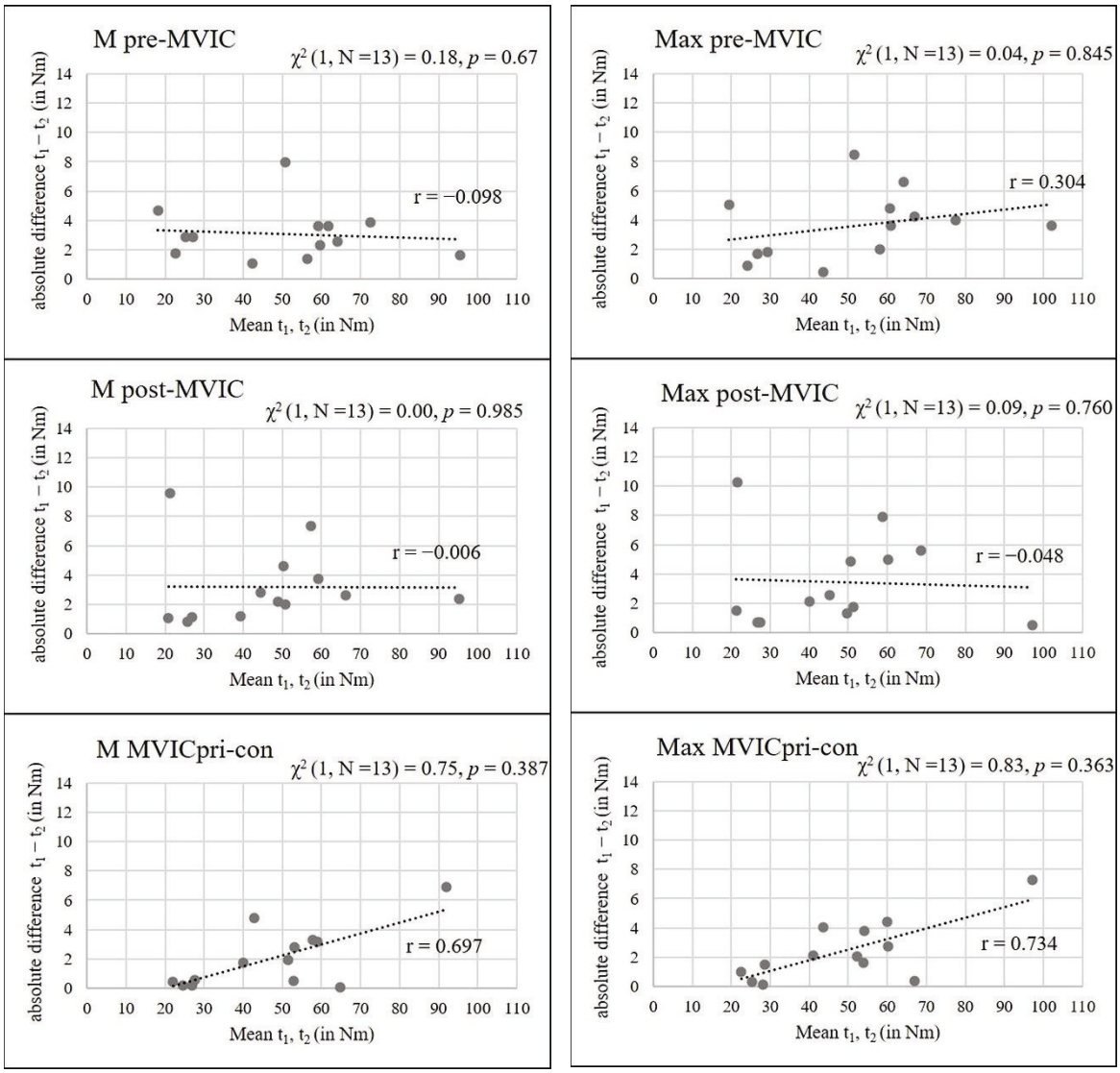

(**a**) (**b**)

Figure S1. Scatter plots of the pre- and post-MVIC (maximal voluntary isometric contraction) and MVICpri-con (MVIC with a prior concentric contraction). The diagrams show the absolute differences between days (t_1 – t_2) of (**a**) the mean (M) and (**b**) the maximal (Max) torques out of 4 measurements against the respective measurement means of t_1 and t_2**.** The result of the Breusch-Pagan-test can be found at the top of each panel. Pearson's r is presented besides the regression line. According to Atkinson and Nevill (1998),[1] r > 0.2 is rated as a heteroscedastic data.

1

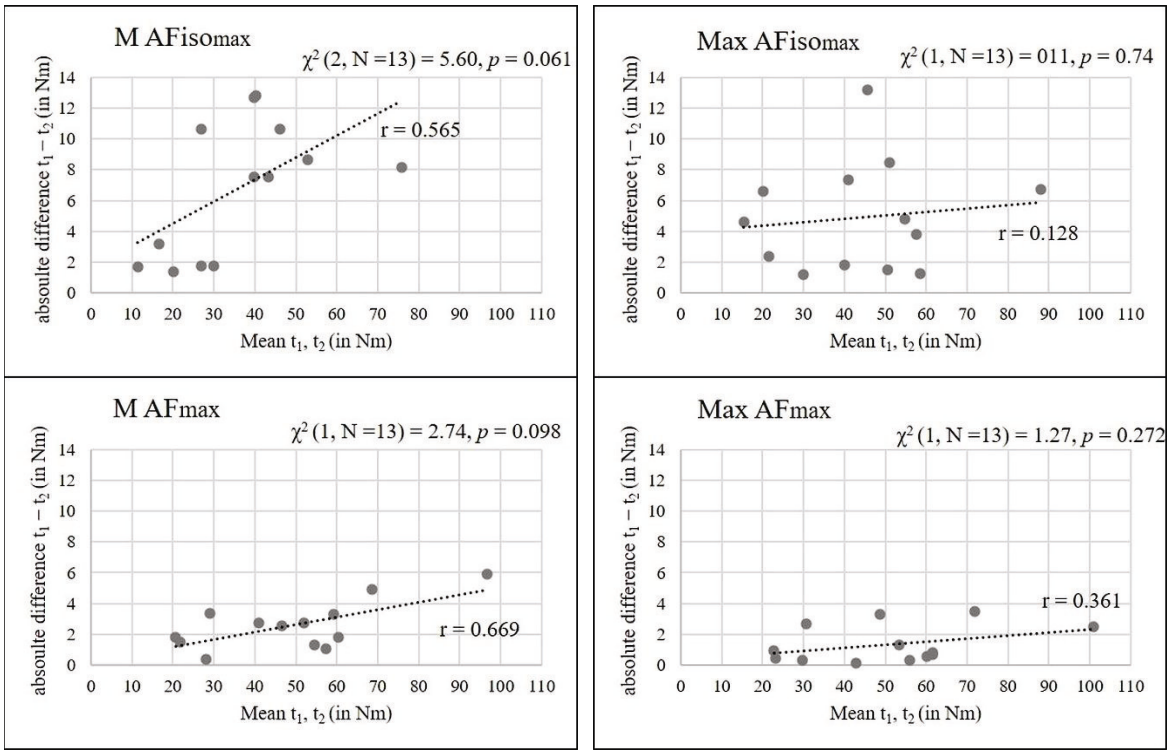

Figure S2. Scatter plots of $AFiso_{max}$ (maximal isometric Adaptive Force) and AF_{max} (maximal Adaptive Force). The diagrams show the absolute differences between days ($t_1 - t_2$) of (**a**) the mean (M) and (**b**) the maximal (Max) torques against the respective means out of t_1 and t_2.The result of the White-test (M $AFiso_{max}$) or Breusch-Pagan-test (other variables) can be found at the top of each panel. Pearson's r is presented besides the regression line. According to Atkinson and Nevill (1998),[1] r > 0.2 is rated as a heteroscedastic data.

Table S1. Torques in Nm of all force types and trials (M1 – 4) at each day (t_1 and t_2).

force type	subject (gender)	day 1 (t_1)				day 2 (t_2)			
		M1	**M2**	**M3**	**M4**	**M1**	**M2**	**M3**	**M4**
pre-MVIC	1 (f)	22.80	28.44	25.64	25.72	24.70	30.11	30.29	28.96
post-MVIC		27.71	27.10	-	-	26.99	25.54	-	-
MVICpri-con		27.73	28.11	27.79	28.01	27.42	28.26	26.56	27.23
$AFiso_{max}$		13.77	16.80	14.46	14.65	17.71	23.38	10.14	21.28
$AFecc_{max}$		27.25	30.00	27.66	27.84	29.68	27.96	27.61	26.08
AF_{max}		27.25	30.00	27.66	27.84	29.68	27.96	27.61	26.08
pre-MVIC	2 (m)	59.77	67.96	69.16	64.51	64.85	64.92	59.06	62.25
post-MVIC		59.34	62.69	-	-	56.86	57.72	-	-
MVICpri-con		61.48	59.96	61.44	59.36	57.31	58.75	57.58	56.04
$AFiso_{max}$		16.04	29.66	57.30	55.20	47.30	52.51	42.00	46.50
$AFecc_{max}$		62.00	61.21	58.81	61.97	55.08	57.29	57.14	61.34
AF_{max}		62.00	61.21	58.81	61.97	55.08	57.29	57.14	61.34
pre-MVIC	3 (m)	60.88	63.00	61.86	58.63	57.96	58.18	56.43	57.20
post-MVIC		48.22	47.94	-	-	52.29	53.06	-	-
MVICpri-con		49.64	51.17	50.99	50.01	52.92	51.51	53.22	51.84
$AFiso_{max}$		59.51	58.91	57.17	53.90	55.73	48.42	50.54	40.12
$AFecc_{max}$		59.90	58.44	57.51	55.00	60.49	56.81	54.69	55.19
AF_{max}		59.90	58.91	57.51	55.00	60.49	56.81	54.69	55.19
pre-MVIC	4 (f)	23.35	24.56	23.36	23.03	19.40	23.67	22.69	21.40
post-MVIC		22.00	20.90	-	-	20.25	20.52	-	-
MVICpri-con		23.12	21.69	22.02	22.24	21.64	21.85	22.10	21.82
$AFiso_{max}$		20.02	19.48	20.39	18.04	22.78	21.24	20.51	18.83
$AFecc_{max}$		22.19	22.67	23.30	22.12	22.86	21.24	20.72	19.51
AF_{max}		22.19	22.67	23.30	22.12	22.86	21.24	20.72	19.51
pre-MVIC	5 (m)	65.91	67.46	58.32	62.62	60.86	60.34	59.69	59.03
post-MVIC		62.67	59.27	-	-	54.76	52.55	-	-
MVICpri-con		60.15	57.56	62.27	58.03	55.61	55.02	56.26	57.84
$AFiso_{max}$		57.74	30.99	59.18	58.22	46.75	57.95	51.73	7.29
$AFecc_{max}$		62.04	60.24	61.71	60.86	59.63	61.24	60.60	56.13
AF_{max}		62.04	60.24	61.71	60.86	59.63	61.24	60.60	56.13
pre-MVIC	6 (m)	42.00	43.39	41.22	40.83	43.84	42.94	42.69	42.22
post-MVIC		38.84	41.12	-	-	39.02	38.57	-	-
MVICpri-con		39.37	38.64	38.32	40.02	40.53	40.40	42.16	40.21
$AFiso_{max}$		29.00	39.19	19.43	28.76	41.03	36.60	13.00	32.79
$AFecc_{max}$		42.18	42.79	41.74	42.89	42.79	39.12	38.18	38.48
AF_{max}		42.18	42.79	41.74	42.89	42.79	39.12	38.18	38.48
pre-MVIC	7 (m)	82.55	92.93	103.95	98.84	100.31	100.00	86.41	98.10
post-MVIC		90.63	97.36	-	-	96.86	95.89	-	-
MVICpri-con		88.09	95.85	97.17	100.74	89.17	80.94	93.46	90.65
$AFiso_{max}$		84.75	59.79	63.15	79.37	67.05	70.71	91.47	90.29
$AFecc_{max}$		91.33	95.43	87.11	99.67	101.63	102.18	92.56	101.79
AF_{max}		91.33	95.43	88.21	99.67	101.63	102.18	92.64	101.79
pre-MVIC	8 (m)	58.99	56.71	59.13	58.96	62.76	61.25	59.49	59.49
post-MVIC		50.47	49.24	-	-	52.23	51.49	-	-
MVICpri-con		53.12	54.69	53.49	50.99	52.73	53.06	52.64	51.89
$AFiso_{max}$		34.75	51.91	47.91	52.18	39.03	30.91	32.93	32.58
$AFecc_{max}$		52.41	53.37	53.67	53.99	52.70	50.43	49.87	49.54
AF_{max}		52.41	53.37	53.67	53.99	52.70	50.43	49.87	49.54
pre-MVIC	9 (m)	79.40	67.40	63.61	72.06	74.89	75.41	72.65	75.05
post-MVIC		65.73	63.88	-	-	71.33	63.52	-	-
MVICpri-con		64.66	62.74	66.75	64.73	67.12	62.21	64.49	65.37
$AFiso_{max}$		36.71	-	55.27	46.28	46.84	20.39	46.73	19.78

$AFecc_{max}$		73.13	73.62	69.03	68.34	69.50	70.12	66.30	58.63
AF_{max}		73.13	73.62	69.03	68.34	69.50	70.12	66.30	58.63
pre-MVIC	10 (f)	27.17	26.41	27.50	25.71	23.25	25.82	21.71	24.41
post-MVIC		23.28	27.12	-	-	26.44	25.62	-	-
MVICpri-con		25.35	25.57	25.12	22.33	24.23	25.23	24.45	23.69
$AFiso_{max}$		17.68	17.10	10.32	4.02	13.07	12.00	11.48	5.95
$AFecc_{max}$		21.86	21.34	20.85	22.29	20.70	17.28	17.90	23.25
AF_{max}		21.86	21.34	20.85	22.29	20.70	17.28	17.90	23.25
pre-MVIC	11 (f)	16.89	16.23	16.38	14.00	20.31	20.89	18.98	21.94
post-MVIC		16.35	16.52	-	-	26.76	25.29	-	-
MVICpri-con		25.99	25.77	29.42	26.22	26.23	26.99	27.92	-
$AFiso_{max}$		21.70	25.97	29.45	27.22	30.67	30.36	23.67	26.74
$AFecc_{max}$		24.93	28.14	-	-	-	32.10	30.66	29.65
AF_{max}		24.93	28.14	29.45	27.22	30.67	32.10	30.66	29.65
pre-MVIC	12 (m)	58.15	59.07	58.21	52.90	55.18	57.08	56.53	54.09
post-MVIC		48.96	46.70	-	-	50.30	49.71	-	-
MVICpri-con		54.94	55.98	52.97	54.22	52.21	51.94	52.15	50.53
$AFiso_{max}$		2.42	46.76	49.88	45.43	51.40	39.50	48.79	35.00
$AFecc_{max}$		56.09	55.39	56.15	53.25	55.84	53.20	54.58	51.97
AF_{max}		56.09	55.39	56.15	53.25	55.84	53.20	54.58	51.97
pre-MVIC	13 (m)	55.77	54.64	54.05	54.24	46.60	46.62	46.29	47.29
post-MVIC		45.29	46.50	-	-	42.28	43.92	-	-
MVICpri-con		45.61	45.35	45.05	44.84	40.73	41.58	39.40	40.08
$AFiso_{max}$		40.23	44.55	44.25	0.08	19.33	0.34	29.75	37.21
$AFecc_{max}$		48.00	50.36	47.09	46.13	47.06	42.71	45.28	46.29
AF_{max}		48.00	50.36	47.09	46.13	47.06	42.71	45.28	46.29

AF_{max} = maximal Adaptive Force; $AFecc_{max}$ = maximal eccentric Adaptive Force; $AFiso_{max}$ = maximal isometric Adaptive Force; f = female; m = male; MVIC = maximal voluntary isometric contraction; MVICpri-con = MVIC with a prior concentric contraction.

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Statutory Declaration

I declare that I have written this cumulative dissertation independently and that I have not used other than indicated sources. I further declare that I have explicitly marked all material which has been quoted and all regulations of good scientific standards were adhered during the writing process. The work has not yet been submitted to another examination office. Indicated parts have have already been published in scientific online journals (open access).

Potsdam, June 2022 Signature