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Rate of force development and purely explosive contractions: from neural and muscular determinants to methods to assess central, peripheral fatigue, and asymmetries

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Rate of force development and purely explosive contractions: from neural and muscular determinants to methods to assess central, peripheral fatigue, and asymmetries

Samuel D'Emanuele
PhD thesis
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Sommario

L'analisi delle curve forza-tempo è stata ampiamente studiata per valutare la funzione neuromuscolare sia a riposo che in condizioni di fatica. Di solito, la massima forza volontaria (MVF) è stata utilizzata come *main outcome* (es., pre- vs. post task affaticante). Tuttavia, il tempo necessario per raggiungere la MVF è ≈ 400/600 ms dall'inizio della contrazione e questo è lontano dal tempo necessario per sviluppare la forza in molte situazioni della vita reale. Infatti, la capacità di generare forza rapidamente (≈200 ms) attraverso vari livelli sub massimali (*neuromuscular quickness*) è alla base di gesti importanti della vita quotidiana, come la stabilizzazione dell'equilibrio posturale a seguito di una sua perdita, e per molti gesti sportivi, che coinvolgono sia gli arti superiori che quelli inferiori, come il lancio del peso, i salti verticali, lo sprint sia in bicicletta che nella corsa ma anche nella corsa di resistenza. Infatti, anche la locomozione umana è stata descritta come da un'eccitazione impulsiva (*burst-like*) con un profilo di attivazione gaussiano. Di conseguenza, la MVF perde importanza quando è correlata a compiti esplosivi/balistici. Per questo motivo sembra più appropriato indagare il tasso di sviluppo della forza (RFD). A questo proposito, il RFD è derivato dalle curve forza/coppia tempo registrate durante le contrazioni volontarie esplosive dall'inizio della forza e rappresenta un indice di rapidità. Nel corso dei decenni, il RFD è stato utilizzato per studiare gli effetti acuti (ad esempio a seguito di task affaticanti), effetti sul danno muscolare, allenamento, differenze di genere ed età, ecc..Tuttavia, sebbene siano state pubblicate linee guida per effettuare misurazioni di RFD valide, i metodi utilizzati in letteratura sono eterogenei. Riguardo a questo punto, il **Capitolo 1** è dedicato a scavare in profondità il *background* dell'RFD e nei modi più appropriati per misurarlo. Inoltre, viene dato spazio ad alcuni concetti di fatica, asimmetrie e RFD-*Scaling factor* (RFD-SF) mantenendo come comune denominatore le contrazioni esplosive. A seguire quindi, obiettivi e ipotesi di questa tesi. Il **Capitolo 2** è dedicato alla ricerca dei determinanti neurali e contrattili delle contrazioni isometriche esplosive *burst-like* degli estensori del ginocchio. Il **Capitolo 3** riporta i risultati di una *scoping review* sul RFD come indicatore di affaticamento neuromuscolare. Successivamente, dopo aver dimostrato la validità del RFD come indicatore di fatica neuromuscolare, il **Capitolo 4** riporta i risultati di uno studio sulla fatica centrale indotta da cento contrazioni puramente esplosive. Il **Capitolo 5** è dedicato ad indagare le asimmetrie degli arti superiori attraverso il RFD-SF dimostrando che le asimmetrie sono muscolo-specifiche e metriche-dipendenti. In conclusione, il **Capitolo 6** è finalizzato alla discussione generale sui principali risultati, limiti e prospettive future.

Abstract

The analysis of force-time curves has been widely investigated to assess the neuromuscular function both in rest and in fatigue conditions. Usually, the *maximal voluntary force* (MVF) has been used as a main outcome (i.e., pre- vs. post-fatiguing task). However, the time required to reach the MVF is close to 400/600 ms from the force onset and this is far from the time required to develop force in many real-life situations. Indeed, the ability to generate and relax muscle forces quickly (i.e., 200 ms) across various submaximal levels (i.e., neuromuscular quickness) is the basis of relevant activities of daily life, such as the stabilization of postural balance following a loss of it, and for many sports gestures, involving both upper and lower extremities, like shot put, vertical jumps, sprint both cycling and running but also in endurance running. Indeed, also human locomotion has been described as generated by an impulsive (burst-like) excitation of the muscle group with a Gaussian activation profile.

Consequently, the MVF loses importance when it is related to explosive/ballistic tasks. For this reason, seems to appear more appropriate to investigate the *rate of force development* (RFD). Concerning that point, RFD is derived from the force/torque time curves recorded during explosive voluntary contractions from the force onset and represents an index of quickness. Over the decades, RFD has been used to investigate the acute effects of, for example, fatiguing tasks, effects on muscle damage, training, gender and age differences etc...

However, although guidelines have been published to carry out valid RFD measurements, the methods used in the literature are heterogeneous. Concerning that point, **Chapter 1** is dedicated to digging deep into the background of RFD and the most appropriate ways to measure it. Furthermore, space is given to some concepts of fatigue, asymmetries, and RFD-Scaling factor (RFD-SF) keeping explosive contractions as a common denominator, and then, aims and hypotheses of this thesis. **Chapter 2** is dedicated to research about neural and contractile determinants of burst-like explosive isometric contractions of knee extensors. Following, **Chapter 3** reports the results of a scoping review of RFD as an indicator of neuromuscular fatigue. Then, having demonstrated the validity of RFD as an indicator of neuromuscular fatigue, **Chapter 4** reports the results of a study about central fatigue induced by one hundred purely explosive contractions. **Chapter 5** is dedicated to investigating the upper limbs asymmetries through the RFD-SF showed that are muscle-specific and metric-dependent. In conclusion, **Chapter 6** is finalised to the general discussion about the main findings, limits, and future perspectives.

Acknowledgements

A roller coaster ride that lasted 1187 days. Every day, confront your limits. However, it's not a path I've taken on my own. Therefore, it is right to give credit to the people who have accompanied me step by step towards this dream goal.

Firstly, my supervisor, Professor Federico Schena, taught me to always look and think in the long term, and because he always trusted my choices, aware that I was always well supervised, also by Professor Cantor Tarperi, Professor Alberto Rainoldi, and Doctor Gennaro Boccia. It is precisely to them that I must express immense gratitude for having taught me practically everything and for being there in the difficult (but also funny) moments that often arise during a doctoral course.

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A heartfelt thanks to all the participants who took part in the various studies (especially to those who underwent octets on the femoral nerve... sorry!), without you, I would not have achieved any of these results.

I can never thank my mother and grandmother enough. Thanks to your support, I was able to reach this milestone. My achievements are also yours.

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List of Abbreviations

AI	Asymmetry index
BAI-1	Bilateral asymmetry index 1
BAI-2	Bilateral asymmetry index 2
BSA	Bilateral strength asymmetry
Ca^{2+}	Calcium
CF	Central fatigue
CNS	Central nervous system
CSA	Cross-sectional area
DL	Dominant limb
EMG	Electromyography
HDsEMG	High-Density Surface Electromyography
ICC	Interclass correlation coefficient
ITT	Interpolated Twitch technique
ICC	Intraclass correlation coefficient
KE	Knee extension
LSI-1	Limb symmetry index 1
LSI-2	Limb symmetry index 2
LSI-3	Limb symmetry index 3
MVC	Maximal voluntary contraction
MVF	Maximal voluntary force
MU	Motor unit
MFCV	Muscle fibre conduction velocity
PF	Peripheral Fatigue

Publications from thesis

The results of this dissertation produced the following papers and communications.

Papers

Boccia G, **D’Emanuele S**, Brustio PR, Rainoldi A, Schena F, Tarperi C. Purely explosive isometric contractions induce mostly central fatigue. *Submitted*

D'Emanuele S, Maffiuletti NA, Tarperi C, Rainoldi A, Schena F, Boccia G. Rate of Force Development as an Indicator of Neuromuscular Fatigue: A Scoping Review. *Front Hum Neurosci*. 2021; 15:701916. Published 2021 Jul 9. doi:10.3389/fnhum.2021.701916

Boccia G, **D'Emanuele S**, Brustio PR, et al. Strength Asymmetries Are Muscle-Specific and Metric-Dependent. *Int J Environ Res Public Health*. 2022;19(14):8495. Published 2022 Jul 12. doi:10.3390/ijerph19148495

D'Emanuele S, Tarperi C, Rainoldi A, Schena F, Boccia G. Neural and contractile determinants of burst-like explosive isometric contractions of the knee extensors. published online ahead of print, 2022 Oct 13. Scand J Med Sci Sports. 2022;10.1111/sms.14244. doi:10.1111/sms.14244

Oral Communications

D’Emanuele S. Neural and contractile determinants of ballistic (burst-like) contractions of knee extensors. *European College of Sport Medicine Congress*. Sevilla, 30 Aug – 4 Sept 2022

D’Emanuele S, Boccia G, Rainoldi A, Schena F, Tarperi C. Neural and contractile determinants of purely explosive isometric contractions of knee extensors. *SISMES XII National Congress*. Padova, 8 – 10 Oct 2021.

Posters

D’Emanuele S, Angius L, Hayman O, Goodall S, Schena F, Tarperi C, Boccia G. Repeated submaximal explosive contractions of dorsiflexor muscles effect the rate of force development and maximal voluntary force. *SISMES XIII National Congress*. Milano, 4 – 6 Nov 2022.

D’Emanuele S, Boccia G, Rainoldi A, Schena F, Tarperi C. Central and peripheral fatigue induced by 100 purely explosive isometric contractions. *The Biomedical Basis of Elite Performance 2022*, The Physiological Society, at the Monica Partridge Building, University of Nottingham, UK on 12 – 13 April 2022.

Boccia G, **D'Emanuele S**, Brustio PR, Tarperi C, Schena F, Rainoldi A. Purely explosive contractions induce greater central than peripheral fatigue. *SISMES XII National Congress*. Padova, 8 – 10 Oct 2021.

Other scientific papers and communications

Papers and oral communications not related to this dissertation

Papers

Skroce K, Bettega S, **D’Emanuele S**, Boccia G, Schena F, Tarperi C. Flat versus simulated mountain trail running, a multidisciplinary comparison in well trained runners. *Under review.*

Brustio PR, Mulasso A, **D’Emanuele S**, Zia G, Feletti L, Del Signore S, Rainoldi A. Indoor Mobility, Frailty, and Disability in Community-Dwelling Older Adults: A Mediation Model. *International Journal of Environmental Research and Public Health*. 2022; 19(18):11386. https://doi.org/10.3390/ijerph191811386

Aranceta-Garza A, Russo A, **D'Emanuele S**, Serafino F, Merletti R. High Density Surface Electromyography Activity of the Lumbar Erector Spinae Muscles and Comfort/Discomfort Assessment in Piano Players: Comparison of Two Chairs. *Front Physiol*. 2021; 12:743730. Published 2021 Dec 1. doi:10.3389/fphys.2021.743730

Oral Communications

D’Emanuele S. What high density surface electromyography can teach us about the postural activation of erector spinae muscles? The case of violinists. *CeRiSM - 8th International Congress – Mountain Sport and Health* – 7 – 8 Nov 2019 – Rovereto (TN) – Short talk

Chapter 1 – Background, aims and hypotheses

1.1 Rate of Force Development

This chapter aims to describe the neural and muscular determinants of the *Rate of force development* (RFD) and then express the methodological considerations for RFD assessment. Thereafter, the *RFD-Scaling factor* (RFD-SF) will be presented as a methodology to investigate the RFD through a series of contractions at a submaximal level (i.e., % of *maximal voluntary force*, MVF). Then, will be discussed in brief the key point about the *fatigue* concept and its offshoots (central and peripheral fatigue). To follow will be presented a summation of the topic of asymmetries. In conclusion, the aims and hypotheses of this dissertation will be clarified.

1.1.1 Background

The ability to generate and relax muscle forces quickly (i.e., 200 ms) across various submaximal levels (i.e., neuromuscular quickness) is the basis of relevant activities of daily life and for many sports gestures, involving both upper and lower extremities (Uygur et al., 2020), like shot put (Zaras et al., 2016), vertical jumps (McLellan et al., 2011), sprint both cycling and running (Stone et al., 2004, Tomazin et al., 2012, Connolly et al., 2022) but also in endurance running (Lieberman et al., 2010). Indeed, also human locomotion has been described as generated by an impulsive (burst-like) excitation of the muscle group with a Gaussian activation profile (Gizzi et al., 2011, Ivanenko et al., 2006, Sartori et al., 2013).

The analysis of force-time curves has been widely investigated to assess the neuromuscular function both in rest and in fatigue conditions (Penailillo et al., 2015, Thorlund et al., 2009, Molina and Denadai, 2012). Usually, the MVF has been used as a main outcome (i.e., pre- vs. post-fatiguing task). However, the time required to reach the MVF is close to 400/600 ms (Aagaard et al., 2002) or 150–400 ms (depending on the relative intensity and exercise used) during dynamic activations (Kawamori et al., 2006), from the force onset and this is far from the time required to develop force in many sport situations/gestures or functional tasks of daily living (Varesco et al., 2019). As aforementioned, many sports gestures such as sprints, changes of direction, throws, kicks, etc. require contraction times lower than 250 ms. Consequently, the MVF loses importance when it is related to explosive/ballistic tasks. For this reason, seems to appear more appropriate to investigate RFD.

The RFD is derived from the force/torque time curves recorded during explosive voluntary contractions from the force onset (Aagaard et al., 2002) and can be expressed in absolute terms ($N \cdot s^{-1}$) or relative to peak force (to yield relative RFD), body mass or muscle cross-sectional area (CSA) (Waugh et al., 2013, Suetta et al., 2004, Aagaard et al., 2002). The RFD appears as a key point, as already mentioned, both in trained athletes that need to perform rapid and forceful movements, and in elderly individuals (Palmer et al., 2022) who need to control unexpected perturbations in postural balance (Aagaard, 2003, Porto et al., 2022, Kamo et al., 2019) or, in general, as a useful indicator/biomarker of changes in neuromuscular function elicited by neurodegeneration (Henderson et al., 2023). Moreover, it could be considered as an adjunctive determinant outcome for return to sport after injuries (Angelozzi et al., 2012) or an indicator of muscle damage (Farup et al., 2016, Ruas et al., 2022, Jenkins et al., 2014). The RFD has also proved to be a useful parameter to investigate and evaluate the effects of training (Tøien et al., 2023, Baiget et al., 2022, Siddique et al., 2022) or may be used as indices to identify players with a high degree of (i.e., soccer playing) ability (Palmer and Akehi, 2022).

As reported by Rodríguez-Rosell et al. (2018) the term RFD often have been changed with other terms such as example, *"explosive strength", "rapid muscle contraction", "rapid force capacity", "explosive force production"* and *"ballistic contraction"* used to describe the same concept, that is *"the ability of the neuromuscular system to produce a high rate of rise in muscle force per unit of time during the initial phase of rising muscle force following contraction onset"* (Rodríguez-Rosell et al., 2018). For example, Mirkov et al. (2004) with the term *explosive force production* defined the ability of the neuromuscular system to perform high-speed muscle actions while RFD refers to the testing of explosive force production. However, other authors suggested that RFD is the most accurate, simple, and unambiguous term to refer to a rapid rise in force production (Aagaard et al., 2002, Andersen et al., 2005, Andersen et al., 2010, Haff et al., 2015). Further, Zatsiorsky (2003) suggested that could be more appropriate to use the term RFD to refer to rapid force generation from the force's onset rather than explosive strength because explosive strength typically is associated with high-speed dynamic movements while RFD can be assessed in both static and dynamic contractions. In detail, when the RFD is calculated *in vivo* during maximal voluntary joint flexion or extension (i.e., knee, elbow, ankle or hip) the slope of the moment–time curve (Δmoment/Δtime) describes the evolution of RFD, whereas multi-joint test contractions (e.g. squat, deadlift, bench press, etc…) or in isolated muscle *in vitro*, the RFD is defined as the slope of the force–time curve (i.e. Δforce/Δtime) (Schmidtbleicher, 1992, Häkkinen et al., 1998, Aagaard et al., 2002, Folland et al., 2014, Suetta et al., 2004, Tillin et al., 2010).

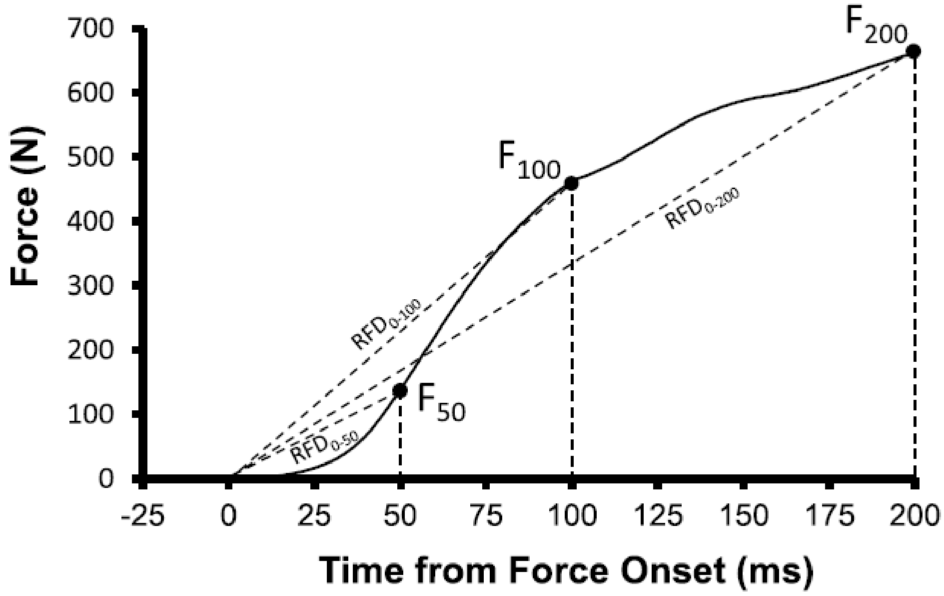

Figure 1. Force at the specific time-locked point. In detail, at 50, 100 and 200 ms from the force's onset and overlapping RFD. Taken from Maffiuletti et al. (2016)

The first appearance of RFD, as a key term, in scientific literature dates to 1962 by Royce (Royce, 1962). He was the first to investigate the difference between MVF and peak RFD after a sustained maximal contraction of the finger flexor for one minute.

A few years later, Viitasalo and Komi (1981b), investigated the difference between peak RFD and MVF through one-hundred explosive contractions of the knee extensors (KE) muscles. In the same year, the other two researchers tried to understand, for the first time, the difference between early (<100 ms from the force-onset) and late RFD (>100 ms from the force-onset). In detail, they investigated RFD across many non-overlapping time intervals and reported that the early part was more influenced than the late following sustained maximal contraction of the finger flexor muscles (Kearney and Stull, 1981). The time interval chosen to calculate RFD will depend on the aim of the measure because different RFD time-locked considered have different neural and contractile underpinning determinants (Andersen and Aagaard, 2006, D'Emanuele et al., 2022, Folland et al., 2014).

Since these pioneering works, numerous studies have been published on the fatigue-related changes in RFD of different muscle groups and through an enormous variety of tasks and exercises, including actual sports situations.

Especially since the last decade, the number of studies regarding RFD and fatigue has exploded with steady growth year on year. Nevertheless, many of the central issues related to RFD as definition, characteristics physiological determinants and methodological considerations are often contradictory and not well understood, although recent reviews have helped to clarify the key points (Maffiuletti et al., 2016, Rodríguez-Rosell et al., 2018). Indeed, while the measurement of voluntary RFD could be perceived as a simple task, it comprises a multifactorial measure which reflects the combined functioning of the neural and musculotendinous systems, respectively (Rodríguez-Rosell et al., 2018). However, albeit seems undeniable the role of neural and structural mechanisms, only a few evidence have been published (Van Cutsem et al., 1998, Griffin and Cafarelli, 2005, Folland et al., 2014) in that matter.

RFD is influenced by numerous factors within the neuromuscular system. Figure 2 summarizes the neuromuscular and musculotendon determinants influencing RFD expression. Moreover, the tight link between neural and muscular properties determines the association between neural drive and RFD during the early and late phases of force generation (see Figure 3) (Del Vecchio, 2023). Each factor affects RFD differently. Those that contribute to maximal muscle strength will improve mean RFD, while those that affect the time to reach a given level of force may additionally affect the RFD measured at different time intervals during the rise in muscle force.

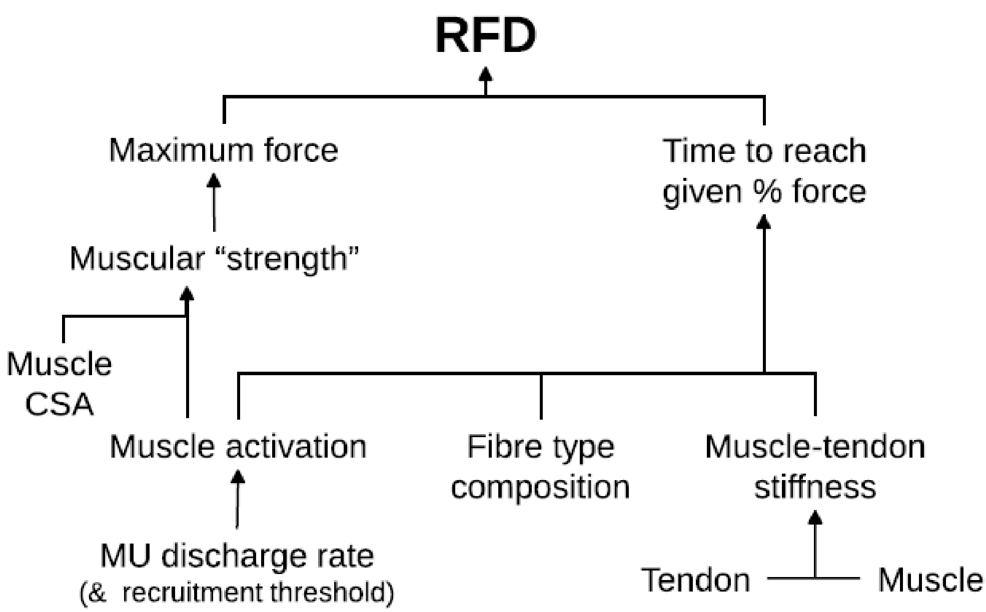

Figure 2. Factors that influenced the RFD. Taken from Maffiuletti et al. (2016).

Moreover, since the RFD is a parameter that can be trained/modified with training (Vila-Chã et al., 2010, Tøien et al., 2023), it appears to be of fundamental importance not only for researchers but also for coaches who, knowing the aetiology and complexity of the RFD (despite the ease of calculation), can obtain useful information from many points of view.

1.1.2 Neural Determinants

1.1.2.1 Motor Unit recruitment, discharge rate and synchronization

RFD is mainly related to neural activation and the magnitude of muscular activation is highly dependent on the number of motor units (MU) recruited and the rates at which motor neurones discharge action potentials. The maximal MUs discharge rate plays an important role in the ability to achieve RFD during the initial phase of rising muscle force and seems to be the most important factor that influenced the rapid force generation (Del Vecchio, 2023), especially during explosive maximal contractions than during maximal contractions performed at a slower RFD (Reece et al., 2021). The order recruitment follows Henneman's principle (Duchateau and Enoka, 2011, De Luca and Contessa, 2012) and the relative contributions of recruitment and discharge rate modulation to the force exerted by a muscle vary with contraction speed. In detail, slow contractions are characterised by a progressive activation of MUs to an upper limit of recruitment that reaches ≈ 80–90 % of the maximum force in most limb muscles (De Luca et al., 1982, Van Cutsem et al., 1997). In contrast, MUs are recruited at much lower forces (i.e., lower recruitment thresholds) during rapid actions. Desmet and Godaux conducted different works to assess this purpose (Desmedt and Godaux, 1977, Desmedt and Godaux, 1978). They demonstrated that in the tibialis anterior-most MUs are recruited during a ballistic contraction when the force is only 1/3 of maximum (Desmedt and Godaux, 1977) and that the reduction in recruitment threshold increased for slow-contracting muscles than for fasting-contracting muscles (Desmedt and Godaux, 1978). Consequently, the increase in muscle force beyond the upper limit of MU recruitment is entirely due to an increased discharge rate. In fact, during such rapid contractions, the activated MUs discharge only a few times (~1–6) (Van Cutsem and Duchateau, 2005, Van Cutsem et al., 1998) while during slower contractions the discharge rate of MUs increases progressively. For this purpose, Duchateau and Baudry (2014) showed that the increase in RFD during ballistic contractions was mainly due to adaptations in motor unit discharge rate. An increase in discharge rate from up to 100-200 Hz augmented substantially the RFD for all units of the pool. These data highlighted the critical role of maximal MU discharge rate on the ability to produce high RFD. Moreover, Klass et al. (2008) demonstrated that speed-related capacity is reduced with ageing. Older adults showed a slower RFD and MU discharge rate at the activation onset of ballistic ankle dorsiflexion compared with young subjects (Klass et al., 2008). However, seems that the ability to produce force quickly depends predominantly on the increase of muscle activation at the onset of the contraction and less on the speed-related properties of the muscle. This is demonstrated by de Ruiter et al. (2004) that shows that the force attained 40 ms after the onset of a rapid voluntary knee extension was less than for an electrically induced tetanic contraction. As well voluntary force, expressed relative to the force produced by electrical stimulation at the same time point, was positively associated with the EMG signals of the quadriceps before the onset of force development but not with that induced by electrical stimulation.

Another crucial point seems to be the synchronization of MUs (Dideriksen et al., 2020). The MUs correspond to the level of correlation between the timing of the action potentials discharged by concurrently active motor units (Duchateau et al., 2006, Folland and Williams, 2007). However, despite its apparent acceptance, the lack of empirical evidence supporting that the increased common synaptic inputs to spinal motor neurons result in enhanced MUs synchronization under voluntary conditions is a fundamental point. A study conducted by Kline and De Luca (2016) concluded that as the force generated by the muscle increases, the firing rate slope decreases, and the synchronization consequently decreases. Accordingly, whether MUs synchronization is a factor able to optimize the RFD expression remains unclear.

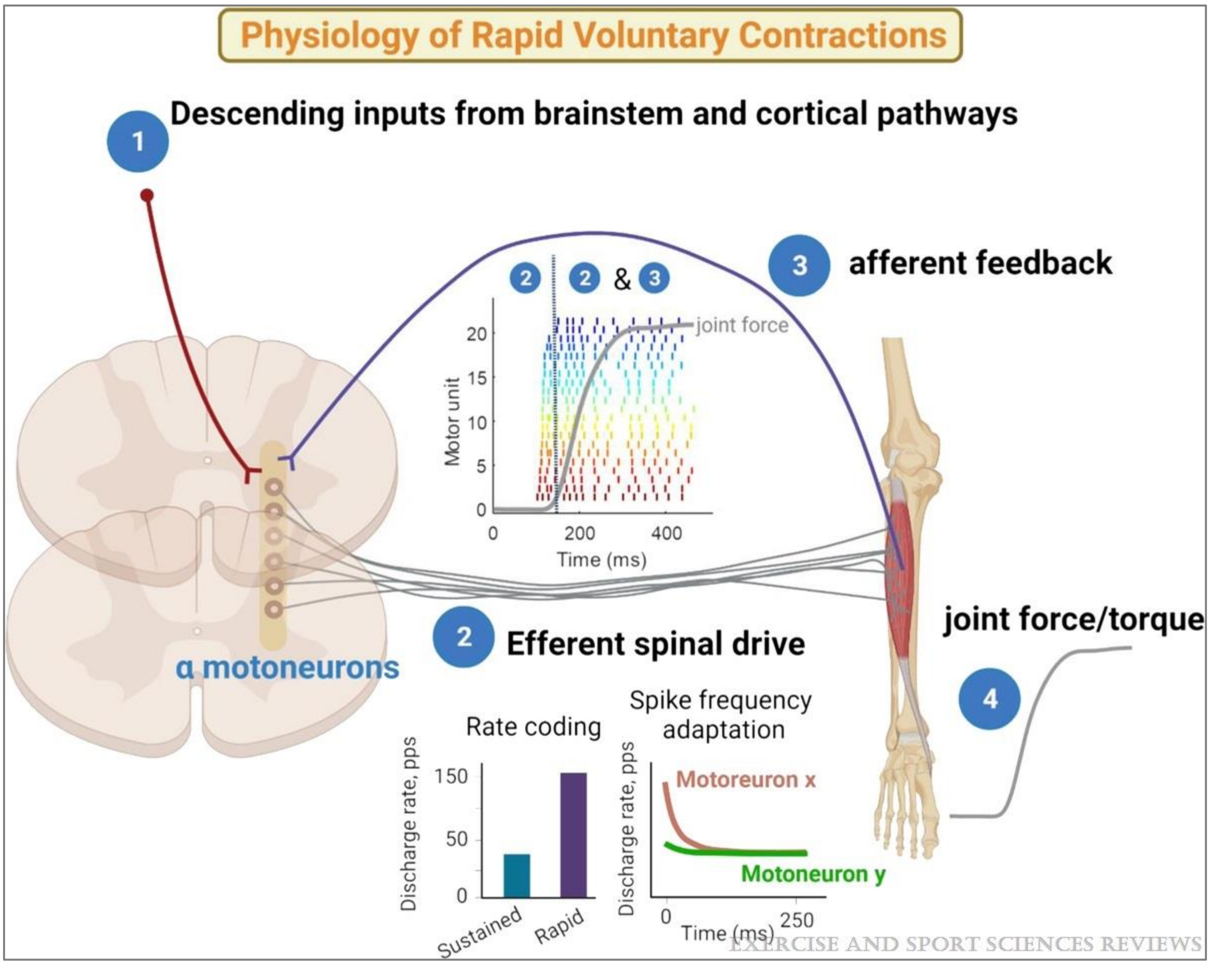

Figure 3. Descending inputs from the cortex and brainstem initiate voluntary movement. The activity of the MUs in the first milliseconds represents the influence of supraspinal inputs on motor neurons (raster plot 2). Bar graph (2) shows that the rate of discharge is significantly higher during rapid contractions than during sustained ones.
The combined activity of efferent and afferent inputs (2,3) determines total joint torque (4), and an individual's RFD can be predicted through the MU recruitment rate. Taken from Del Vecchio (2023).

1.1.2.2 Voluntary and electrically evoked muscle activation and association with RFD

Researchers used the electrical stimulation and voluntary activation of muscles to compare the relative contributors of neural and muscular determinants during explosive contractions. Several approaches have been used through single twitch, doublet, octet, and tetanic contractions. Since the tetanic contraction induced by nerve electrical stimulation appears painful and potentially dangerous (Millet et al., 2011), the use of evoked octets (eight stimuli delivered at 300 Hz) is considered the first choice to evaluate the maximal contractile (involuntary) RFD (de Ruiter et al., 1999, de Ruiter et al., 2004, Folland et al., 2014) since unique method able to activate the whole muscle.

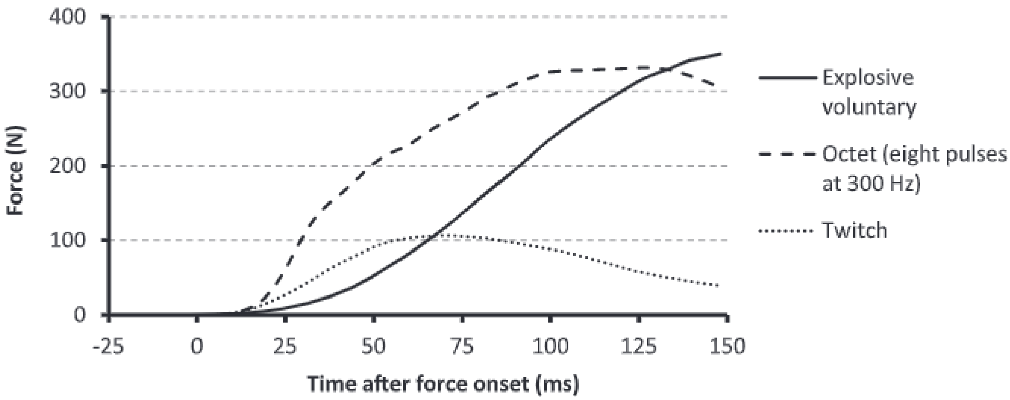

Figure 4. Force track during explosive voluntary, electrically evoked twitch, and octet contractions. Taken from Folland et al. (2014).

Folland et al. (2014) examined the relative contribution of neural and contractile determinants by recording surface EMG activity in the knee extensors (KE) throughout the rising phase of the force–time curve. Through multiple linear regressions, they analysed the contribution of neural determinants of voluntary explosive force attained at different time points. They have demonstrated that the primary determinant of voluntary RFD changed throughout the rising phase of the contraction. The results indicated that agonist EMG activity was an important contributor to the explained variance in force throughout the entire 150 ms of rising muscle force, but more particularly in the early phase from the onset (25–75 ms). Moreover, the evoked RFD evaluated from the octet contraction was the primary determinant of the steeper phase of voluntary RFD (50–100 ms) (Folland et al., 2014). These results are in line with previous works indicating a role for neural factors at the onset (<75 ms) of a rapid contraction (Aagaard et al., 2002, de Ruiter et al., 2004, Klass et al., 2008, Van Cutsem et al., 1998). Indeed, the greater the time elapsed from contraction onset the more muscular factors predominate on neural ones. Agonist muscle excitation, as measured by the EMG amplitude calculated over the first 50 ms from the contraction onset, is strongly correlated ($r \approx 0.7$–0.8) to the RFD in the first 50 ms. Moreover, Del Vecchio et al. (2019), demonstrated that the rates of MUs recruitment and MU firing are the most influential factors associated with the RFD in the first 50 ms of contractions in the tibialis anterior. Instead, for longer contractions (> 75 ms) the voluntary RFD becomes more strongly influenced by the speed-related properties of the muscle and MVF (Andersen and Aagaard, 2006, D'Emanuele et al., 2022, Folland et al., 2014).

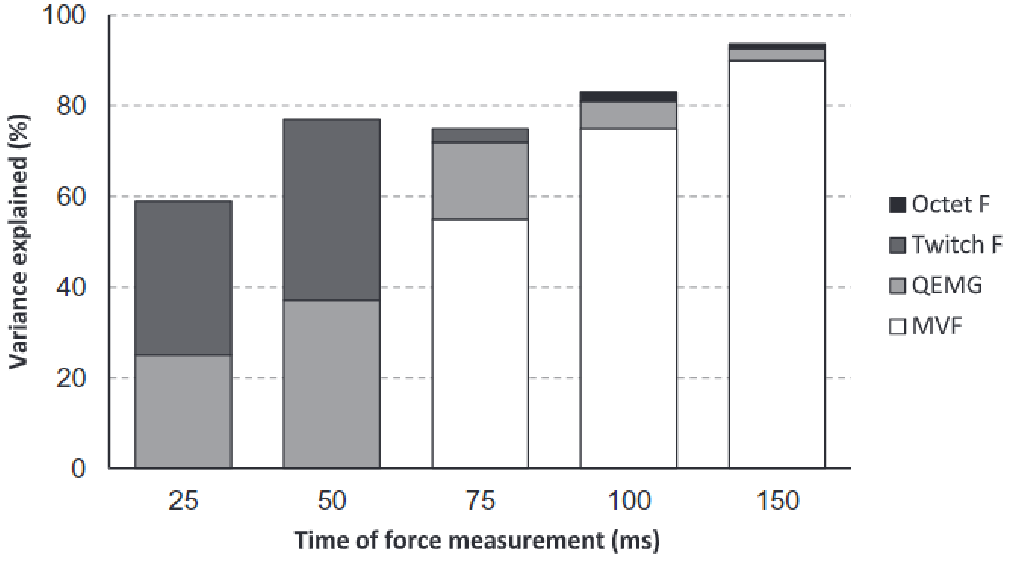

Figure 5. Determinants of the absolute voluntary explosive force of the knee extensors during the first 150 ms of contraction. Legenda: Octet F and Twitch F, evoked twitch/octet force; QEMG, quadriceps EMG assessed from onset to each respective time point; MVF, maximum voluntary force. Taken from Folland et al. (2014).

1.1.3 Muscular and structural determinants

Seeing as how MVF is strongly associated with the late RFD (> 100 ms) from the force onset (Andersen and Aagaard, 2006, D'Emanuele et al., 2022, Folland et al., 2014) many factors that influence muscle strength, such as muscle size, myofiber phenotype and architecture as well as others, might also influence RFD.

1.1.3.1 Fibre type

Fibre type is often considered a major factor influencing muscular RFD. Based on the observation that the rate of tension development is faster in type II than type I fibres, because muscles as well as isolated fibres that contain high proportions of MHC-IIX and/or MHC-IIA are characterized by high intrinsic RFD (Buchthal and Schmalbruch, 1970, Harridge et al., 1996). Although Schilling et al. (2005) reported that the variance in RFD explained by the percentage of MHC-IIX expression was only 2 - 7%, other several studies have reported positive correlations to exist between peak RFD and type IIX fibre area percentage (Viitasalo and Komi, 1978, Viitasalo and Komi, 1981b, Häkkinen et al., 1984, Harridge et al., 1996, Korhonen et al., 2006, Farup et al., 2014) and these observations seem to indicate that may exist between RFD and fibre-type composition. Taylor et al. (1997) reported a moderate, albeit non-significant, correlation (R^2 = 0.34) between VL type II fibre percentage and peak RFD assessed in KE, whilst Hvid et al. (2010) reported a significant correlation (R^2 = 0.49) between

VL type II fibre area and KE in early RFD in young men, but not in older men. Another study conducted by Dalton and colleagues (2022) showed that single fibre RFD was unrelated to joint-level RFD in young, older adults and trended ($p = 0.052-0.055$) towards significant relationships between RFD at joint-level and type I single fibre RFD assessed at 30 ms ($R^2 = 0.48$) and 50 ms ($R^2 = 0.49$) time epochs. They concluded that electrically evoked twitches are good predictors of early voluntary RFD in young, but not in older adults. Only the older adults showed a potential relationship between type I fibre and RFD at the joint level.

As aforementioned, Folland et al. (2014) and Andersen and Aagaard (2006), showed that associations between fibre type and early RFD are consistent with the moderate-to-strong correlations observed between RFD measured during twitch and voluntary, given that twitch contractile properties are strongly influenced by muscle fibre type (Harridge et al., 1996), particularly in the early force rise. Together, these works highlighted the need for further research aimed to elucidate the role of fibre composition on the expression of RFD, especially because a large portion of the variance in voluntary RFD remained unaccounted for, indicating that other factors in the muscle–tendon unit and/or the nervous system must account for much of the variance.

1.1.3.2 Myofiber cross-sectional area, muscle size, geometry, and musculotendinous stiffness

CSA and fibres type are factors that influence RFD expression (Aagaard, 2003, Harridge et al., 1996) and this is demonstrated by several studies that have investigated the relationship between RFD of KE and quadriceps CSA (Izquierdo et al., 1999, Rodriguez-Lopez et al., 2022). About myofiber type CSA, Aagard and colleagues (2007), investigated the mechanical muscle function, morphology, and fibre type in lifelong trained and untrained older people and showed that contractile RFD was elevated in strength-trained compared with untrained subjects, and the strength-trained participants also demonstrated greater type II fibre CSA than did untrained and endurance-trained subjects. Also, the related-age differences in absolute and normalized plantarflexion RFD at early (0-50 ms) and late (100-200 ms) were analysed and showed that the older men were weaker (23.9%, $P < 0.001$) and had lower later absolute and normalized RFD ($P = 0.001-0.034$) variables when compared with the young men. In detail, there were no differences in early RFD, fascicle length and muscle size between groups but lower late RFD values were related to smaller pennation angles demonstrating age-related alterations in architecture, and muscle activation may influence rapid torque production at late time intervals (≥100 ms) from contraction onset (Gerstner et al., 2017). Furthermore, is well-known that a period of resistance training can lead to significant increases in CSA and consequently in RFD in elderly subjects (Suetta et al., 2004, Siddique et al., 2022). In addition, other studies have observed parallel increments in muscle fibre CSA and RFD following 14–21 weeks of resistance training (Andersen et al., 2010, Hakkinen et al., 2003). These works show that when the training is structured to obtain a gain in muscle hypertrophy and consequence CSA increased, then the RFD will be interested in a gain in his expression.

A recent work (Werkhausen et al., 2022) showed that the RFD was not related to optimal fascicle length for any measured time interval (0-50, 50-100, 100-150 ms), but RFD was positively correlated to fascicle shortening velocity during all intervals (R = 0.49-0.69). They also showed that except for early RFD, for the other timing epochs, the RFD was also related to changes in muscle length and pennation angle (calculated as the angle between fascicle orientation and lower aponeurosis orientation, R = 0.45-0.63) but not to architectural gear ratio. However, another work by Kubo (2023) was not found a significant correlation between the maximal fascicle shortening velocity and the RFD at each time point. Appears evident the theoretical importance of fascicle shortening velocity and force-length-velocity properties for rapid force production although the results are conflicting. Lastly, the lack of a relationship between static muscle architecture measurements and RFD indirectly supports the dominant influence of neural factors on rapid force production. This is supported by other evidence that shows that the increase in muscle fascicle shortening velocity reduces the force-generating capacity of the muscle, therefore requiring a greater neural drive to generate the same forces (Aeles et al., 2022).

The time course of force development is affected by the tendon's mechanical properties (Bojsen-Møller et al., 2005). Indeed, a tissue characterised by greater stiffness has a greater force transmission capacity (Maganaris and Paul, 2002, Maganaris et al., 1998) as it can provide greater tensile force per unit of length change. Thus, tendon stiffness affects the time required to stretch the series elastic component and therefore affects RFD (Bojsen-Møller et al., 2005, Driss et al., 2015). A greater stiffness of the tendinous structures would allow a more effective force transmission from the contractile elements to the bone, increasing RFD (Waugh et al., 2013, Waugh et al., 2014). This is supported by Monte and Zignoli (2021) that found that during fixed-end contractions of the gastrocnemius medialis, muscle and tendon stiffness as well as belly gear were positively correlated with the RFD. This suggests that these mechanical parameters can positively affect RFD. However, small reductions in VL tendon stiffness after a period of bed rest were not correlated with the decline in RFD ($R^2 = 0.19$). Kubo et al. (2000), suggest that changes in tendon properties and RFD may be divergent. To this end, as suggested by Maffiuletti et al. (2016), variations in RFD may be partly expected to be influenced by musculotendinous stiffness, however, existing data are inconsistent, and a causative relationship has not been clearly demonstrated.

1.1.4 Methodological considerations for RFD assessment

The RFD has been shown to be more sensitive than MVF to detect chronic changes induced for example by ageing (Thompson et al., 2014, Siddique et al., 2022), immobilization/disuse (de Boer et al., 2007), strength training (Andersen et al., 2014), rehabilitation (Angelozzi et al., 2012, Suzuki et al., 2022), muscle damage (Penailillo et al., 2015), pain (Rice et al., 2019) and for acute adjustments associated to exercise (Buckthorpe et al., 2014, Varesco et al., 2022). However, it is well-known that RFD measures are less reliable than MVF, especially in the early phase of contraction. Therefore, there is a need for a strict methodological approach to maximise reliability and collect worthwhile data (Maffiuletti et al., 2016). As shown in Figure 6, the methodological factors are many and include both testing procedure and setup choice.

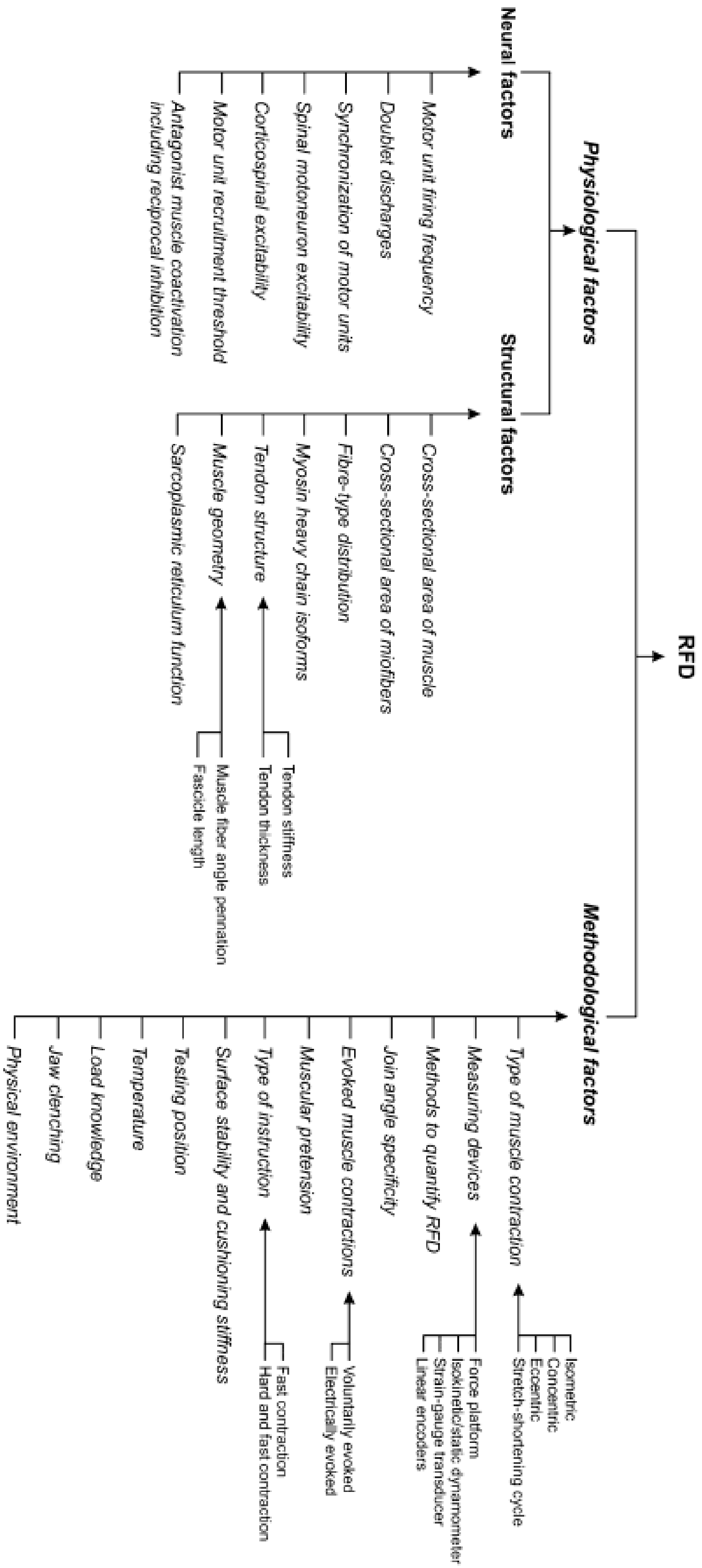

Figure 6. Physiological and methodological factors that contribute to RFD. Taken from Rodríguez-Rosell et al. (2018).

The following chapters aim to discuss these factors to clarify some guidelines that researchers should follow if the purpose of their work is to investigate RFD.

1.1.4.1 Task choice

The task choice depends on the consequences, practical or experimental, that the researchers want to reach. If the purpose is practical, the task should be specific to the practical activity of interest, as RFD is known to be influenced by the muscle group and joint angle at which it is measured (Bellumori et al., 2011, de Ruiter et al., 2004, Tillin et al., 2012, Henderson et al., 2023). Usually, the RFD assessment takes place in isometric conditions, sometimes in dynamic or through jumps, on a single limb in extension/flexion, and in commercial or hand-made setups equipped with dynamometers. In a few cases, multi-joint task (James et al., 2022), mid-tight pull (Haff et al., 2015), and leg press (Stratton et al., 2022) were used to assess the RFD, especially when the aim was to practical consequences. Instead, isolated single-joint tasks typically provide an experimentally controlled situation in which to assess the underlying physiological determinants of RFD, whereas multiple-joint tasks may be more appropriate/relevant for practical outcomes (Maffiuletti et al., 2016).

1.1.4.2 Setup choice and compliance

Many different devices have been used for RFD assessment, such as force plates (Kawamori et al., 2005), isokinetic dynamometers (Qiu et al., 2022, Suzuki et al., 2022), linear position (Chiu et al., 2004, González-Badillo and Marques, 2010) and velocity transducers (Balsalobre-Fernández et al., 2015, Fernandez-Del-Olmo et al., 2014, Hernández-Davó et al., 2015). However, linear or velocity transducers are not recommended inasmuch as these devices do not directly measure the applied force and the force values exhibited are derived from the load mass and the acceleration of the load. Therefore, these devices should not be used as a standalone measure of RFD because these setups do not allow measurement of RFD in the static phase of dynamic contraction (before the displacement begins), where the peak RFD is achieved. Moreover, exist also differences between the RFD values obtained by the force platform and linear position transducer. These differences could be due to the signal processing (i.e., filtering), which likely is different for each different device. Therefore, it is recommended to use force platforms for calculating dynamic RFD values, as these devices allow to directly and instantaneously measure the force applied throughout the range of motion (Rodríguez-Rosell et al., 2018).

System rigidity is another key factor to record high-quality data for RFD assessment. Every dissipation and attenuation of force is undesirable. Since is impossible to avoid biological compliance due to the compression of soft tissue, is fundamental to have a dynamometer with a high level of rigidity. However, commercial ones are usually equipped with soft cushioning to improve the comfort of the tested subject. For these reasons, Maffiuletti et al. (2016) recommend the use of custom-built dynamometers or the customization of commercial dynamometers for minimal compliance. For example, to avoid pain and maintain structural stiffness, a standard hard shin protector could be placed between the thrust surface and the tibia (de Ruiter et al., 2007). Concerning multiple-joint tasks, there are more degrees of freedom and movement available within the musculoskeletal system which makes the assessment more problematic.

1.1.4.3 Muscular pre-tension

Multi-joint tasks are considered ecological but more problematic and some authors suggest starting the explosive contraction from a standardized low level of active pre-tension (Tillin et al., 2013a), even if it may partly affect peak RFD (Van Cutsem and Duchateau, 2005). In this regard, Viitasalo (1982) analysed the force–time curve characteristics during isometric knee extension using different pre-tensioning levels. The contractions were performed from 0%, 20%, 30%, 40%, 50%, 60% and 70% of MVF value. All levels of pretension caused a significant reduction in peak RFD, which was more pronounced as initial pretension increased. Also, Van Cutsem and Duchateau (2005) showed greater peak RFD when the contraction was performed from a resting condition compared to a ballistic contraction from ≈ 25% of MVF pretension level during isometric plantar flexion. In conclusion, appears that RFD assessment should be conducted with no or minimal levels of muscular pretension to obtain a more valid measure.

1.1.4.4 Type of instruction

When the main outcome is the MVF assessment, researchers must encourage the tested subject to produce the higher possible force through verbal instruction. Since the scope is in the possible MVF, the instruction is *"push/pull as hard as possible"*. Sahaly et al. (2001) conducted a study to evaluate the importance of instruction upon MVF and peak RFD. In detail, they compared the effect of two types of instructions: *"hard and fast" vs. "fast"* in elbow flexors and knee extensors in 26 young healthy males. They found that the differences in relative peak RFD (normalized for MVF) between *"hard and fast"* and *"fast"* were significant (F = 52.1; p < 0.001). These results are confirmed also by another work conducted by Sahaly and colleagues (2003) which compared again the two types of instructions by adding the EMG to the agonist muscle. They found that EMG was significantly higher with the instruction *"fast"* at the onset of force development for all the muscles investigated (except the soleus muscle during the bilateral leg exercise) but not at higher force. The steeper force development seems to be explained by the better activation of the agonist muscles at the onset of force development. Accordingly to Bemben et al. (1990), when the main outcome is the peak RFD instruction that concentrates on a fast contraction without concern for achieving MVF should be used. Thus, Maffiuletti et al. (2016) suggest that contractions used to measure MVF force should be separated from those used to measure RFD, and the instruction in both situations should be specific to the objective of that contraction, i.e., as *"hard"* as possible for MVF or as *"fast"* as possible for RFD and suggest also to discard any contractions with low peak forces, e.g., < 70 % (de Ruiter et al., 2004) or < 80 % MVF (Folland et al., 2014).

In conclusion, since MU discharge rate is an RFD key determinant (Del Vecchio, 2023), Škarabot et al. (2022) have shown how using a startling cue (110 dB with visual feedback) can produce a higher number of discharges per motor unit per second and greater RFD after a startling auditory stimulus suggesting a possible subcortical contribution.

1.1.4.5 Acquisition and filtering

A low noise level is fundamental to recording high-quality force signals to measure RFD, especially because will improve the accuracy of the determination of contraction onset. For this purpose, the force signal should be sampled at a high frequency (≥1000 Hz) for several reasons. Firstly, to accurately measure the high RFD that human skeletal muscle can produce (de Ruiter et al., 1999); second, to accurately identify contraction onset especially when the onset is manually identified (Tillin et al., 2013b); and least, to synchronise the force signal with EMG; to accurately assess the electromechanical delay, which can be <7 ms for involuntary and <13 ms for voluntary contractions (Tillin et al., 2010).

After the data acquisition, another key point is filtering. It should be minimal to avoid time shifts caused by the smoothing function, which is particularly problematic if relating contraction onset to the onset of other biological responses, as EMG is used to determine electromechanical delay. So, if filtering is inevitable due to high baseline noise amplitude, then is recommended to use a zero lag, low-pass digital filter (e.g., fourth-order Butterworth) at the highest possible cut-off frequency, to minimise time shifts (Maffiuletti et al., 2016).

1.1.4.6 Reliability

The reliability of RFD assessment is another key factor, especially when the aim is compared, for example, the RFD pre- vs. post-training. In this regard, Juneau et al. (2022) assessed the intersession variability of knee extension kinetics using a strain gauge device and showed that RFD had large variability. Indeed, they concluded that RFD changes across sessions should be approached with caution. Have been suggested, for example, to use backrests and thigh straps (based on the setup) with the main goal to improve RFD variability, and at least one familiarisation session should be provided.

1.1.4.7 Force-onset detection

The force-onset detection is an essential point since it can radically modify the results obtained when RFD is the main outcome. In this regard, different approaches were evaluated, i.e., automatic threshold methods (Thompson et al., 2012) and manual modes (Tillin et al., 2013b). The automatic methods appear reliable and time efficient because the determination of contraction onset as the point at which force increases above a specified threshold is easy to set. In this regard, the threshold level can be set at absolute values (Blazevich et al., 2009, Andersen and Aagaard, 2006) or relative to individual MVF (Granacher et al., 2009). Nevertheless, albeit absolute threshold provides a simple approach they may be unsuitable for comparisons of individuals, cohorts or muscle groups that have differing levels of function. Therefore, relative thresholds would seem to be preferable assuming they are based on a reference measurement with a low noise level. Otherwise, recent studies using a low-noise dynamometer and systematic manual onset detection have found that KE torques of > 5 Nm or 2.5 % MVC are not achieved until > 25 ms after contraction onset (Haider and Folland, 2014, Hannah et al., 2012). This degree of inaccuracy for high-threshold automatic methods may invalidate measurements of RFD during the early phase of the contraction (Tillin et al., 2013b). As it stands, manual/visual approaches are considered the gold standard because this approach provides good validity (Tillin et al., 2013b) albeit the potential influence of subjectivity could compromise its reliability (Staude and Wolf, 1999), and it is less time efficient than automated methods.

1.1.4.8 Analytic methods to quantify and normalize the rate of force development

The peak RFD is the most common variable assessed within the works that provide information about the force quickness in the force-time relationship. However, as shown by different authors (Andersen and Aagaard, 2006, Folland et al., 2014, Del Vecchio et al., 2018), the neural and muscular determinants that imply the differences through the contraction and therefore the choice of different time-locked from the force onset to assess the RFD is extremely important. Different time epochs have been used to assess RFD (i.e. 0–30, 0–50, 0–100, 0–200 and even 0–400 ms), relative to the onset of contraction, whereas peak RFD typically has been quantified as the peak slope of the force–time curve (Aagaard et al., 2002, Bojsen-Møller et al., 2005, Haff et al., 2015, Mirkov et al., 2004, Suetta et al., 2004). Anyway, exist less common methods to assess RFD values like the use of time to achieve a specific force (Häkkinen and Keskinen, 1989, Hannah and Folland, 2015), or the time to increase from one force to another (Mirkov et al., 2004). Regarding dynamic tasks, like *countermovement jump* for example, is possible to assess the RFD during the eccentric phase of the jump (Hori et al., 2009) because is the only phase during the CMJ in which it makes sense to measure RFD, as the applied force during the initial part of the concentric phase tends to plateau or be lower than the force produced during the final part of the eccentric phase. Consequently, the change in force in relation to time (Δforce/ Δtime = RFD) is expected to be very small or even negative in the concentric take-off phase, which may result in very low RFD values.

Despite as discussed above, the peak RFD is the only variable independent from the contraction onset. Actually, in literature, the choice of different time-epochs is not always well justified, despite is well-known that different timings have different main determinants.

The RFD usually is expressed in absolute terms ($N \cdot s^{-1}$) or relative to peak force. However, it is possible also normalized to body mass or muscle CSA, useful to compare individuals or groups of differing body size (Aagaard et al., 2002, Suetta et al., 2004, Waugh et al., 2013) but it is also possible to normalize from the onset of contraction to the level of one-sixth, one-half and two-thirds of maximum isometric force, respectively (Thorlund et al., 2008).

Normalizing the RFD values for the MVF allows measurement of the ability to express the force generation capability available in a ballistic situation. It is possible, although less common, to normalize the RFD values evoked through electrical stimulations such as twitches or, better, octets (8 stimuli at 300 Hz) as able to evoke the maximum RFD during the first phase of contraction (de Ruiter et al., 2004). The voluntary force: octet ratio at 50 ms in the contraction has been termed *"neural efficacy"* (Buckthorpe et al., 2012, Hannah et al., 2012) as it indicates the efficacy of the voluntary neural drive to utilize the full capacity of the muscle for bursts force / RFD.

1.1.4.9 Concluding remarks about the methodological assessment

The present paragraph reports, as have been published by Maffiuletti et al. (2016), the eleven points that should be respected for the measurement of RFD to provide uniformity in the methodological parameters among the various research groups that use RFD as the main outcome.

1. using rigid custom-built dynamometers (or customising commercially available dynamometers) where possible to minimise both compliance and baseline noise.
2. sampling the force signal at more than 1 kHz to maximise accuracy.
3. avoiding (or minimising) signal filtering and smoothing to maintain baseline noise and prevent time shifts.
4. completing a separate familiarisation session.
5. instructing participants to contract *"as fast and hard as possible"* with particular emphasis on a fast increase in force.
6. using short (~1 s) contractions interspersed by short rest periods (e.g., 20 s) to record RFD separately from MVF, where possible.
7. collecting at least five good contractions, from which the average RFD of the three best trials is retained.
8. rejecting trials with an unstable baseline (uncontrolled pre-tension and visible countermovement).
9. detecting the force onset with low-threshold automated or systematic manual methods.
10. quantifying RFD/impulse at multiple time points rather than at a single instant.
11. considering that reliability is consistently lower during the early phase of the contraction.

1.2 RFD-Scaling Factor

Wierzbicka et al. (1991) have shown a positive linear relationship between the peak force of a quick pulse and the corresponding RFD. The slope of this relationship between peak force and RFD can be treated as a dependent measure that in literature is defined as RFD scaling factor (RFD-SF) (Bellumori et al., 2011) and the linearity of this relationship (reflected in R^2 coefficient) reflects the consistency of scaling RFD to peak force (Kozinc et al., 2022).

Bellumori and colleagues (2011) were the first to work on the RFD-SF to identify its utility and methodology. Indeed, suggested that the measurement of RFD-SF is interesting as it can be used to quantify the quick force production across the full continuum of force amplitudes, and the resulting units of this measure make it mathematically independent of strength and therefore size of the muscle group of interest. This is interesting because facilitates comparisons between individuals and between muscle groups concerning the underlying neuromuscular determinants of quickness. At last, also because the RFD-SF reflects neural and muscular factors.

The RFD-peak force relationship was computed from sets of several rapid isometric contractions performed across a full range of amplitudes. For reliable results, it has been suggested that the subject performs approximately 100–125 fast contractions (ICC = 0.8 – 0.92), across different ranges of contraction intensities (20%, 40%, 60% and 80% relative to MVF) while acceptable reliability can be achieved with an even smaller number of pulses (> 50, ICC = 0.7) (Bellumori et al., 2011). This methodology has been shown moderate to high reliability of RFD-SF, both when calculated within the session (Haberland and Uygur, 2017, Bellumori et al., 2011) and between days (Bellumori et al., 2011, Maffiuletti et al., 2016).

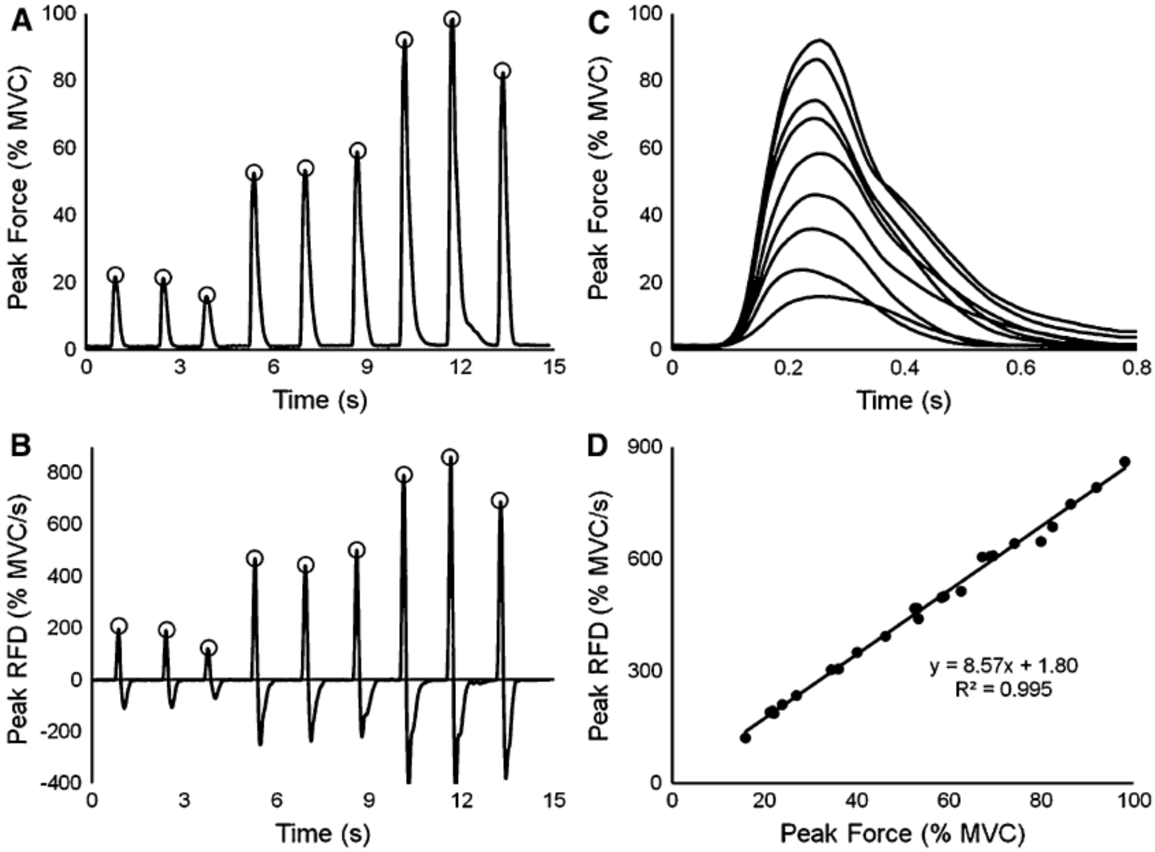

Figure 7. A) example of a recording of quick pulses to a variety level of intensities; B) Corresponding RFD computed using the finite difference method and overlapping .1-s intervals of the force recording. C) Overlapping explosive force contractions from one subject; D) Peak Force-RFD plot with data points taken from the peaks of each contraction. Taken from Bellumori et al. (2011).

The RFD-SF protocol has been used to assess different aspects such as limb symmetries (Boccia et al., 2018a, Smajla et al., 2021a), different dynamic task as drop jump (Sarabon et al., 2020), different populations as patients with knee osteoarthritis with adapted protocols (Šarabon et al., 2020).

From the first publication about the RFD-SF (Bellumori et al., 2011), some small advancements in protocols and methodological aspects were published (Djordjevic and Uygur, 2017, Šarabon et al., 2020, Smajla et al., 2021b, Kozinc et al., 2022). Participants are usually asked to perform quick isometric contractions, usually 100 - 125, at different target intensities varying from 20 to 80% of the value assessed during sustained maximal voluntary contractions. As for the RFD assessment, RFD-SF quickness and some practice trials are mandatory. Indeed, the subjects must be instructed to perform every contraction emphasising quickness and not accuracy (Casartelli et al., 2014, Djordjevic and Uygur, 2017, Uygur et al., 2020) and this requires takes some time to familiarise with the task. In this regard, some studies have used a target line as visual feedback for each level assessed (Bellumori et al., 2011, Bellumori et al., 2013, Brustio et al., 2019, Smajla et al., 2021a). Moreover, the reliability of the calculated RFD-SF of the tested different muscle groups was moderate to good (Djordjevic and Uygur, 2017) though Casartelli et al. (2014) concluded that if hip adductor, flexor, and external rotator RFD-SF can be evaluated with confidence, provided the analysis is modified for external rotators, for the hip abductor and internal rotator RFD-SF assessment is not recommended.

Because previous studies have reported that the RFD-SF protocol induces negligible fatigue (Mathern et al., 2019, Uygur et al., 2020) thus, short resting periods are likely sufficient to avoid fatigue. In this regard, is suggested that the contractions to each intensity are performed in blocks in a balanced order (e.g., four blocks of 20 pulses, with each block containing five contractions for each intensity) (Bellumori et al., 2011). However, Smajla et al. (2021b) investigated the possibility of using a protocol with a reduced number of contractions. They tried to compare the "classic" protocol with 100-120 burst-like contractions with a reduced protocol with 36 contractions organized in a block of nine for each of four levels (20, 40, 60, 80% of MVF). They found excellent reliability of the reduced RFD-SF protocol and can be used as a practical and useful tool for neuromuscular testing both for healthy subjects and participants with various impairments. However, albeit the excellent reliability with 36 pulses, the authors recommend performing ≈ 60 pulses to ensure that there are enough pulses available for the calculation.

1.2.1 Concluding remarks about the methodological assessment

Since RFD-SF is calculated from the relationship between peak force and corresponding RFD, all the methodological concerns inherent to RFD measurement directly affect RFD-SF assessment (Djordjevic and Uygur, 2017). Indeed, as done by Maffiuletti and colleagues (2016) for RFD (see 1.1.4.9 Concluding remarks about the methodological assessment) seems appropriate to report the recommendations presented by Kozinc et al. (2022) for the evaluation of the RFD-SF:

- Participant and device setup - Use rigid isometric dynamometers, to ensure the best possible fixation. Participants need to receive real-time visual feedback (force signal).
- Choice of contraction levels - Optimally, use 20, 40, 60 and 80% of MVF. Record MVF in advance if possible. The number of levels may be reduced or MVF estimated, without seriously compromising the validity of the measurements.

- Instruction to the participant - Instruct the participants to perform explosive contractions, aiming for a given target, and relax immediately after the target is reached. Quickness should be emphasized over accuracy. A short break (1–2 s) should be included between successive contractions.
- Familiarization - At each intensity, allow the participants to perform 5–10 familiarization trials to get accustomed to each force target level.
- Number of pulses and breaks - Aim for 20–25 contractions per level (80–100 in total). In case of pain or other limitations, ~ 10 contractions are sufficient for reliable assessment of knee extensors. Provide sufficient breaks (60–120 s) between blocks with different target levels.
- Data acquisition and filtering - Aim for sampling frequency at 1000 Hz if possible. It is recommended to filter the data with a fourth-order zero-lag 50 Hz low-pass filter.
- Individual contraction data - It is recommended that peak force and peak RFD are taken from each contraction.
- RFD-SF calculation - Use peak force (x-axis) and peak RFD (y-axis) data in linear regression. The slope of the trend line represents the RFD-SF. Consider the R^2 coefficient and y-intercept in addition to RFD-SF. For statistical analyses, R^2 should be transformed with Fisher's Z-transformation.

1.3 Fatigue

RFD represents a valid alternative/complement to the classical evaluation of pure maximal strength in unfatigued conditions (Maffiuletti et al., 2016) but it has also been used to investigate the effects of fatiguing tasks (Dunn et al., 2022, Varesco et al., 2022). For these reasons, seems appropriate to introduce the basic concepts that underlie what is commonly identified in the literature as *fatigue*.

1.3.1 Defining Fatigue

The topic of fatigue, in every facet, has intrigued physiologists since the late 1800s. From a historical point of view, the first physiologist to publish a treatise on this topic was Angelo Mosso who in 1891 published his work entitled *"La Fatica"*. In his book, he tried to compare voluntary performance with that reproduced by external electrical stimulation of the muscles. Mosso demonstrated that the reduction in force-generating capacity was not solely a product of muscular failure, but that it could be also negatively affected by intense cognitive tasks. Indeed, suggested that fatigue entails two phenomena: *"The first is the diminution of the muscular force. The second is fatigue as a sensation. That is to say, we have a physical fact which can be measured and compared, and a psychic fact which eludes measurement"* (Marino et al., 2011).

However, after over one century, the taxonomy that defined the concept of fatigue is always under discussion. One of the most used definitions was proposed by Bigland-Ritchie and Woods (1984) that defined fatigue as *"any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained"*. In 1990 a roundtable of physicians understood the importance of the concept of fatigue also at a clinical level in the respiratory muscles and proposed a new definition of muscle fatigue as *"a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load and which is reversible by rest"* (NHLBI, 1990).

The fatigue phenomenon involved also psychological symptoms not necessarily related to the performance of pathological or physiological symptoms. For these reasons only recently the role of sensations and perceptions on fatigue received considerable attention (St Clair Gibson et al., 2018, St Clair Gibson et al., 2003).

Enoka and Duchateau (2016) proposed a new taxonomy (Figure 8) to include the new findings about the concept of fatigue. For this purpose, they suggest dividing the concept of fatigue as a continuum composed of *performance fatigability*, described as the decline in an objective measure of performance over a discrete period, and *perceived fatigability*, namely the changes in the sensations that regulate the integrity of the performer. *Fatigue* is defined in terms of fatigability to normalize the level of fatigue reported by an individual relative to the demands of the task that produces it (Enoka and Duchateau, 2016). They suggest that *performance fatigability* is affected by the contractile function of the muscles involved, as well as the level of activation of the muscles by the central nervous system, terms that have previously been classified as *peripheral* and *central fatigue*, respectively (Gandevia, 2001). Anyway, to demonstrate the continuum between *perceived* and *performance fatigability*, the authors proposed an example that explains that the capacity of the central nervous system (CNS) to voluntarily activate the muscle can be modulated by blood glucose (Nybo, 2003), core temperature (Nybo et al., 2014) and arousal (Klass et al., 2012), all of which contribute to perceived fatigability, but have physiological consequences and affect performance fatigability as well (Enoka and Duchateau, 2016).

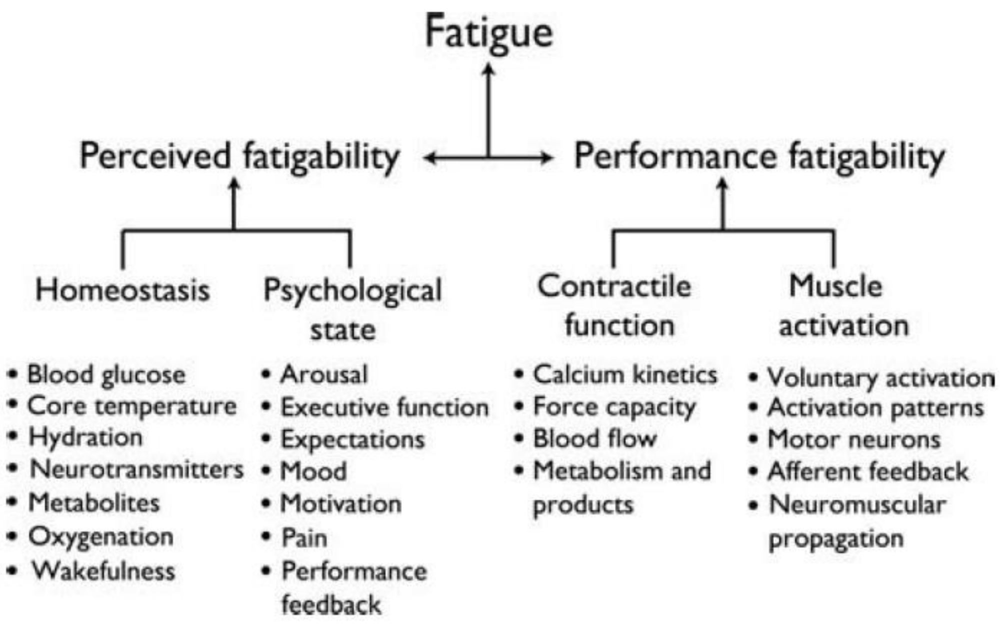

Figure 8. Taxonomy proposed by Enoka and Duchateau (2016)

Since fatigue is a general concept intended to denote an acute impairment of performance that include multifactorial and aetiology, some authors (Enoka and Stuart, 1992) do not consider it appropriate to accompany the term fatigue with an adjective (i.e., central, peripheral, muscular). However, in scientific literature, the distinction, especially, between central and peripheral fatigue is very common. For this reason, in this dissertation, we will use the definitions proposed by Gandevia (2001) to clearly distinguish the phenomena of fatigue at a central and/or peripheral level.

1.3.2 Mechanism of exercise-induced neuromuscular fatigue

Neuromuscular fatigue can be defined as *"a reduction in the force-generating capacity of a muscle or muscle group"* (Bigland-Ritchie et al., 1986a; Gandevia, 2001). Many factors are known to influence the development of neuromuscular fatigue. Being task-dependent (Enoka and Stuart, 1992) the exercise modality (e.g., sustained or intermittent) (Bilodeau, 2006), intensity and duration (Behm et al., 1996, Place et al., 2009) are key factors but also the fibre type of the tested muscle (Harridge et al., 1996) and age (Cesanelli et al., 2022) and sex of the participants (Hunter, 2009, Sundberg et al., 2017) are factors that need to be considered.

The expression of voluntary force is like a chain of sequential events happening in the motor pathway (see Figure 9) (Gandevia, 2001). Firstly, the movement is planned upstream from the motor cortex. After that, the descending neural drive is transmitted from the motor cortex to the spinal motor neurons and leads to the recruitment of the motor units needed to accomplish the task. Here the action potentials go through the motor axons, to reach the neuromuscular junction, where they are transmitted to the muscle fibres. In the end, the propagation along the muscle membrane and the consequent Ca^{2+} ions released from the sarcoplasmic reticulum leads to the cross-bridge formation in the actomyosin complex and the production of muscle force. An impairment of neuromuscular function may result from failure at any step of this chain. If the failure is close to the neuromuscular junction, we can consider that as *central fatigue*, while if the failure happens at or distal to the neuromuscular junction, we can consider it as *peripheral fatigue* (Gandevia, 2001)

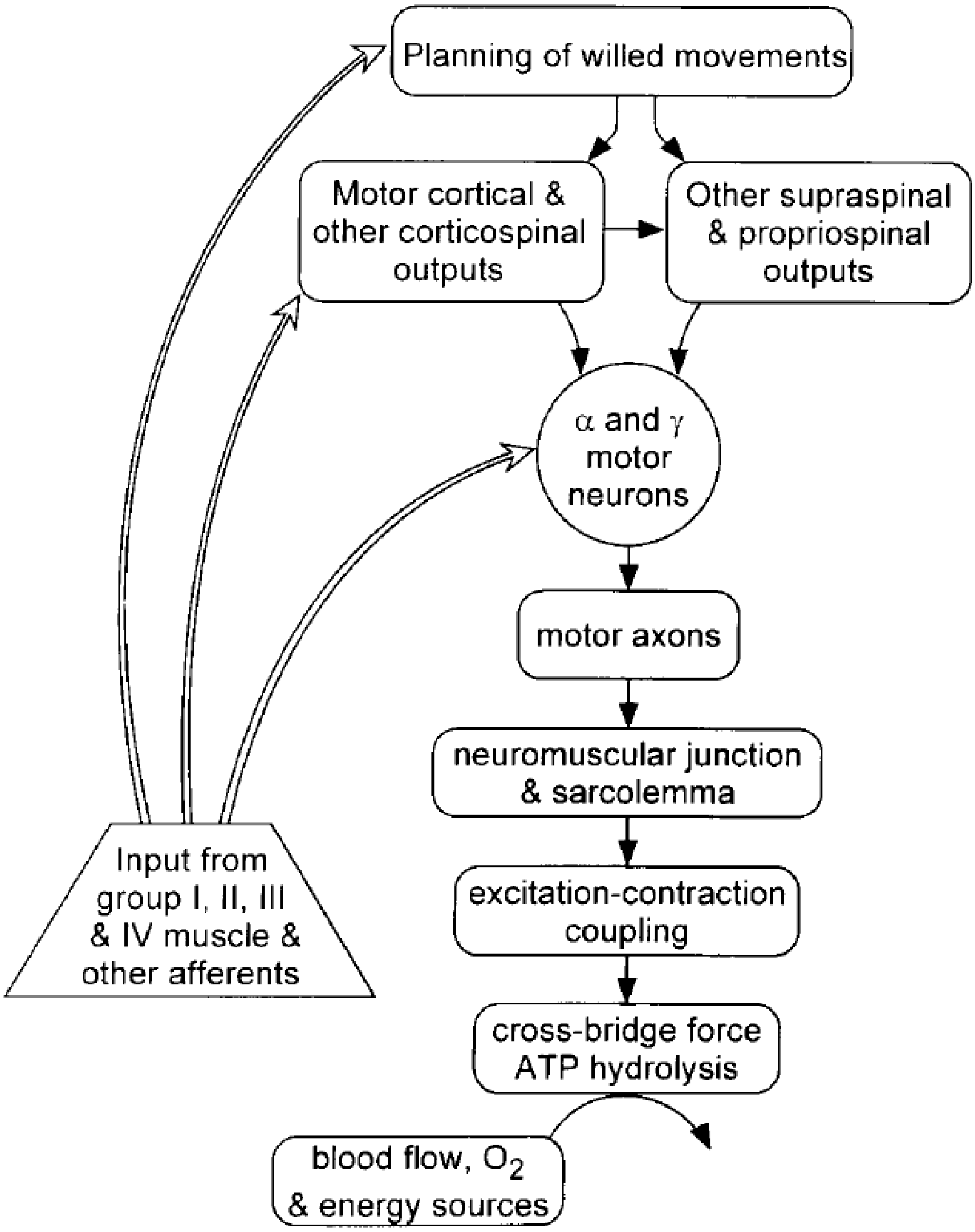

Figure 9. Process chain involved in voluntary force production. Taken from Gandevia (2001).

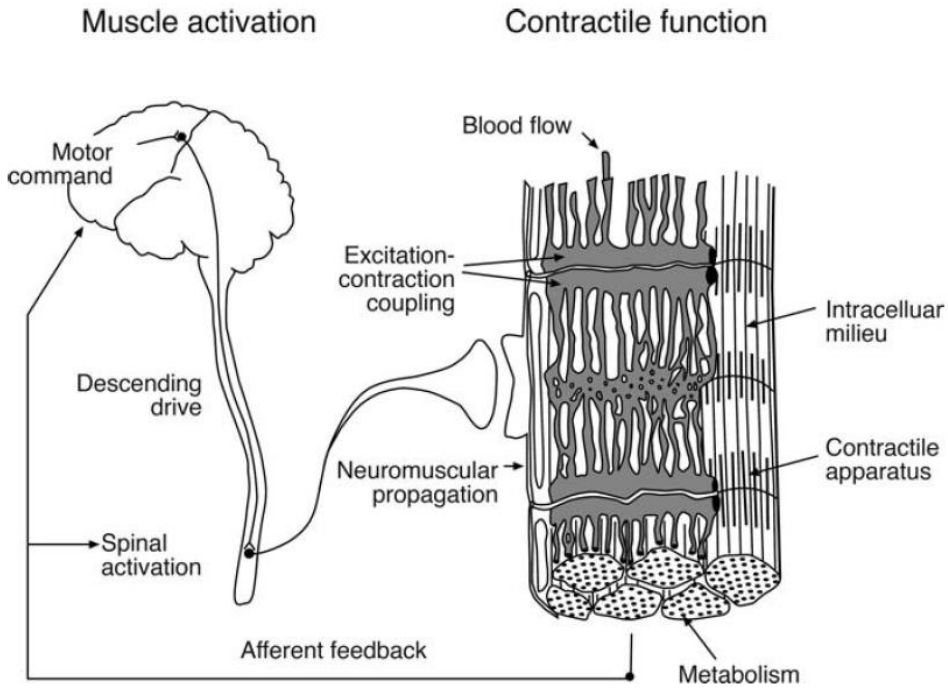

Figure 10. The chain of processes that can contribute to fatigue is categorized into two domains: those that establish the level of muscle activation and those that influence contractile function, respectively central and peripheral. Taken from Enoka and Duchateau (2016).

1.3.2.1 Peripheral Fatigue

Peripheral fatigue (PF) is commonly defined as *"fatigue produced by changes at or distal to the neuromuscular junction"*. Usually, the presence of PF can be demonstrated by a fall in the twitch or tetanic force produced by peripheral nerve stimulation (Merton, 1954) while the muscle is at rest and can be caused by alterations in any process distal to the neuromuscular junction (Fitts, 2008). Albeit a lot of studies are "*in-vitro-based*", PF is generally investigated *in vivo*. To assess the presence of PF the researchers used different techniques that include single, doublet or train of electrically evoked stimuli of the nerve investigated (Behm et al., 1996, Millet et al., 2011). Stimulation of the motor nerve can be performed in multiple ways; a single stimulus evokes an electromyographical response termed the M-wave, as well as a mechanical response or twitch. The M-wave is commonly considered to reflect the propagation of the action potential across the sarcolemma (Bigland-Ritchie and Woods, 1984, Place et al., 2010), a key step in the excitation and recruitment of MUs. However, is necessary to use a supramaximal intensity because, with the development of neuromuscular fatigue, the threshold for axonal excitation may increase (Kernell and Monster, 1982). Indeed, the assessment of PF is usually performed with a supramaximal intensity (usually 120% of the intensity that evokes an M-Wave plateau) compared to the one needed to evoke a maximal response in twitch force and M-wave. Indeed, is important to consider the phenomenon of potentiation because when assessing the force response to evoked electrical stimulation, is mandatory to consider that this response is influenced by fatigue and potentiation (Kufel et al., 2002, Rassier and Macintosh, 2000). The potentiation phenomenon occurs due to previous activation of the muscle, which phosphorylation or the myosin light chain and increases Ca^{2+} sensitivity of the actomyosin complex (Vandenboom and Houston, 1996, Blazevich and Babault, 2019). For this reason, is recommended to perform 2/3 MVCs to achieve full potentiation (Kufel et al., 2002). However, the simultaneous presence of muscle potentiation and fatigue can sometimes make interpretation difficult (Taylor and Gandevia, 2008). While CF is more evident through a low level of contraction, the presence of PF appears when the requested task/level of force is intense (Taylor and Gandevia, 2008). This observation may be related to muscle perfusion and restriction of blood flow happening during muscle contractions due to the higher pressure exerted by the muscle on the vasculature (Barcroft and Millen, 1939). This explanation may be justifying also the difference between males and females in the task that require high level of contraction. Usually, female subjects are slower to reach the time to exhaustion or time to fatigue, probably due to this greater force of muscle contraction which in men causes greater vasoconstriction (Hunter, 2018).

In conclusion, a reduction in the intrinsic muscle force production with fatigue may be the result of two phenomena: a failure in the neuromuscular transmission of the action potentials at the level of the sarcolemma or the impairment of the contractile processes downstream from it (Place et al., 2010). The M-Wave response (i.e., decrease in M-Wave amplitude) is used to assess the sarcolemma excitability. However, a change in sarcolemma excitability seems not to be mandatory to highlight fatigue because some studies have shown an unchanged M-Wave response after the fatiguing task (Place et al., 2010) although some authors (Rodriguez-Falces and Place, 2018) have described that the M-Wave behaviour is related to the exercise modality and intensity of the task. After all, the force production can be impaired in three ways: 1) a decrease in the myofibrillar force-generating capacity, 2) an impaired myofibrillar Ca^{2+} sensitivity, 3) and an impaired Ca^{2+} release from the sarcoplasmic reticulum (Allen et al., 2008, Westerblad et al., 1991). Considering that the progressive accumulation of metabolites and glycogen depletion may cause excitation-contraction coupling failure and inhibition of the contractile machinery by any of the three abovementioned mechanisms (Allen et al., 2008).

1.3.2.2 Central Fatigue

Central Fatigue (CF) can be defined as *"a progressive reduction in voluntary activation of muscle during exercise"* (Gandevia, 2001). The common method used to assess the CF was conceived by Merton (1954) and consists in evaluating the voluntary activation (VA) through the *interpolated twitch technique* (ITT) during a maximal voluntary contraction. In brief, this supramaximal electrical or magnetic stimulation will activate any MU which is not recruited or firing fast enough, resulting in an extra twitch (called superimposed twitch, SIT) in the force output. When this SIT is apparent, voluntary activation of the muscle is less than 100%, demonstrating a central deficit in the ability of producing force. To quantify VA, the SIT is normalised to the response to the same stimulus delivered in the potentiated, relaxed muscle (potentiated twitch, $Q_{tw,pot}$) using the formula shown in the equation below:

$$VA = 100 \cdot (1 - \frac{SIT}{Q_{tw,pot}})$$

Exercise-induced changes in VA represent evidence of CF (Gandevia, 2001), implying further decrements in the ability of the CNS to recruit and maximally fire the available motor units. However, albeit ITT has some pitfalls, and it has been often the subject of scrutiny (de Haan et al., 2009, Dotan et al., 2021), it is generally accepted as the most useful tool for assessing VA (Taylor, 2009).

1.3.3 Methods to assess and induced fatigue through different types of contraction

Different exercise modalities can induce different responses in terms of fatigue. We can categorize the effects on PF and CF within three different domains: modality, duration, and intensity (Carroll et al., 2017), see Table 1.

Peripheral Fatigue	**Central Fatigue**
Exercise Modality	
Sustained MVC	**Sustained MVC**
metabolite accumulation (e.g., K^+) fast recovery with re-perfusion (<30 s)	↓ VA due to group III/IV firing fast recovery with reperfusion (<90 s)
Intermittent Shortening/Isometric	**Intermittent Shortening/Isometric**
less blood occlusion and K^+ build-up slower recovery due to Ca^{2+} effects (min to h)	↓ VA and recovery time course depends on exercise duration can vary from 1 to 30+ min
Lengthening	**Lengthening**
damages muscle fibres slow recovery (days to weeks)	muscle damage leads to ↓ VA slow recovery (days)
Exercise duration	
Short Duration (<2–3 min)	**Short Duration (<2–3 min)**
metabolite accumulation crucial (e.g., K^+) fast recovery with re-perfusion (<30 s)	short-lasting ↓ VA (<90 s) ↓ motoneuron responsiveness (min)
Long Duration (>6 min)	**Long Duration (>6 min)**
recovery depends on the number of high episodes (intensity and duration) effects can last min to h glycogen depletion possible (h)	recovery appears closely related to duration (mechanisms unknown) and can vary from 1 to 30+ min
Exercise Intensity	
High (near MVC/sprints)	**High (near MVC/sprints)**
all muscle fibres recruited metabolite accumulation crucial (e.g., K^+) fast recovery with re-perfusion (<30 s)	↓ VA due to group III/IV firing fast recovery with reperfusion (<90 s) responsiveness of all motoneurons reduced
Low (low forces/endurance exercise)	**Low (low forces/endurance exercise)**
low threshold, fatigue-resistant units recovery depends on the duration	↓ VA occurs if the duration long recovery can vary from 1 to 30+ min low threshold motoneuron excitability ↓ (min)

Table 1. Summary of central and peripheral fatigue responses to exercise and recovery, categorized by modality, duration, and intensity of exercise. VA, voluntary activation. Modified from (Carroll et al., 2017).

A reduction in the maximal force assessed during an isometric MVC provides the most straightforward demonstration of fatigue (Carroll et al., 2017). Accordingly, tasks involving a sustained MVC provide a convenient model to study fatigue for several reasons. Indeed, MVC test the entire motor pathway and the fatigue phenomenon develops within seconds. Then, CP can only be measured during maximal efforts as the superimposed twitch then represents a failure to drive the muscle maximally. Moreover, the task for the nervous system is maximal throughout the exercise. Lastly, all the motoneurons are undergoing similar processes. That is, all should be recruited and fired at high rates from the start (Taylor and Gandevia, 2008).

Although measures obtained during MVC provide valid and easily interpreted information about the neuromuscular function, such measures may not be ideally sensitive to some physiological changes that are important for exercise performance (Carroll et al., 2017). For example, the ability to develop force rapidly, through explosive contractions, is considered functionally more important than MVC during explosive movements, such as sprinting (Stone et al., 2004, Tomazin et al., 2012, Connolly et al., 2022), jumping (McLellan et al., 2011) or restabilizing the postural balance following a loss of balance (Porto et al., 2022, Kamo et al., 2019). Indeed, several studies adopted explosive contractions to induce fatigue and study the underlying mechanisms (Viitasalo and Komi, 1981b, Buckthorpe et al., 2014, Hannah et al., 2012). In detail, Viitasalo and Komi (1981b) showed that one-hundred explosive contractions (lasted 2.5 s) induced –24% of MVF and –36% of RFD. Hannah et al. (2012) investigated the difference between males and females in terms of explosive neuromuscular performance through ten explosive contractions (lasted ≈1s) showing that males are stronger (MVF) and explosive (RFD) than females, but these differences disappear when the data were normalized. Buckthorpe et al. (2014) through ten sets of five explosive MVCs (each lasting 3 s) and separated by 2 s of rest, showed that the MVF and RFD were substantially reduced, respectively –42% and –47–56%. Moreover, absolute RFD declined by 39–56%, with reductions in normalized peak RFD (–26%) and $RFD_{0–50}$ (–29%) but not in other time windows. Therefore, explosive force declined more rapidly and in a more pronounced manner than MVF. The authors suggest that both neural and contractile fatigue mechanisms appeared to contribute to the decline in absolute explosive force (especially the early RFD) and MVF. Then, the –34% in neural efficacy (assessed through the ratio between voluntary and electrically evoked octets) has been interpreted as a sign that repeated explosive contractions caused central fatigue. However, those protocols adopted a series of short muscle contractions constituted by a first phase of explosiveness phases followed by a holding phase of 1 to 3 s (Viitasalo and Komi, 1981b, Buckthorpe et al., 2014, Hannah et al., 2012). This must take into account because the main cause of fatigue could be the holding phase that follows the explosive phase during an explosive contraction. So, those valuables works are not able to explain the peculiar way the rapidity/explosiveness induces fatigue because neuromuscular mechanisms underlying explosive and plateau phases of contraction are critically different. Therefore, the literature is lacking in explaining the fatiguing effect of the contraction explosiveness per se beyond the influence of any holding phase.

1.4 Asymmetries

Maloney in his critical review about the relationship between asymmetry and athletic performance introduces the concept of symmetry as follows: *"Symmetry may be defined as the quality of an object to demonstrate an exact correspondence of size, shape, and form across its 2 halves when split along a given axis. In the human body, we typically consider mirror symmetry along the coronal axis, which partitions the body into left and right halves. Thus, deviation from mirror symmetry across the coronal axis is termed bilateral asymmetry"* (Maloney, 2019).

Three kinds of asymmetry were outlined by Van Valen (1962) to highlight the deviations of an organism or part of an organism from perfect symmetry.

1. *Directional asymmetries* - occurs whenever there is normally a greater development of a character on one side of the plane or planes of symmetry than on the other.
2. *Antisymmetry* - describes a characteristic that typically developed toward a certain side, however, the side to which this occurs is variable (i.e., handedness or limb preference).
3. *Fluctuating asymmetry* - results from the inability of organisms to develop in precisely determined paths (i.e., nostril width or ear size).

As noted by Van Valen (1962) any two or all three of these types of asymmetry can occur together in the same character. To this end, Maloney (2019) highlighted that if seeking to explore potential relationships between asymmetries and performance, it is important to consider the type of asymmetry that has been determined.

Indeed, motor task and asymmetry have a relationship highlighted by Guiard (1987) and in line with the proposed, Maloney (2019) divided motor tasks into four groups: 1) unilateral (i.e., long jump take off), 2) bilateral asymmetric (i.e., golf swing), 3) out-of-phase bilateral symmetric (i.e., cycling), and 4) in-phase bilateral symmetric (i.e., weightlifting). This codification is essential to understanding some asymmetries sport specific. For example, group 1 sports require a high volume of unilateral tasks (i.e., lunges for fencing) and this may be produced asymmetric adaptation. For this reason, Maloney (2019) proposed to add *sporting asymmetry* as the fourth type of asymmetry in addition to those proposed by Van Valen (1962) since the magnitude of *sporting asymmetry* developed by an athlete is likely to depend on the type of sport.

The investigation of inter-limb asymmetries has increased in recent years typically exploring the impact on athletic performance (Bishop et al., 2018, Maloney, 2019), screening inter-limb asymmetry with injury risk (Pavlović et al., 2022, Cossich et al., 2022), and monitoring of inter-limb asymmetry during injury rehabilitation (Read et al., 2020) but also between different populations such as males vs. females (Bailey et al., 2015, San Jose et al., 2022), professional vs academy players (Bishop et al., 2021a, Beato et al., 2021) and age groups (Read et al., 2018).

A bilateral muscle strength asymmetry has been reported in numerous studies and a relative strength difference greater than 10 - 15% between limbs has been adopted as a criterion of inter-limb asymmetry (Kannus, 1994, Impellizzeri et al., 2007, Jones and Bampouras, 2010). However, if some studies have found differences regarding the asymmetries of the lower limb (Fousekis et al., 2010, Lehance et al., 2009) others have not found significant differences (Zakas, 2006, Ruas et al., 2015). These differences could be explained by the fact that many different tasks and formulas are used in the literature for the evaluation of asymmetries. For example, if an athlete may state that their right limb is their dominant, but if scores are inserted into an equation using the stronger and weaker classification, a different score may be reported if the stronger limb is not the dominant limb. Consequently, the reference value/method used has a profound effect on the asymmetry result (Bishop et al., 2016). Sure enough, many tests have been used for these types of assessments such as *countermovement jump* (Bell et al., 2014, Buoite Stella et al., 2022), *single-leg countermovement jump* (Chapelle et al., 2022b, Chapelle et al., 2022a), *single-leg hops* (Mesfar et al., 2022, Moreno-Azze et al., 2021) and laboratory-based test as isometric multi-joint (Bailey et al., 2015), single joint (Boccia et al., 2018a) and isokinetic assessment (Menzel et al., 2013).

Moreover, the wide variety of equations proposed by researchers over the years may be influenced the level of asymmetry. Table 2 is reported an example of an asymmetry score, using hypothetical jump height scores of 25 and 20 cm, calculated through different equations proposed by different researchers.

Asymmetry Name	Equation	Asymmetry score (%)	Reference
Limb symmetry index 1 (LSI-1)	(NDL / DL) *100	80	(Ceroni et al., 2012)
Limb symmetry index 2 (LSI-2)	(1 – NDL / DL) * 100	20	(Schiltz et al., 2009)
Limb symmetry index 3 (LSI-3)	(Right - left)/0.5 (right + left) * 100	22.2	(Marshall et al., 2015a, Bell et al., 2014)
Bilateral strength asymmetry (BSA)	(Stronger limb - weaker limb)/stronger limb * 100	20	(Nunn and Mayhew, 1988, Impellizzeri et al., 2007)
Bilateral asymmetry index 1 (BAI-1)	(DL - NDL) / (DL + NDL) * 100	11.1	(Kobayashi et al., 2013)
Bilateral asymmetry index 2 (BAI-2)	{2 * (DL - NDL) / (DL + NDL)} * 100	22.2	(Wong et al., 2007, Sugiyama et al., 2014)
Asymmetry index (AI)	(DL - NDL) / (DL + NDL/2) * 100	22.2	(Robinson et al., 1987, Bini and Hume, 2014)
Symmetry index (SI)	(High - low) / Total * 100	11.1	(Shorter et al., 2008, Sato and Heise, 2012)
Symmetry angle (SA)	(45° - arctan (left / right)) /90° * 100	7.04	(Zifchock et al., 2008)

Table 2. Different equations for calculating asymmetries (using hypothetical jump height scores of 25 and 20 cm). DL = dominant limb; NDL = nondominant limb. Reprinted from Bishop et al. (2016).

The choice of the most appropriate equation has been extensively discussed by Bishop et al. (2016). They grouped the equations that produced the same score and then discussed the details. For example, LSI-1 is considered a measure of symmetry rather than asymmetry. LSI-2 focuses on asymmetry levels for a given test. BSA was used as a method for calculating asymmetries through a bilateral CMJ but with some limitations that must be considered. Indeed, there is the possibility that the stronger limb could become weaker at a later testing date, yet the criteria used in this equation do not consider this. To avoid any problems, the stronger and weaker limb must be identified during the assessment. The authors suggested that LSI-3 could be removed among the various options available as Bell et al. (2014) have defined the asymmetry between left and right but as mentioned above, many sports are asymmetric by nature. Consequently, the authors suggested, that would seem plausible to use either the BAI-2 or the AI should these equations be accepted for asymmetry detection.

SI, compared with BAI-1, only calculates asymmetries via the highest and lowest scores. This is again a problem as these values could change depending on factors such as injury history and training exposure. For this reason, the authors suggested that BAI-1 should be preferred as a method over SI. However, any comparison between the BAI-1 and any previously suggested methods requires further research.

The last equation proposed by Zifchock et al. (2008) is based on a deviation from a hypothetical 45° angle, considered optimal. An optimal angle of 45° is created when two values are plotted against each other forming a vector in relation to the x-axis. This occurs when hypothetically two points have identical values. Zifchock's rationale for the symmetry angle was that all other methods require a "reference value" (i.e., the value of the strongest limb) arbitrarily selected. The result obtained with the SA equation can then be multiplied by 100 converting it to a percentage, thus is possible to compare with all other equations.

To conclude is undeniable that the choice of task and equation are two mandatory points which must be carefully chosen and analysed based on the objective.

1.4.1 RFD & Asymmetries

As detailed in the chapter "1.1 Rate of Force Development", the RFD reflects the ability to rapidly produce force from the onset of a voluntary contraction (Maffiuletti et al., 2016) and this parameter has been adopted to assess rapid strength deficits after anterior cruciate reconstruction (San Jose et al., 2022) in both injured (Knezevic et al., 2014) and contralateral limb (Mirkov et al., 2017) and also has been proposed to be an adjunctive outcome measure for return-to-sport decisions (Angelozzi et al., 2012).

Moreover, some studies have analysed the peak RFD of contractions over 80% MVF although not all motor tasks have such a high quickness requirement. Indeed, in some tasks/situations that require precision such as passing, dribbling, and scoring, soccer players must be trying to produce submaximal torque as quickly as possible (Thorlund et al., 2009). For this reason, while a deficit in producing ballistic contraction of maximal amplitude may be relevant for some tasks, an impairment in the capacity to quickly produce ballistic contractions of submaximal amplitude may be more relevant for some specific skills (Boccia et al., 2018a). For this purpose, the RFD-SF (see 1.2 RFD-Scaling Factor) has been used by some authors to assess interlimb asymmetry (Boccia et al., 2018a, Smajla et al., 2020, Smajla et al., 2021a) also because, unlike peak RFD, RFD-SF is independent of muscle strength (Bellumori et al., 2011), which facilitates comparisons among the different population and muscle groups. In detail, Boccia et al. (2018a) aimed to compare the RFD-SF with other measurements usually adopted to identify asymmetry as MVF, peak RFD and concentric isokinetic test in soccer players. They compared the prevalence of asymmetry by adopting these indices and have been calculated the correlations between them.

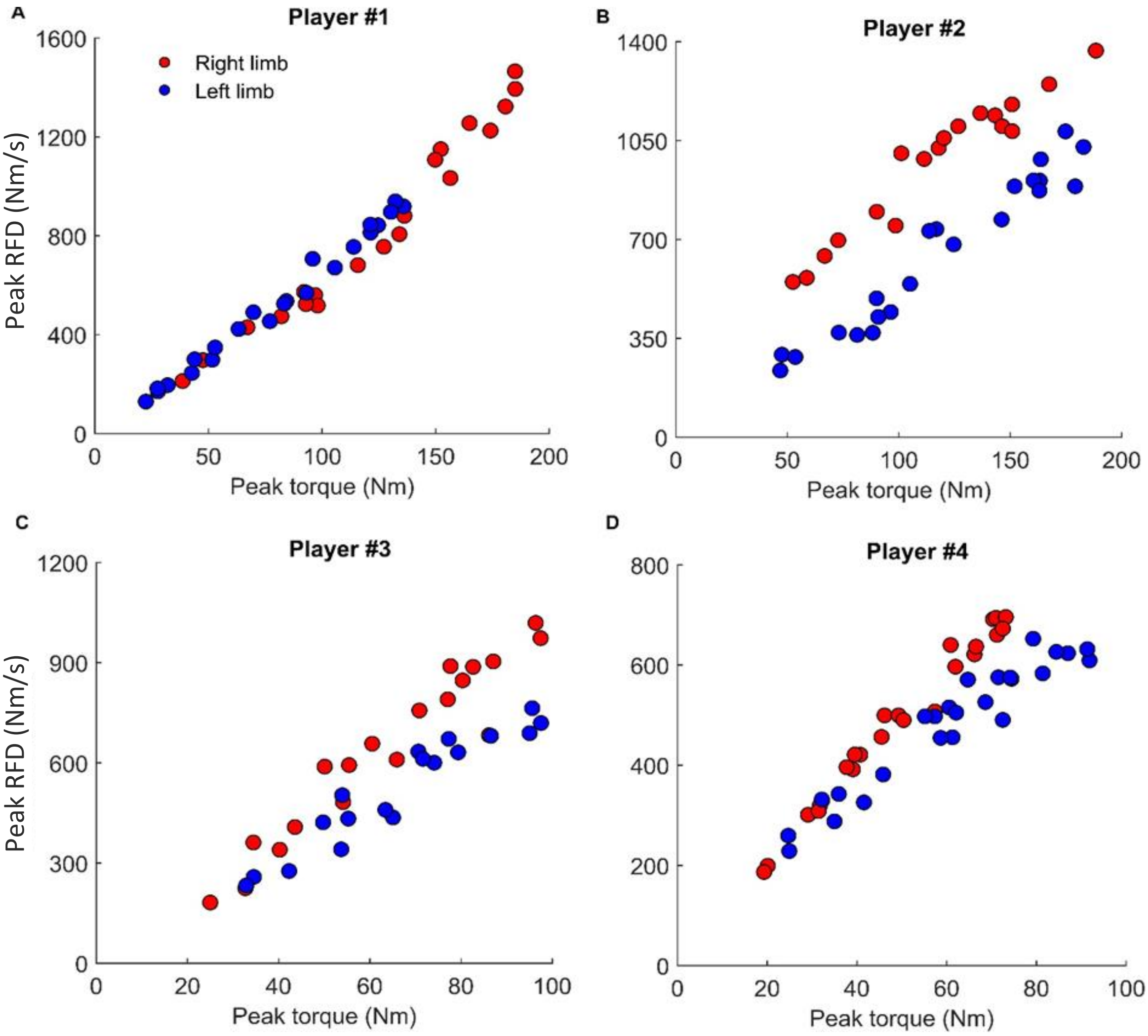

Figure 11. Examples of four subjects performing the RFD-SF protocol with levels from 20 to 100% of MVF. Each circle represents the peak torque and rate of force development (RFD) produced in each ballistic contraction. Panels (A, B) are referred to the quadriceps muscle, and panels (C, D) are referred to the hamstrings muscle. Modified from Boccia et al. (2018a)

The main findings of their work were that 1) most subjects showed interlimb asymmetry (cut-off 15%) in RFD across a large part of submaximal torques, not only when targeting maximal torque; 2) there was a large prevalence of RFD-SF asymmetry in both quadriceps and hamstrings (identified ≈70% of players with an interlimb asymmetry in hamstrings); 3) the prevalence of asymmetry was larger for RFD-SF than for the other indices of asymmetry. However, as with other indices, the RFD-SF asymmetry index did not correlate with the other inter-limb indices, and this supported again the need to choose the right test based on the aim because inter-limb asymmetries are metric- and task-specific (Smajla et al., 2021c).

As aforementioned, the *"classic"* RFD-SF protocol (Bellumori et al., 2011) consists of 100-125 pulses but Smajla et al. (2021a) demonstrated that a reduced protocol with 36 pulses is sufficient to highlight any asymmetries.

In conclusion, the RFD-SF appear like a valuable measure with higher ecological validity to evaluate inter-limb differences for rapid force production during different submaximal exercises (Boccia et al., 2018a).

1.5 Aims & hypotheses

As this literature review has outlined, the ability to generate and relax muscle forces quickly (i.e., 200 ms) across various submaximal levels is the basis of relevant activities of daily life and for many sports gestures, involving both upper and lower limbs. Indeed, RFD, which is derived from the force or torque time curves recorded during explosive voluntary contractions (Aagaard et al., 2002, Maffiuletti et al., 2016) seems to be a key parameter to understanding different aspects such as fatigue and asymmetries.

To follow a logical thread in this thesis, it is of primary importance to investigate the impact of neural and contractile determinants underpinning the burst-like contractions. Then, to compare with the existing literature on the possibility of using RFD (peak, early or late) as a valid measure to determine fatigue following fatiguing tasks. And then go through the identification of any central or peripheral fatigue following a hundred purely explosive contractions, with the use of High-Density surface Electromyography (HDsEMG) and electrical nerve stimulation (octets and twitch) concluding with the use of RFD-SF as a method to assess the asymmetries in upper limbs. Finally, the findings of the thesis are discussed collectively (Chapter 6 – General Discussion), with practical implications and directions for future research closing this chapter.

The specific aims of this dissertation are specified for every chapter:

Chapter 2 - Neural and contractile determinants of burst-like explosive isometric contractions of the knee extensors

Aims: to investigate the neural and contractile determinants of time-locked (0-50 ms, 0-100 ms and 0-150 ms) RFD and peak RFD in burst-like isometric contractions of knee extensors.

Hypothesis: the RFD, assessed through a time-locked analysis may demonstrate a different aetiology with different neuromuscular determinants if we consider the early or the late phase from the force onset.

Chapter 3 - Rate of Force Development as an Indicator of Neuromuscular Fatigue: A Scoping Review

Aims: determine if the RFD is a valid indicator of neuromuscular fatigue and understand what the most sensitive RFD variable is for evaluating neuromuscular fatigue.

Hypothesis: basis on the existing literature, the RFD may be more sensitive to quantify the changes in neuromuscular fatigue after different fatiguing tasks and the early RFD (0-50 ms) may be more sensitive to assess these changes.

Chapter 4 -

Aims: Investigate the possible effects of fatigue, in terms of central and peripheral fatigue, after one-hundred burst-like explosive isometric contractions.

Hypothesis: one-hundred isometric repeated purely explosive contractions mainly cause a decrease in RFD compared to MVF. Furthermore, as the force production in the first 50 ms of contraction is primarily dependent on neural excitation, we hypothesised that repeated purely explosive contractions mostly induced a decrement in the net neural drive (central fatigue).

Chapter 5 - Strength Asymmetries Are Muscle-Specific and Metric-Dependent

Aims: to examine if dominance affected muscle function. Secondly, investigated if muscle function asymmetries are muscle-specific or, conversely, if one side is overall more performative than the other independently of the muscle group. Thirdly, to investigate if, within each muscle group, asymmetry direction is consistent among various muscle performance metrics (MVF, RFD, and RFD-SF). Finally, as a secondary objective, we want to test the inter-day repeatability of the custom-made isometric dynamometer adopted in the present study.

Hypothesis: we hypothesize that the dominance does not affect muscle functions (MVF, RFD, and RFD-SF) and then the asymmetry direction agreement among heterologous muscles (i.e., elbow flexor and extensors) is low; we hypothesize that the asymmetry direction agreement among the metrics adopted (MVF, RFD, RFD-SF) in homologous muscles is low. Finally, as a secondary objective, we want to test the inter-day repeatability of the custom-made isometric dynamometer adopted in the present study.

Chapter 2 - Neural and contractile determinants of burst-like explosive isometric contractions of the knee extensors

2.1 Abstract

Walking and running are based on rapid burst-like muscle contractions. Burst-like contractions generate a Gaussian-shaped force profile, in which neuromuscular determinants have never been assessed. We investigated the neural and contractile determinants of the rate of force development (RFD) in burst-like isometric knee extensions. Together with maximal voluntary force (MVF), voluntary and electrically evoked (8 stimuli at 300 Hz, octets) forces were measured in the first 50, 100 and 150 ms of burst-like quadriceps contractions in 24 adults. High-density surface electromyography (HDsEMG) was adopted to measure the root mean square (RMS) and muscle fibre conduction velocity (MFCV) from the vastus lateralis and medialis. The determinants of voluntary force at 50, 100 and 150 ms were assessed by stepwise multiple regression analysis. Force at 50 ms was explained by RMS (R^2 = 0.361); force at 100 ms was explained by octet (R^2 = 0.646); force at 150 ms was explained by MVF (R^2 = 0.711) and octet (R^2 = 0.061). Peak RFD (which occurred at 60 ± 10 ms from contraction onset) was explained by MVF (R^2 = 0.518) and by RMS_{50} (R^2 = 0.074). MFCV did not emerge as a determinant of RFD.

Muscle excitation was the sole determinant of early RFD (50 ms), while contractile characteristics were more relevant for late RFD (≥100 ms). As peak RFD is mostly determined by MVF, it may not be more informative than MVF itself. Therefore, a time-locked analysis of RFD provides more insights into the neuromuscular characteristics of explosive contractions.

2.2 Introduction

The rate of force development (RFD) reflects the ability to rapidly increase muscle force after the onset of a ballistic contraction (Aagaard et al., 2002, Maffiuletti et al., 2016). The RFD of knee extensor muscles has been shown to be an important determinant of performance in explosive tasks such as vertical jumping (McLellan et al., 2011), weightlifting (Zaras et al., 2020) and cycling (Stone et al., 2004). In addition, the relevance of possessing a high RFD has also been demonstrated in locomotor tasks such as endurance running (Lieberman et al., 2010) and in functional activities of daily living (Varesco et al., 2019, Clark et al., 2011). All the aforementioned movements are indeed characterised by time-constrained contractions, typically lasting less than 150-200 ms.

The intersubject variance in voluntary knee extensors' RFD can be partially explained by variance in MVF. However, the role of MVF is more pronounced in the late phase of the contraction, and it was found to be the primary determinant of RFD from 75 ms onwards (Andersen and Aagaard, 2006, Folland et al., 2014). The contribution of neural and contractile mechanisms vary throughout the time course of the force-time curve rise. Indeed, the greater the time elapsed from contraction onset, the more muscular factors predominate on neural ones. Agonist muscle excitation, as measured by the EMG amplitude calculated over the first 50 ms from the contraction onset, is strongly correlated ($r \approx 0.7$-0.8) to the RFD in the first 50 ms (Folland et al., 2014, Cossich and Maffiuletti, 2020, Hannah et al., 2012, de Ruiter et al., 2004). This was even more elegantly demonstrated by Del Vecchio et al. (Del Vecchio et al., 2019) in the tibialis anterior, where the rates of motor unit recruitment and motor unit firing are the most influential factors associated with the RFD in the first 50 ms of contractions. Conversely, the quadriceps muscle thickness (Cossich and Maffiuletti, 2020) and volume (Maden-Wilkinson et al., 2021) are mostly correlated to the RFD in the later phases of the contraction ($\geq$ 100 ms). The responses to electrically evoked octets (eight stimuli delivered at 300 Hz) have been used to evaluate the maximal contractile (involuntary) RFD (de Ruiter et al., 1999, de Ruiter et al., 2004). Electrically evoked responses correlate to voluntary RFD throughout the whole contraction (Pearson's r ranging from 0.4 to 0.8 from 25 to 150 ms), with a stronger relation with later RFD ($\geq$100 ms). Finally, RFD is also partially explained by muscle and tendon stiffness (Bojsen-Møller et al., 2005). However, the correlation between RFD and tendon stiffness was found to be no longer present when the effect of MVF was accounted for (Hannah and Folland, 2015, Maden-Wilkinson et al., 2021).

The timing and shape of force production during ballistic contractions is crucial. To elucidate the neuromuscular determinants of RFD, the above-mentioned studies adopted ballistic contractions with various durations from ≈1 to 3 s. Indeed, some studies adopted explosive contractions lasting 3 s (Andersen and Aagaard, 2006, Cossich and Maffiuletti, 2020), others explosive contractions lasting 1 s (Maden-Wilkinson et al., 2021, Folland et al., 2014, Hannah and Folland, 2015), and others did not mention the length of the contraction(de Ruiter et al., 2007). Human locomotion has been described as being generated by an impulsive (burst-like) excitation of muscle groups (Sartori et al., 2013). The activation profiles are Gaussian-shaped curves (Ivanenko et al., 2006, Gizzi et al., 2011) without any holding phase. Requesting that participants maintain the muscle contraction for 1 s is an effective strategy to reach a high level of force (> 70% of MVF), which is necessary to produce the maximum possible RFD. Nevertheless, the muscle activation profile of such a motor task does not reflect the ones adopted in locomotion. Therefore, we still do not have a clear understanding of RFD determinants in Gaussian-shaped muscle activation profiles closer to locomotion requirements (Ivanenko et al., 2006, Gizzi et al., 2011).

Two recent reviews investigating the effect of strength training (Blazevich et al., 2020) and muscle fatigue (D'Emanuele et al., 2021) on RFD reported that the most studied variable of RFD is the RFD_{peak}, i.e., the local maximum of the first derivative of force with respect to time. While RFD_{peak} is the most popular RFD-related variable, the contractile and neural determinants of RFD_{peak} have never been investigated, as all previous studies focused on time-locked RFD variables such as RFD in the first 50, 100 or 150 ms.

Therefore, we aimed to investigate the neural and contractile determinants of 1) time-locked RFD and 2) in RFD_{peak} in burst-like isometric knee extensions.

2.3 Material and Methods

2.3.1 Participants

Twenty-four (five female) healthy adults volunteered (mean ± SD.; 25 ± 2 years; 71.2 ± 10.6 kg; 174 ± 8 cm) for this study. Participants were physically active practicing leisure physical activity for at least 2 times per week. Exclusion criteria were any previous history of neuromuscular disorders or lower limb injury in the previous six months. All the participants were informed about the testing procedure and provided written informed consent prior to their participation in this study, which was approved by the Ethical Advisory Committee (University of Verona—approval no: 13.R1/2021) and performed in accordance with the Helsinki Declaration.

Participants visited the laboratory only once and avoided strenuous exercise for 24 h and caffeine for 6 h before the experimental session. The experimental session was divided into two parts. The first part was constituted of a warm-up and familiarisation with real-time visual feedback, which continued until the participant was able to perform five consecutives explosive contractions without countermovement or holding phase. The second part was constituted by the actual measurement, lasting 30 minutes. All measurements were taken from the participant's right lower limb (which was the dominant limb in 22 of 24 participants).

Participants were seated on a custom-made chair that allowed the assessment of the right knee extensors. Straps were fastened across the chest and hips to avoid lateral and frontal displacements. The participant's knee and hip were flexed at 90° from full extension. The strain gauge load cell (546QD- 220 kg; DSEurope, Milan, Italy) was positioned 2 cm above the malleolus perpendicular to the tibial alignment. To avoid pain and maintain structural stiffness, a standard hard shin protector was placed between the thrust surface and the tibia.

2.3.2 Voluntary Contractions

Participants performed a series of 10 warm-up contractions at progressively higher levels of force before completing two maximal voluntary contractions, with 2 minutes of rest in between. Participants were instructed to push as hard as possible for 5 s, and they received standardised strong verbal encouragement. Participants also received visual real-time feedback regarding the force response through a screen placed in their line of sight.

After 3 min of rest, the participants performed 10 explosive contractions (brief pulses) interspersed by 15 s of rest. The contractions were characterised by a short active phase (lasting ≈ 200 ms) and by avoiding any holding phase, resulting in a burst-like shape (Figure 12A). Participants were instructed to push "as fast and as hard as possible" (Sahaly et al., 2001). A visual line on the screen depicted 80% of MVF with a target error of ± 10% (Folland et al., 2014) during the contractions, and participants were instructed to achieve a peak force above this level during each explosive contraction.

The analog force signal was amplified (gain 150) and sampled at 2048 Hz with an external analog-to-digital converter (QUATTROCENTO; OT Bioelettronica, Turin, Italy) and the data were recorded with the software OT BioLab (OT Bioelettronica, Turin, Italy) and analysed with MATLAB (v. 2020b, The Mathworks, Natick, MA).

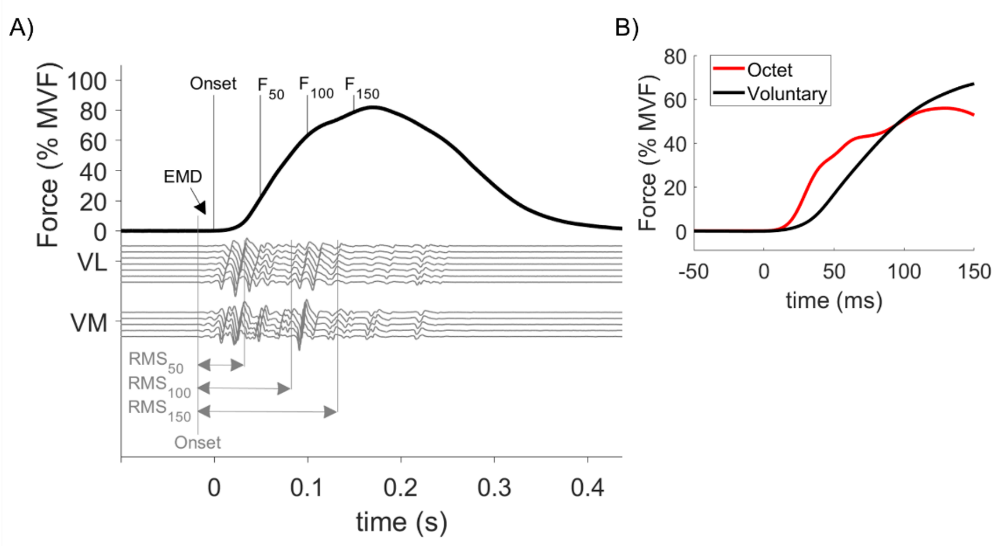

Figure 12. A) Example recordings of force (black) and HDsEMG channels (grey) during a burst-like (i.e. Gaussian-shaped) explosive isometric voluntary contraction. It should be noted that the duration is approximately 200 ms and that the EMG onset starts a few milliseconds before the force onset. The force expressed at 50 (F_{50}), 100 (F_{100}) and 150 ms (F_{150}) after the onset of contraction were considered the dependent variables in the stepwise multiple regression models. Only one representative column of each matrix of electrodes are reported for vastus lateralis (VL) and medialis (VM) muscles. The time periods over which the EMG variables were calculated (RMS and muscle fiber conduction velocity) are highlighted by the grey arrows. B) Representative example of the first 150 ms of the voluntary (black) and electrically evoked octet (red) contractions.

2.3.3 Electrically evoked twitch and octet contractions

Electrical stimuli were delivered via percutaneous stimulation of the femoral nerve in the femoral triangle via a constant-current, variable-voltage stimulator (DS7AH; Digitimer Ltd, Welwyn Garden City, UK). The anode (50 x 90 mm) was placed over the greater trochanter and the cathode (Ø = 32 mm) was placed within the femoral triangle, near the femoral nerve We adopted square-wave pulses (0.2 ms in duration) with maximal voltage of 400 V to elicit either single or octet-train contractions (eight pulses at 300 Hz). The adoption of octets has been utilised to determine the maximal capacity of the muscle–tendon unit to produce explosive force(de Ruiter et al., 2004), see Figure 12B. While this procedure was painful for the participants, we did not have any drop-out because of this.

A series of incremental (starting from 20 mA and increasing by 20 mA at each step) single stimuli were introduced until there was a plateau in the M-wave amplitude response (Folland et al., 2014), which was visually evaluated. One representative channel of the 64 available for the vastus lateralis (VL) was adopted for this aim (see 2.3.4 High-Density Surface **Electromyography**). Another series of incremental stimuli was used to find the force signal plateau for octet stimulation (de Ruiter et al., 2004). During all stimulations, the experimenter pressed with his hand on the anode to bring it closer to the cathode and to obtain a better response. The intensity plateau values (range: 120–400 mA) for single and octets were each increased by 20% to ensure supramaximal stimulation. Two single twitches and two octet contractions (each one interspersed by 10 s) were delivered.

2.3.4 High-Density Surface Electromyography

High-Density Surface Electromyography (HDsEMG) signals were recorded from the vastus lateralis (VL) and vastus medialis (VM) muscles in a single differential configuration using two matrices of 64 electrodes each (13 rows x 5 columns, 8 mm inter-electrode distance, gold-coated; model: GR08MM1305, OT Bioelettronica, Turin, Italy). The reference electrode (24 mm, model: CDE-S. OT Bioelettronica, Turin, Italy) was placed on the patella of the same limb. Before the placement of the electrodes, the skin area was shaved and then was slightly abraded with abrasive paste and cleaned with water (Merletti and Cerone, 2020). To ensure proper electrode–skin contact, the electrode cavities of the matrix were filled with conductive paste (Spes-Medica, Battipaglia, Italy). The electrode arrays were fixed with an extensible tape. The EMG signals were amplified (gain 150), sampled at 2048 Hz and converted to digital data with a 16-bit A/D converter (Quattrocento; OT Bioelettronica, Turin, Italy). Signals, in single-differential configuration, were visualised during acquisition and then stored on a personal computer using OT BioLab+ software version 1.5.5.0 (OT Bioelettronica, Turin, Italy) for further analysis.

2.4 Data Analysis

2.4.1 Force signals

The force signals were low-pass-filtered at 50 Hz using a fourth-order zero-lag Butterworth. MVF was defined as the highest force over the two maximal voluntary contractions. The onset of each voluntary and evoked contraction was visually assessed (Tillin et al., 2010) by the same researcher through a hand-customized MATLAB code. In the case of countermovement, the contraction was discarded. Force was assessed at 50, 100 and 150 ms after the contraction's onset for voluntary (F_{50}, F_{100}, F_{150}), evoked single (F_{single_50}, F_{single_100}, F_{single_150}) and octet (F_{octet_50}, F_{octet_100}, F_{octet_150}) stimuli. RFD_{peak} was calculated as the maximum of the first derivative of force overtime on the filtered signals. Out of 10 ballistic contractions, we discarded the contractions showing the highest and lowest RFD_{peak}. Then, we averaged the force and EMG variables (see next paragraph) calculated from the remaining eight contractions to increase the precision of the estimates. Regarding the evoked contractions, we averaged the values calculated from the two single and two octet contractions.

2.4.2 High-Density Surface Electromyography

The EMG signals were band-pass-filtered at 30-450 Hz using a fourth-order zero-lag Butterworth filter prior to analysis. We first removed the EMG channels showing excessive noise or artefacts through visual analysis. Signals for each column of electrodes were visually inspected, and the four to eight (depending on columns) single-differential HDsEMG signal channels with clear motor unit action potential propagation without shape change were chosen for the analysis. The average number of selected signals were 6 (from 4 to 8 depending on columns). The onset of each EMG signal of each contraction was visually selected(Crotty et al., 2021) by the same researcher through a hand-customized MATLAB code. The RMS was calculated across all available channels, divided by the M-wave amplitude (elicited by the single stimuli) calculated over the same electrodes. RMS was then averaged across VL and VM channels to obtain a single estimate calculated over the first 50, 100 and 150 ms from EMG onset (RMS_{50}, RMS_{100}, RMS_{150}).

MFCV was calculated using an algorithm that allows the estimation of conduction velocities from multichannel EMG signals in explosive burst-like contractions (Pozzo et al., 2004). The algorithm provides highly accurate estimates over epochs as short as 50 ms. Therefore, the MFCV was calculated over the first 50, 100 and 150 ms from EMG onset (defined as $MFCV_{50}$, $MFCV_{100}$, $MFCV_{150}$) for the ballistic contractions. We also calculated the MFCV of the M-wave over the same channels adopted for the voluntary contractions. Then, MFCV was also calculated in relative terms with the M-wave conduction velocity (defined as $MFCV_{rel\_50}$, $MFCV_{rel\ \_100}$, $MFCV_{rel\ \_150}$). Finally, the MFCV estimates of voluntary contractions and M-wave were calculated over the five columns of electrodes (for each muscle) and then averaged.

2.4.3 Statistical Analysis

Descriptive statistics are presented as mean ± SD. and coefficient of variation (COV, %) where needed. Statistical analyses were performed using JASP (Version 0.16) and statistical significance was set at $p<0.05$. Preliminary analysis with Pearson's correlation between purely explosive voluntary force and individual predictor variables was performed. To answer the first experimental question, multiple stepwise linear regression between voluntary force calculated over successive 50 ms time periods (50, 100 and 150 ms) and predictor variables was performed to assess the influence of all the entered predictor variables simultaneously. Predictor variables were assessed at the identical time period of the relevant voluntary force measurement. For example, the possible predictors of F_{50} were F_{octet_50}, F_{single_50}, $MFCV_{rel\ \_50}$, RMS_{50} and MVF. However, for evoked measures, which were of shorter duration, we always adopted the response at 50 ms (i.e., F_{octet_50} and F_{single_50}). To answer the second experimental question, stepwise linear regression analysis between RFD_{peak} and predictor variables was performed. To make it clearer: the mechanical variables (MVF, F_{50}, F_{100}, F_{150}) were entered as dependent variables in absolute terms. To avoid the effect of some confounding factors (such as for example subcutaneous adipose tissue), we normalized the EMG variables for the M-wave characteristics: RMS was divided by the M-wave amplitude; MFCV was divided by the MFCV of M-wave.

2.5 Results

2.5.1 Interindividual Variability

The MVF of knee extensors was 424 ± 91 N with a COV of 21%, ideally in line with the data reported by Folland and colleagues (2014). The COV of variables assessed during the voluntary contractions is reported in Table 3. Briefly, the COV of force ranged from 37% at 50 ms to 23% at 150 ms. The COV of RMS (normalised by M-wave amplitude) ranged from 43% at 50 ms to 23% at 150 ms. The COV of MFCV (normalised by M-wave conduction velocity) ranged from 10% at 50 ms to 11% at 150 ms. The COV of absolute MFCV ranged from 12% at 50 ms to 15% at 150 ms. The peak-to-peak amplitude of M-Wave was 3,801 ± 1,048 mV and the COV was 28%. To confirm the brevity of the explosive contraction, through calculation, we determined that the time to peak force was 180 ± 30 ms with a COV of 16%.

	RMS			*RMS (%)*			*MFCV_abs*			*MFCV_rel*		
	Mean	SD	COV	Mean	SD	COV	Mean	SD	COV	Mean	SD	COV
50	0.037	0.016	43	1.098	0.708	64	4.7	0.6	12	1.074	0.103	10
100	0.063	0.014	22	1.847	0.888	48	4.9	0.6	13	1.113	0.107	10
150	0.064	0.015	23	1.871	0.946	51	5.3	0.8	15	1.197	0.138	12
	Force_abs			**Force (%)**			**Twitch**			**Octet**		
	Mean	SD	COV	Mean	SD	COV	Mean	SD	COV	Mean	SD	COV
50	72	27	37	17.5	6.9	39	71.9	22	31	139.2	32.1	23
100	223	49	22	53.2	7.7	14	78.1	28.9	37	205.9	60.5	29
150	287	66	23	67.9	8.2	12	43.1	18.9	44	216.3	65.5	30

Table 3. The table shows the mean, standard deviation (SD) and coefficient of variation (COV, %) assessed at 50, 100 and 150 ms for RMS (mV), MFCV (m/s) in absolute (MFCV_abs) and relative (normalized for M-Wave; MFCV_rel) terms, force, twitch and octet. RMS (mV) is reported as the mean of the values assessed from VL and VM. Force (N), twitch (N) and octet (N) are reported in absolute terms. RMS (%) is expressed as percentage of Maximal M-Wave whereas Force (%) as percentage of MVF.

	F_{50}	F_{100}	F_{150}	RFD_{peak}
MVF	0.202	0.775^{***}	0.851^{***}	0.734^{***}
RMS	0.624^{**}	-0.024	0.084	0.257
MFCV_rel	-0.322	-0.122	0.053	-0.033
MFCV_abs	-0.195	-0.249	-0.131	-0.140
TWITCH	0.173	0.681^{***}	0.723^{***}	0.463^{*}
OCTET	0.229	0.813^{***}	0.829^{***}	0.638^{***}

*Table 4. Pearson's correlation coefficients between predictor variables and voluntary explosive force of the knee extensors during the first, 50 (F_{50}), 100 (F_{100}) and 150 ms (F_{150}) of contraction (n= 24). All the variables are considered in absolute terms, except for MFCV_rel, which is expressed in relative terms with M-wave. RMS, MFCV_abs and MFCV_rel are considered as mean values assessed in VL and VM. *p < .05, **p < .01, ***p < .001.*

The Pearson's correlation coefficients between predictor variables and voluntary force are reported in Table 4. Briefly, F_{50} was significantly positively correlated only with RMS_{50}, while F_{100} and F_{150} were positively correlated with MVF, single twitch and octets.

2.5.2 Determinants of Explosive Absolute Force

The multiple regression analysis showed that the total variance in explosive force explained by the predictor variables increased throughout the contraction from 36% at 50 ms to 65% at 100 ms and to 77% at 150 ms, but the contribution of specific predictor variables changed over the contraction duration. Figure 13 represents the variance accounted for by predictors from 50 to 150 ms of contraction. Briefly, F_{50} was explained by only RMS_{50} (R^2 = 0.361, p=0.001). F_{100} was explained by F_{octet_50} (R^2 = 0.646, p<0.001). F_{150} was explained by MVF (R^2 = 0.711, p<0.001) and F_{octet_50} (R^2 = 0.061, p=0.016).

2.5.3 RFD_{peak}

The average RFD_{peak} was 4752 ± 1185 $N{\cdot}s^{-1}$ with a COV of 25%. The time to peak RFD was 60 ± 10 ms with a COV of 21%. The Pearson's correlation analysis showed that RFD_{peak} positively correlated with MVF, single twitch and octets (see Table 4). The multiple regression analysis showed that the RFD_{peak} was explained by MVF (R^2 = 0.518, p<0.001) and by RMS_{50} (R^2 = 0.074, p = 0.036), accounting for a total of 59.2% of the variance.

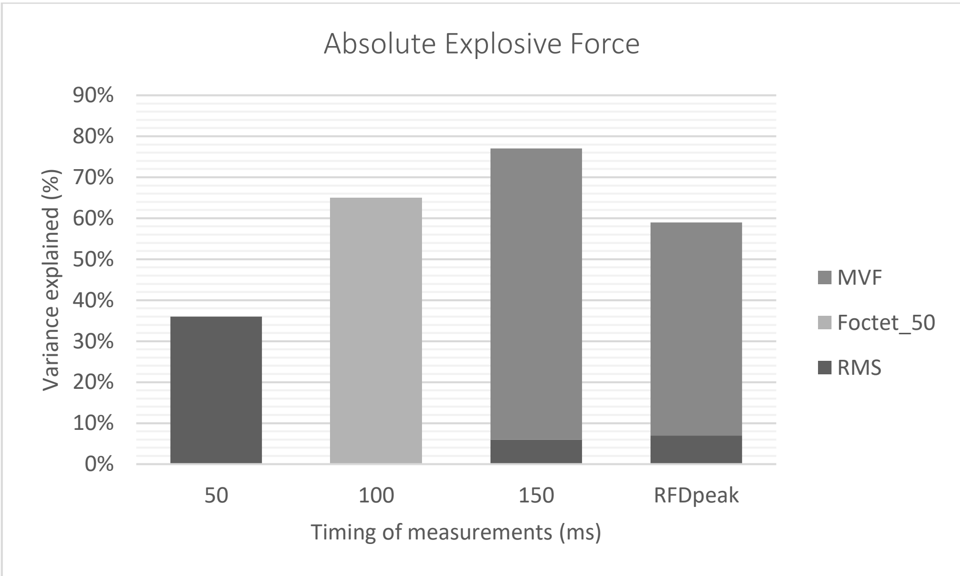

Figure 13. Determinants of RFD peak and absolute voluntary purely explosive force of the knee extensors during the first 150 ms of contraction. Predictor variables that independently explained a significant proportion of the total variance assessed with stepwise multiple linear regressions are shown.

2.6 Discussion

We analysed neural and contractile determinants of burst-like explosive contractions in the knee extensors of healthy young adults through the application of electrically evoked single twitches, octets and HDsEMG. The force production was related to different neuromuscular factors that changed through the contraction timing from onset: while the early RFD (F_{50}) was correlated only to RMS_{50}, late RFD (F_{100} and F_{150}) was more correlated to F_{octet_50} and MVF.

The multiple regression analysis showed that 36% of the variance of F_{50} was explained by RMS_{50}; 65% of the variance of F_{100} was explained by F_{octet_50}; 71% of the variance of F_{150} was explained by MVF and another 6% by F_{octet_50}. For the RFD_{peak} (which occurred, on average, 60 ms after force onset) 52% was explained by MVF and another 7% by RMS_{50}. MFCV calculated from HDsEMG did not contribute to explaining the variance of any variables considered.

This is the first study that has inspected the neural and contractile determinants of burst-like explosive isometric contractions. This is particularly relevant because while, in real-life, the muscle activation profiles are Gaussian-shaped (Ivanenko et al., 2006, Gizzi et al., 2011), i.e. without holding the phase of maximal contraction. Differently, previous studies adopted explosive contractions with a holding phase (of at least 1s) (Andersen and Aagaard, 2006, Cossich and Maffiuletti, 2020, Maden-Wilkinson et al., 2021, Folland et al., 2014, Hannah and Folland, 2015). Therefore, while our results are mostly in line with previous works adopting contractions with an holding phase (Andersen and Aagaard, 2006, Cossich and Maffiuletti, 2020, Del Vecchio et al., 2018, Folland et al., 2014), in the present study we refine the determinants of RFD on explosive contraction of Gaussian-shaped and shorter (< 200ms) duration.

The main determinant of early RFD was the muscle excitation over the first 50 ms of contraction. This finding is in line with previous works (Cossich and Maffiuletti, 2020, Tillin et al., 2010) and it supports the hypothesis that the physiological variation in the rate by which motor units are recruited during ballistic contractions is the main determinant of the variability in RFD across individuals (Del Vecchio et al., 2019, Dideriksen et al., 2020). For this reason, athletes that showed greater RFD also showed greater muscle excitation over the first 50 ms of an explosive contraction compared to non-trained adults (Tillin et al., 2010). Indeed, after a period of ballistic training, the motor unit discharge rates tend to increase and early RFD depends on the motor unit discharge rate (Van Cutsem et al., 1998). As a methodological note, we calculated the RMS over dozens of electrodes from HD-EMG; we consider this measure more reliable than previous works adopting only couples of electrodes. Furthermore, as we divided the RMS calculated from each channel by the M-wave amplitude of each channel, the muscle excitation calculated in this study can be considered more valid than that calculated using absolute RMS.

Late RFD (≥100 ms) was correlated to both contractile properties (F_{single_50} and F_{octet_50}) and MVF (see Table 4), with some differences regarding the determinants of force at 100 and 150 ms. Force production at 100 ms was mostly explained by the contractile properties (F_{octet_50}), and this is in line with Folland et al. (2014), which found that F_{octet_50} was the primary determinant of voluntary RFD assessed at 50-100 ms, accounting for 68% of variance. Quadriceps muscle volume can also influence contractile properties (measured with the evoked octet) and consequently late RFD (Maden-Wilkinson et al., 2021). Contractile properties are also dependent on fibre type composition (Viitasalo and Komi, 1978) and muscle-tendon unit stiffness (Bojsen-Møller et al., 2005, Monte and Zignoli, 2021), which has been related to RFD in the first 50 – 100 ms. Force at 150 ms was in part explained by MVF, and this confirms the results of Cossich and Maffiuletti (Cossich and Maffiuletti, 2020), who found that the relationship between MVF and RFD was stronger with the late than early RFD. This is also in line with Andersen and Aagaard (2006) as they found that voluntary RFD became increasingly dependent on MVF and less dependent on evoked twitch as the time from the onset of contraction increased.

Unexpectedly, MFCV did not correlate with force production in any time interval, from 50 to 150 ms (see Table 4). Analysis of MFCV has been suggested to provide an indirect assessment of the properties of active motor units (Andreassen and Arendt-Nielsen, 1987). It is well known that the MFCV is dependent on fibre diameter (Andreassen and Arendt-Nielsen, 1987, Blijham et al., 2006). Therefore, MFCV is considered a size principle parameter (Andreassen and Arendt-Nielsen, 1987) since the muscle fibres of high-threshold motor units have greater diameters than those of lower-threshold motor units (Andreassen and Arendt-Nielsen, 1987). For this reason, we expected that participants able to more rapidly recruit larger motor units would be able to exert a higher RFD. Indeed, Del Vecchio et al.(2018) found a positive correlation between the early RFD (50 ms) of elbow flexion and MFCV of biceps brachii. Besides the investigation of different muscles (VM and VL in our study), we are unable to identify any methodological difference that could explain the disagreement between our study and that of Del Vecchio et al.(2018) as we adopted the same algorithm to calculate MFCV over a short period of time (Pozzo et al., 2004). To account for differences in muscle fibre diameter, we normalised MFCV to M-wave MFCV, but in this case, as well, we did not find any correlation with force production. The present results do not corroborate the usefulness of analysing MFCV in explosive contraction. However, we could not exclude that the muscle of interest and the sample characteristics may play a role in the relationship between MFCV and RFD.

Despite its wide popularity (Blazevich et al., 2020, D'Emanuele et al., 2021), the physiological determinants of RFD_{peak} have been little studied. As the time to peak RFD was, on average, 60 ± 10 ms, we expected that the determinants of RFD_{peak} would have been more similar those of F_{50} than F_{100} and F_{150}. Contrary to our expectations, the main determinant of RFD_{peak} was MVF (see Figure 13Figure 13. Determinants of RFD peak and absolute voluntary purely explosive force of the knee extensors during the first 150 ms of contraction. Predictor variables that independently explained a significant proportion of the total variance assessed with stepwise multiple linear regressions are shown.), while that of F_{50} was RMS_{50}. This means that the highest steepness of the force–time curve is related to the highest level of voluntary force. The analysis of RFD_{peak} is easy to perform because it does not require the identification of the onset of the muscle contraction, as occurs in the time-locked analysis of RFD. However, the present results suggest that RFD_{peak} is in part related to MVF and therefore may provide similar information to this parameter. Conversely, time-locked analysis of RFD, especially in the first 50 ms, may provide further insight into the neuromuscular characteristics of explosive contractions.

Regarding the limitations of the present study, in addition to the non-homogeneity of the sample with only three female participants, we should consider that many physiological variables such as muscle size and architecture (Cossich and Maffiuletti, 2020, Maden-Wilkinson et al., 2021), muscle-tendon stiffness (Massey et al., 2017), belly-gearing (Monte and Zignoli, 2021), motor units recruitment speed and discharge rate (Del Vecchio et al., 2018) played a role and were not investigated. In addition, we focused only on the initial milliseconds of force contractions, and we didn’t assess voluntary activation over the plateau phase of a maximal voluntary contraction through. Furthermore, we only focused on isometric contraction (Tillin et al., 2012); therefore, the present results might not be valid for dynamic contractions.

2.7 Perspectives

The analysis of Gaussian-shaped muscle contractions is scarce compared to that of other forms of explosive contractions with some sort of holding phase. In accordance with Folland et al. (2014), the relative contribution of different determinants changed during the phase of contraction, and this finding may be useful in the design of interventions to improve explosive force production.

The time intervals for RFD calculation should be better justified and the distinction between "early" and "late" RFD should be based on physiological relevance. In the present study, we found that the force production at 100 ms has determinants similar to that at 150 ms (i.e., both time windows include peripheral factors); therefore, the RFD calculated over 100 ms of contraction should be considered "late RFD", while the RFD in the first 50 ms should be considered "early RFD". Moreover, the fact that the RFD_{peak} is in part explained by MVF must be taken into account in experimental studies as it may provide similar information to MVF without sufficiently differentiating from it. Therefore, the analysis of time-locked intervals is preferred as it provides more insights into the neuromuscular characteristics of explosive contractions.

2.8 Conclusions

The force production of burst-like explosive knee extensor contractions was regulated by different neuromuscular factors that changed throughout the contraction duration. The main determinant of force production in the first 50 ms (early RFD) was the muscle excitation calculated over the vastus medialis and lateralis muscles. The main determinants of force production in the first 100 and 150 ms (late RFD) were contractile properties and MVF. In particular, contractile properties were more determinant for force production in the first 100 ms, while MVF was more determinant for force production in the first 150 ms. The main determinant of the peak of RFD was the MVF, which means that RFD_{peak} as an index of explosive contraction may not provide more information to differentiate between participants.

Chapter 3 - Rate of Force Development as an Indicator of Neuromuscular Fatigue: A Scoping Review

3.1 Abstract

Because rate of force development (RFD) is an emerging outcome measure for the assessment of neuromuscular function in unfatigued conditions, and it represents a valid alternative/complement to the classical evaluation of pure maximal strength, this scoping review aimed to map the available evidence regarding RFD as an indicator of neuromuscular fatigue. Thus, following a general overview of the main studies published on this topic, we arbitrarily compared the amount of neuromuscular fatigue between the "gold standard" measure (maximal voluntary force, MVF) and peak, early (≤100 ms) and late (>100 ms) RFD. Seventy full-text articles were included in the review. The most-common fatiguing exercises were resistance exercises (37% of the studies), endurance exercises/locomotor activities (23%), isokinetic contractions (17%), and simulated/real sport situations (13%). The most widely tested tasks were knee extension (60%) and plantar flexion (10%). The reason (i.e., rationale) for evaluating RFD was lacking in 36% of the studies. On average, the amount of fatigue for MVF (−19%) was comparable to late RFD (−19%) but lower compared to both peak RFD (−25%) and early RFD (−23%). Even if the rationale for evaluating RFD in the fatigued state was often lacking and the specificity between test task and fatiguing exercise characteristics was not always respected in the included studies, RFD seems to be a valid indicator of neuromuscular fatigue. Based on our arbitrary analyses, peak RFD and early phase RFD appear even to be more sensitive to quantify neuromuscular fatigue than MVF and late phase RFD.

3.2 Introduction

The magnitude of neuromuscular fatigue—also referred to as muscle fatigue (Gandevia, 2001) or neuromuscular fatigability (Chartogne et al., 2020)– is universally evaluated as the exercise-induced decline in the isometric maximal voluntary contraction force (hereafter abbreviated as MVF) of a muscle/muscle group. In this context, pre- to post-fatigue percent declines in knee extension MVF ranging from 8 to 34% have been reported for a multitude of exercise types of different duration and intensity (Millet and Lepers, 2004). Nevertheless, the validity of this approach/variable can partially be questioned as the characteristics of the fatiguing exercise (e.g., explosive jumps) do not always correspond to those of the testing contraction/task (e.g., slow ramp and hold knee extension). This lack of task specificity may result in an underestimation of the magnitude of neuromuscular fatigue, thereby suggesting the need for evaluating outcome measures other than the classical MVF.

The rate of force development (RFD)—which is basically obtained from the ascending part of the force-time curve of an explosive contraction either as a mean time-locked value or a maximal force per time ratio—has received increasing interest in the last few years for the evaluation of explosive strength in multiple situations (Maffiuletti et al., 2016, Rodríguez-Rosell et al., 2018). As such, RFD has been shown to be more sensitive than MVF to detect chronic changes induced for example by aging (Thompson et al., 2014), immobilization/disuse (de Boer et al., 2007), strength training (Andersen et al., 2010) and rehabilitation (Angelozzi et al., 2012), but also acute adjustments associated to exercise (Buckthorpe et al., 2014), muscle damage (Penailillo et al., 2015), and pain (Rice et al., 2019). Despite being more functionally relevant than pure maximal strength (McLellan et al., 2011, Tillin et al., 2010), RFD—particularly the one derived from the earlier phase of the contraction (≤100 ms; early RFD)—has been suggested to be largely influenced by neural mechanisms, mainly in relation with motor unit behavior (Del Vecchio et al., 2019). This unique physiological feature of RFD could explain, at least in part, why this variable has often been found to be more sensitive to changes than MVF.

Although the effect of neuromuscular fatigue on maximal strength was documented 130 years ago by Angelo Mosso (1891), the impact of fatigue on the ascending part of the force-time curve was described only recently. Royce (1962)was the first to report a similar fatigue-related decline in MVF (47%) and peak RFD (50%) after a sustained (1 min) maximal contraction of the finger flexors. Later, Viitasalo and Komi (1981b) found that 100 explosive contractions of the knee extensor muscles decreased MVF and peak RFD, respectively, by 24 and 36%. In the same year, Kearney and Stull (1981) investigated RFD across many non-overlapping time intervals, and reported that early RFD was more affected than late RFD (> 100 ms) following a sustained maximal contraction of the finger flexor muscles. Since these seminal reports, numerous studies have been published on the fatigue-related changes in RFD of different muscle groups and for different types of exercises, including actual sport situations. Nevertheless, a comprehensive understanding of the effect of neuromuscular fatigue on RFD—and more particularly so in relation with MVF—is still lacking.

Because RFD represents a valid alternative/complement to the classical evaluation of pure maximal strength in unfatigued conditions (Maffiuletti et al., 2016), the aim of this scoping review was to map the available evidence regarding RFD as a possible indicator of neuromuscular fatigue. Thus, following a general overview of the different studies published on this topic, we formulated two main research questions. The primary question was: "Is RFD a valid indicator of neuromuscular fatigue?" To address this question, we arbitrarily compared the magnitude of neuromuscular fatigue—characterized by the exercise-induced decline in selected variables—between MVF ("gold standard") and peak RFD (i.e., the most commonly evaluated RFD variable). The secondary research question of this study was: "What is the most sensitive RFD variable for evaluating neuromuscular fatigue?" To address this question, we arbitrarily compared the magnitude of neuromuscular fatigue between different RFD variables—basically peak, early and late RFD—always in relation with MVF.

3.3 Methods

3.3.1 Protocol and Eligibility Criteria

The protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols for Scoping Review (PRISMA-ScR) (Tricco et al., 2018). A literature search was conducted in February 2020 on PubMed, Scopus, and Web of Science databases. Peer-reviewed journal articles in English were included if: (1) the study involved healthy human participants, (2) at least one key term of the search string (see below) was included within the title, abstract, or keywords, (3) voluntary contractions were used to evaluate RFD before (pre-test) and within 1 h after the end of a standardized fatiguing exercise (post-test). The exclusion criteria were: (1) reviews, (2) studies whose main focus was not neuromuscular fatigue (e.g., post-activation potentiation), (3) studies in which fatigue was induced by non-voluntary contractions, (4) studies in which RFD was evaluated during vertical jumps due to the impossible comparison with MVF, (5) studies with missing data not obtained even after having contacted the corresponding author by e-mail. If the study design included the ingestion of dietary supplements, only the control group was considered.

3.3.2 Search Strategy

A Boolean search strategy was applied using the following string: ("rate of force development" OR "rate of torque development" OR "explosive contraction" OR "ballistic contraction" OR "time to peak force" OR "time to peak torque" OR "time to maximal force" OR "rate of force production" OR "force pulses" OR "force impulses" OR "torque pulses" OR "torque impulses" OR "rapid contraction") AND ("fatigue" OR "fatiguing" OR "fatigability").

3.3.3 Selection of Sources of Evidence

The final search results were exported into EndNote, and duplicates were removed. Further on, the reference list was imported into Rayyan, and abstracts were evaluated independently by two authors (SD'E and GB), in a blinded mode. At last, all selected articles were read. Corresponding authors of the selected articles were eventually contacted by e-mail to request any missing relevant information.

3.3.4 Data Items

We extracted the following data from the included articles: (1) subject characteristics (sample size, gender, age group, sport/training status); (2) fatiguing exercise characteristics; (3) test task characteristics; (4) percent decline (pre- to post-test) for four variables of interest: MVF, peak RFD, early RFD (≤100 ms), and late RFD (>100 ms). If there was more than one estimate for early and late RFD (e.g., RFD 0–50 and 0–100 ms for early RFD) or more than one arm for each study, we averaged the values for each variable of interest. If percent declines of MVF and RFD were not available, they were calculated from absolute data using the following formula:

$$\% = \frac{(POST - PRE)}{PRE} \cdot 100$$

3.3.5 Arbitrary Synthesis of the Data

We arbitrarily clustered the fatiguing exercises in two groups: “strength exercises,” including isometric and isokinetic contractions, vertical jumps, resistance/strength exercises, etc., and “other exercises” including endurance exercises/locomotor activities (e.g., running, cycling, swimming), simulated/real sport situations (e.g., half-marathon, soccer match, handball training session) and combined (strength and endurance) exercises. To arbitrarily synthesize the results, we averaged the percent declines of MVF, peak RFD, early and late RFD by fatiguing exercise type (strength vs. other exercises). The primary research question (concurrent validity of RFD) was addressed by comparing the percent decline of MVF to peak RFD. The secondary research question (sensitivity of RFD to changes induced by exercise) was addressed by comparing percent declines between the different RFD variables. Then, we also categorized studies based on whether the test task corresponded or not to the fatiguing task. When fatigue was evaluated with the same task adopted to induce fatigue (e.g., knee extension)—irrespective of the action mode—the test was considered “specific,” otherwise it was considered “non-specific.” Finally, we also verified if the reason (i.e., the scientific rationale) for evaluating RFD was provided in the introduction of all selected studies.

3.4 Results

3.4.1 Selection of Sources of Evidence

The electronic database search resulted in the identification of 8,867 potential studies after duplicate removal (Figure 14). Following a preliminary inspection of title, abstract and keywords, 8,066 articles were excluded, and 801 studies were available for screening. Through accurate examination of the abstracts, 678 studies were excluded, and 123 studies were assessed for eligibility. Based on the exclusion criteria, 53 studies were excluded, and 70 full-text articles were ultimately included in the review.

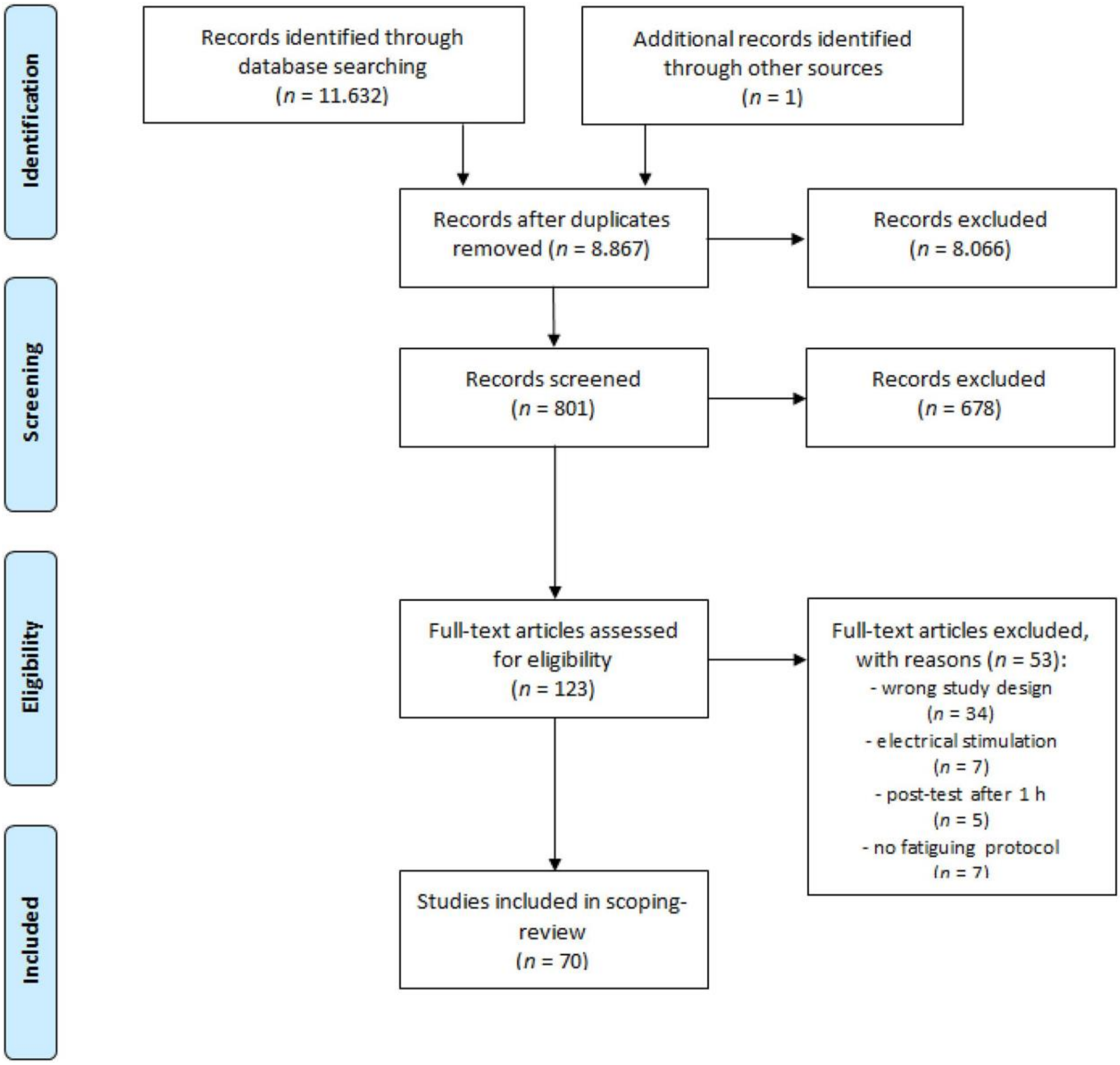

Figure 14. PRISMA flow diagram.

3.4.2 Results of Individual Sources of Evidence

The characteristics of the subjects, fatiguing exercise and test task, as well as the pre- to post-test percent declines for MVF, peak RFD, early RFD and late RFD are presented in Table 5 and Table 6 for strength exercises (43 studies) and other exercises (27 studies), respectively. Publication dates ranged from 1981 to 2020 with a notable increment starting from 2012. Only 14.5% of the total number of subjects (n = 1,206) were women. The training status of the participants was distributed as follows: physically active (56%), elite/professional athletes (11%), inactive (7%), or not declared (26%). Age groups were distributed as follows: adults (51%), young adults (43%), old (4%), middle-aged adults (1%), and children (1%). The fatiguing exercise was conducted in laboratory conditions in 59 studies (84%) and on the field in 11 studies (16%). The most-common fatiguing exercises consisted of resistance exercises

(37%), endurance exercises/locomotor activities (23%), isokinetic contractions (17%), simulated/real sport situations (13%), and vertical jumps (6%). The most widely tested task was knee extension (42 studies, 60%), followed by plantar flexion (7 studies, 10%), and knee flexion (6 studies, 9%). RFD was tested using isometric contractions in 67 studies (96%), and with dynamic actions in only three studies (4%). The rationale for evaluating RFD was lacking in 25 studies (36%), this variable not even being mentioned in the study aims.

References	Subjects	Fatiguing exercise	Test task	MVF decline	Peak RFD decline	Early RFD decline	Late RFD decline
(Alhammoud et al., 2018)	22♂ elite alpine skiers	35 max isokinetic KE	KE	-20%		-5%§	-5%§
(Andersen et al., 2014)	20♀	100 max isometric SE	SE	↓	↓	NA	NA
(Balshaw et al., 2016)	10♂ resistance-trained	4x3x3 concentric-eccentric KE protocols ≠ loads and durations (eccentric phase)	KE	-4%§	NA	-2%§	-2%§
(Battazza et al., 2019)	20♂	10x8 concentric KE-KF	KE	-55%	-76%	NA	NA
(Behrens et al., 2012)	8♂; 7♀	4x25 max concentric-eccentric	KE	−40%	-40%	NA	NA
(Brandon et al., 2015)	10♂ elite strength and power athletes	10x5 50-85% squat	KE	-8%§	-17%§	NA	NA
(Buckthorpe et al., 2014)	11♂ untrained	10x5 (3 s) explosive KE	KE	-42%	-26%	-29%	NA
(Cadore et al., 2013)	11♂ national rugby players	100/200/300 hurdle jumps	KE	-12%§	-13%§	NA	NA
(Cadore et al., 2018)	14♀ and 8♂ active	4x20 max concentric or eccentric contractions KF and KE	KE	-24%§	-40%§	NA	NA
(Cerqueira et al., 2019)	13♂ active/very active	Intermittent isometric HG 45%max until time to fatigue	HG	NA	NA	-44%§	-52%
(Conchola et al., 2015)	17♂ resistance-trained	5x8 80%max or 5x16 40%max squat	KE	-18%§	-29%§	-27%§	-21%§
(Drake et al., 2019)	8♂ and 2♀ resistance-trained	8x3 squat	SQUAT	-9%§	-9%§	-1%§	-8%§
(Ereline et al., 2004)	11♂ powerlifters and 14♂ untrained	30 max concentric isokinetic KE	KE	↓	NA	NA	↓
(Ewing Jr and Stull, 1984)	28♀	HG max time to fatigue 40, 60 and 80%max	HG	-31%§	NA	-30%§	-36%§
(Farney et al., 2020)	11♂ trained	3x barbell thruster+ jump squats+ lunge jumps+ forward jumps	MTP	-5%	-4%	NA	NA
(Gordon et al., 2017)	9♂ and 10♂ middle-aged recreationally active adults	8x10 concentric KE - eccentric KF	KE	-29%§	NA	NA	-37%§
(Häkkinen and Myllylä, 1990)	33♂active or endurance or resistance-trained	Bilateral KE until time to exhaustion 60%max	KE	-26%	-33%	NA	NA
(Hatzikotoulas et al., 2014)	10♂ children and 11♂ active	Time to exhaustion PF 100%max	PF	-49%§	↓§	NA	NA
(Jenkins et al., 2014)	18♂	6x10 max eccentric isokinetic FF	FF	-47%	-55%	-60%§	-52%
(Kearney and Stull, 1981)	15♂	Time to fatigue HG ≠loads (40, 60, 80%max)	HG	-40%§	NA	-53%§	-29%§
(King et al., 2012)	13♂ non sedentary and 12♂ non sedentary young olds	max isokinetic PF	PF	-50%§	-10%§	NA	NA
(Linnamo et al., 1998)	8♂ and 8♀ physically fit	5x10 and 5x10 40%10max KE	KE	-17%§	-21%§	NA	NA
(Marshall et al., 2012)	14♂ resistance trained	5x4; 5x4, with 20s inter-set rest intervals; rest-pause method squat	SQUAT	-8%§	-11%§	NA	NA
(Marshall et al., 2015b)	10♂ resistance trained	2x30s KE 80%max + time to exhaustion and 2x60 KE 40%max+ time to exhaustion	KE	↓§	↓§	↓§	NA
(Marshall et al., 2018)	8♂ resistance trained	Full-body resistance-training 3-4 sets x 4-12 reps	KE	-28%	NS	NS§	NA
(Marshall et al., 2020)	8♂ and 8♀ resistance trained	Full-body resistance-training 4x6 ≠ intensities	KE	-11%	NS	NA	NA
(McCaulley et al., 2009)	10♂ strength trained	Squat 4x10 75%max or 11x3 90%max or 8x6 jumps	SQUAT	↓	↓	NA	NA

(Metcalf et al., 2019)	8♂ and 8♀ resistance trained	Pyramidal KE from 60%max to 90%max + time to exhaustion 80%max	KE	-26%§	↓§	↓§	NA
(Minshull and James, 2013)	10♂ recreationally active	3x30s max KE	KE	-12%	NA	-21%	NA
(Moreira et al., 2015)	19♂ professional soccer players	max isokinetic concentric contractions, alternating between KE and KF until time to fatigue	KE KF	-24% -24%	NA	-25%§ -38%§	-24% -35%
(Morel et al., 2015)	11♂ well trained	20x8 isokinetic max KE	KE	+33%	NA	-45%	NA
(Nicholson et al., 2014)	7♂ resistance-trained	4x6 85%max and 4x10 70%max squat	SQUAT	-16%§	NA	-22%§	-21%
(Orssatto et al., 2018)	7♀ and 15♂ young olds	LP and KF 60% and 85%max	KE	-16%§	NA	-26%§	-19%§
(Patrizio et al., 2018)	10♂ trained	Full-body resistance-training exercises 3x8 80%max	KE	-9%	NA	NA	-8%
(Power et al., 2013)	8♂ and 8♀ recreationally active	5x30 eccentric isokinetic DF	DF	-28%§	-22%§	NA	NA
(Storey et al., 2012)	13♂ and 3♀ weightlifters and 13♂ and 3♀ resistance-trained	10 front squat 90%max	FSQT	-16%§	NS§	NS§	NS§
(Strojnik and Komi, 2000)	12♂ active	Sledge jumps 60% of max height time to exhaustion	KE	-18%	-38%	NA	NA
(Váczi et al., 2013)	8♂ active	Two protocols: 10x10 one-leg stair-jump and level jump	KE	-7%§	NA	-25%§	NA
(Valkeinen et al., 2002)	29♂ and 28♀ inactive or moderately active	NE and NF – time to exhaustion 60%max	NE NF	-15%§	-17%§	NA	NA
(Vila-Chã et al., 2012)	10♂ adults	4x25 max eccentric KE	KE	-14%	-14%	NA	NA
(Wallace et al., 2016)	10♂ olds recreationally active and 10♂ active	2x25 PF 20%max	PF	-23%§	-37%§	NA	NA
(Zhou, 1996)	7♂ and 4♀ physical education students	25 isometric KE max	KE	-57%	-56%	NA	NA
(Zhou et al., 1998)	4♂ and 3♀	25 isometric KE max	KE	-55%	-53%	NA	NA
GRAND MEAN				**-23%**	**-30%**	**-28%**	**-25%**
ST.DEV.				**18%**	**19%**	**17%**	**16%**

Table 5. Study characteristics and pre-to-post fatigue percent declines of selected variables induced by strength exercises. If not specified, subjects are considered adults. DF, dorsiflexion; FF, forearm flexion; FSQT, front squat; HG, handgrip; KE, knee extension; KF, knee flexion; MTP, mid-thigh pull; MVF, maximal voluntary force; NA, not available; NE, neck extension; NF, neck flexion; NS, not significant; PF, plantar flexion; RFD, rate of force development; SE, shoulder elevation;↓ or ↑, the authors reported a decrease or increase without reporting an unequivocal value; §, mean of values when merging arms of the study.

References	Subjects	Fatiguing exercise	Test task	MVF decline	Peak RFD decline	Early RFD decline	Late RFD decline
(Bassan et al., 2016)	15♂ swimmers	Time to exhaustion swimming	EF EE	-16% -10%	-18% -9%	NA	NA
(Boccia et al., 2017)	14♂ amateur runners	Half-marathon	KE	-22%	-24%	-33%§	-27%
(Boccia et al., 2017)	16♂ well trained XC skiers	56km cross-country skiing	KE EE	-13% -6%	-11% -26%	-18%§ -22%§	-10%§ -8%§
(Boccia et al., 2018b)	23♂ runners	Half-marathon	KE	-21%	-19%	NA	NA
(Boccia et al., 2018c)	11♂ and 10♀amateur runners	Half-marathon	KE	-11%§	-15%§	NA	NA
(Conceição et al., 2014)	13♂ active	6x8 75%max squat or 6x8 counter movement jump+ cycling time to exhaustion 2nd ventilatory threshold	LL	-16%§	-21%§	NA	NA
(Dorneles et al., 2020)	22♂ and 2♀	30min walking	HF	-4%	NA	-15%§	-11%
(Girard et al., 2013)	12♂ active	10x6s all out + 5x6s cycling sprints	KE	-12%	NA	-29%§	-16%
(Girard et al., 2014)	12♂ tennis players	≈2h tennis in hot and cool condition	KE PF	-16%§ -12%§	-16%§ -1%§	NA	NA
(Girard et al., 2015)	17♂ elite soccer players	Soccer match in hot and cool condition	PF	-6%§	-13%§	NA	NA
(Girard et al., 2016)	13♂ recreational team sport athletes	8x5-s all-out run sprints	KE	-9%	-5%	-8%	-10%
(Grazioli et al., 2019)	16♂ professional soccer players	Soccer match	KE KF	0% -1%	NA	+22% -16%	+3% -11%
(Greco et al., 2013)	22♂ professional soccer players	Soccer specific intermittent protocol	KE KF	-14% -18%	NA	-14%§ -17%§	NA
(Kelly et al., 2011)	12♂ recreational athletes	1h running at 1st ventilatory threshold+10%, 1% inclined	PF	-17%	NA	NA	-17%
(Krüger et al., 2019)	10♂ physically active	Three cycling protocols: 30s all-out/10min severe intensity/90min moderate intensity	LL	-26%§	↓§	NA	NA
(Lapole et al., 2013)	10♂ volleyball players	10min Volleyball specific circuit	PF	-12%	-18%	NA	NA
(Marshall et al., 2014)	8♂ amateur soccer players	Soccer-specific aerobic field test	KF	-24%	-31%	-67%§	NA
(Oliveira et al., 2013)	8♂ physically active	≈35min running 95% onset of blood lactate accumulation	KE	-4%	NA	-15%	NA
(Penailillo et al., 2015)	10♂	30min eccentric cycling 60% peak power output	KE	-19%	NA	NA	-23%
(Pereira et al., 2018)	119♂ from young adults to olds	30min sit-to-stand or time to exhaustion	LL	-11%§	NA	-14%§	-2%§
(Ravier et al., 2018)	9♂ professional handball players	Handball specific circuit	KE	-19%	NA	-24%	NA

(Rissanen et al., 2020)	27♂ active	Three different protocols with resistance-training or cycling or combined	LP	-16%§	-27%§	NA	NA
(Siegler et al., 2013)	8♂ and 2♀ active	Cycling 120% peak power output for 30 s with 30s recovery periods until time to exhaustion	LL	-27%	-32%	-55%§	-29%
(Taipale and Hakkinen, 2013)	12♂ and 10♀ recreational runners	45min resistance-training circuit + 60min running steady state or viceversa	LP	-16%§	-19%§	NA	NA
(Thorlund et al., 2008)	10♂ elite handball players	Simulated hand-ball match	KE KF	-11% -10%	-21% -21%	-17%§ -2%§	-16% -17%
(Thorlund et al., 2009)	9♂ soccer players	Soccer match play	KE KF	-11% -7%	NA	-7% -7%	-8% -9%
(Zhou et al., 1996)	6♂ untrained	Cycling 4x30s all out	KE	-49%	-62%	NA	NA
GRAND MEAN				**-14%**	**-20%**	**-19%**	**-13%**
ST.DEV.				**9%**	**13%**	**19%**	**8%**

Table 6. Study characteristics and pre-to-post fatigue percent declines of selected variables induced by "other" exercises (endurance, locomotor, sport, combined). If not specified, subjects are considered adults. EE, elbow extension; EF, elbow flexion; HF, hip flexion; KE, knee extension; KF, knee flexion; LL, lower limb; LP, leg press; MVF, maximal voluntary force; NA, not available; PF, plantar flexion; RFD, rate of force development; ↓ or ↑, the authors reported a decrease or increase without reporting an unequivocal value; §, mean of values when merging arms of the stud

3.4.3 Arbitrary Synthesis of Results

On average, the mean percent decline of peak RFD (−25%) was 6% larger compared to MVF (−19%), and this result was observed in 28 out of 41 studies. The greater decline of peak RFD against MVF was consistently observed for both strength exercises (MVF: −23%, peak RFD: −30%) and other exercises (MVF: −14%, peak RFD: −20%). Similarly, the mean percent decline of early RFD (−23%) was 4% larger compared to late RFD (−19%), this result being observed in 13 out of 21 studies and for both strength and other exercises. Of note, percent declines were similar for late RFD and MVF (both −19%), as well as for early RFD and peak RFD (−23 and −25%, respectively).

When fatigue was evaluated with the same task adopted to induce fatigue (50% of the studies), both MVF and peak RFD percent declines (MVF: −27%, peak RFD: −33%) were larger compared to when fatigue was evaluated with a non-specific task (MVF: −15%, peak RFD: −23%), e.g., when knee extension was used to quantify fatigue induced by a locomotor exercise.

3.5 Discussion

In this scoping review, we identified 70 primary studies addressing the acute effect of different types of fatiguing exercises on RFD. Our findings indicate that the classical exercise-induced alteration in MVF was typically accompanied by a decline in RFD, this latter being markedly affected by neuromuscular fatigue. Early phase RFD and peak RFD appeared to be more sensitive to detect neuromuscular fatigue than MVF and late phase RFD. However, the rationale for evaluating RFD in the fatigued state was often lacking and the specificity between test task and fatiguing exercise characteristics was not always respected in the included studies.

3.5.1 Peak RFD vs. MVF

In the presence of an exercise-induced decrease in maximal strength (MVF), an impairment in explosive strength (RFD) should also be expected as the force-time curve is typically shifted to the right under fatigued conditions (Valkeinen et al., 2002). Consequently, it takes longer to produce the same amount of force and the force available at a given time point is lower. Peak RFD, which is calculated as the highest rate of force increase along the force-time curve (steepest slope), is usually the most investigated RFD variable (see also Table 5 and Table 6). On average, peak RFD decreased more than MVF (−25 and −19%, respectively), and most studies reported, at least in one arm of their experiments, a larger decline in peak RFD than in MVF. Therefore, peak RFD was more susceptible to exercise-induced neuromuscular fatigue compared to MVF. Interestingly, it was true even if the between-session reliability of peak RFD—despite being acceptable and better than the other RFD variables—was generally lower compared to MVF (Buckthorpe et al., 2012, Haff et al., 2015). For example, Buckthorpe et al. (2012) reported intraclass correlation coefficients of 0.95, 0.90, and 0.80 for knee extension MVF, peak RFD and early RFD (0–50 ms), respectively. Nevertheless, there were also fatigue studies reporting similar or even smaller changes for peak RFD than for MVF. The large variety of experimental and methodological conditions did not allow to formulate a more specific hypothesis on which fatigue protocols may induce larger declines in RFD compared to MVF.

3.5.2 Early vs. Late RFD

Different mechanisms seem to govern early, and late RFD and their relative contribution may vary throughout the time course of the force-time curve rise (Cossich and Maffiuletti, 2020). Broadly speaking, early RFD is poorly correlated to MVF (Andersen and Aagaard, 2006) and is largely dependent on motor unit recruitment speed and maximal discharge rate (Del Vecchio et al., 2019). On the other hand, late RFD is strongly correlated to MVF and therefore seems to depend more on structural variables such as muscle cross-sectional area and architecture (Andersen et al., 2010, Folland et al., 2014). Therefore, analysing RFD at different time intervals provides the framework for a more articulated understanding of the underlying mechanisms. On average, early RFD decreased more than late RFD (−23 and −19%, respectively) as a result of fatiguing exercise. This may suggest that early contraction phases may be particularly sensitive to identifying neuromuscular fatigue. Of note, the average decline in late RFD was very similar to the one of MVF. This seems to confirm that late RFD would provide similar results than MVF likely because these two variables are highly correlated and share similar physiological determinants (Andersen et al., 2010, Folland et al., 2014). Based on the current data, it can be recommended that including the analysis of early RFD would add meaningful insights to neuromuscular fatigue quantification, while late RFD may be redundant with respect to MVF.

3.5.3 Peak RFD

As already discussed, the most reliable RFD variable is peak RFD (Buckthorpe et al., 2012) and it is also probably the easiest to calculate, as it only requires extracting the maximal value from the first derivative of the force signal. This may explain, for example, why Drake et al. (2019) observed a significant decline of peak RFD after a strength training session but no changes in RFD for different time intervals up to 200 ms. Such higher reliability of peak RFD may help disclosing fatigue-related differences otherwise undetected by time-locked RFD variables. On a side note, peak RFD typically occurs between 30 and 100 ms after contraction onset (Gruber and Gollhofer, 2004), this could explain why fatigue-induced changes in peak RFD are consistent with early RFD changes.

3.5.4 Rationale for RFD and Methodological Considerations

Although RFD is increasingly considered as a relevant index of neuromuscular function (Buckthorpe and Roi, 2017, Maffiuletti et al., 2016), very few fatigue studies were specifically designed to measure RFD as the primary outcome and no rationale was clearly presented for its evaluation. It seems indeed quite contradictory to implement RFD assessments before and after fatiguing exercise induced by non-explosive contractions such as slow resistance exercise or walking. We rather believe that RFD should better be evaluated following fatiguing exercises based on (relatively) rapid contractions. Several methodological details regarding RFD evaluation were not provided in most of the studies included in the present review. These details - reviewed here: (Maffiuletti et al., 2016) include the instructions given to participants, the time window for peak RFD quantification and the eventual length of the moving window, the method adopted to identify contraction onset, and the number of test trials (that is particularly relevant in fatigued conditions). More efforts should be made in future fatigue studies in this direction.

3.5.5 RFD During Recovery

Besides the magnitude of neuromuscular fatigue, recovery time-course can also be influenced by the choice of the outcome. Four studies showed that RFD recovery was slower than MVF after exercise termination (Conchola et al., 2015, Krüger et al., 2019, Viitasalo and Komi, 1981b, Zhou, 1996). For example, Zhou (1996) found that after 25 maximal voluntary contractions, MVF was restored in 10 min but peak RFD did not completely recover even after 20 min. While there were also studies showing similar recovery profiles between RFD and

MVF (Linnamo et al., 1998, Marshall et al., 2012), there was an overall trend for longer-lasting exercise-induced declines of RFD as compared to MVF. If future studies would confirm this observation, it would make RFD a promising indirect marker of post-exercise recovery kinetics. As low-frequency fatigue is suspected to be one of the neuromuscular impairments lasting for longer after exercise termination (Jones, 1996), this may suggest that the more protracted RFD depression may be linked to low-frequency fatigue (Krüger et al., 2019), such as in the presence of eccentric-induced muscle damage. Interestingly, both early and late RFD have been found to be more affected than MVF following 60 eccentric contractions (Jenkins et al., 2014) and 30 min of eccentric cycling (Penailillo et al., 2015). This would potentially indicate that RFD may be more sensitive than MVF to muscle damage induced by eccentric contractions. However, it is still unclear which time interval would be more suitable to consider.

3.5.6 Test Specificity

The similarity between the test and the fatiguing exercise in terms of task and contraction characteristics is crucial. When the task adopted to quantify fatigue was similar to the task adopted to induce fatigue in the studies we considered, the decline in peak RFD was on average 33 vs. 23% when fatigue was evaluated with a non-specific task. Neuromuscular fatigue induced by locomotor activities or multi-joint resistance exercises was often quantified using single-joint tasks, such as the universally employed knee extension. This was done in the hope that the single-joint task may provide a surrogate measure of fatigue occurring in the multi-joint task. While being the easiest and fastest way to evaluate RFD, this approach inevitably minimizes the magnitude of fatigue and left rooms of unknown. In an attempt to increase the external validity of measuring RFD in fatigued conditions, we recommend that the test task should be as specific as possible to the fatiguing task, as done for example by Marshall et al. (2012) and Drake et al. (2019).

3.5.7 Limitations

This review has some limitations. We did not perform a meta-analysis of percent decline data because the study design and calculating/reporting of RFD were too disparate in the included studies. Furthermore, many studies did not fully report the basic data (e.g., mean and standard deviation of pre- and post-tests), and these data were still unavailable even after having contacted the corresponding authors. When the percent decline was lacking, we calculated it based on averaged group estimates, and this may have induced inconsistencies among studies. As most studies investigated the knee extensor muscles, it is unclear if the present results may be extended with confidence to other muscle groups. As only 14.5% of participants were women, the main findings of the present review are probably more meaningful for men, even though the studies that investigated gender differences found similar percent declines between men and women (Marshall et al., 2020, Lanning et al., 2017, Linnamo et al., 1998, Valkeinen et al., 2002, Boccia et al., 2018c). Finally, due to the already-discussed heterogeneity across studies, the relative effect of age and training status could not be examined, and no attempt was made to discuss the main results in relation with the origin of neuromuscular fatigue (central vs. peripheral).

3.6 Conclusions

We conclude by suggesting that RFD is a valid indicator of neuromuscular fatigue. More specifically, we demonstrated that peak RFD may be more susceptible to exercise-induced fatigue compared to the classical MVF, and the analysis of early RFD might provide more useful information than late RFD.

Chapter 4 - Repeated purely explosive contractions induce central fatigue

4.1 Abstract

The neural drive to the muscle is the primary determinant of the rate of force development (RFD) in the first 50 ms of an explosive contraction. However, it is still unproven if repetitive explosive contractions specifically induce central fatigue, thus impairing the net neural drive.

To isolate the fatiguing effect of contraction explosiveness, 17 young volunteers performed 100 purely explosive isometric contractions (i.e. brief force pulses without holding phase) of the knee extensors. The response to electrically evoked single and octet femoral nerve stimulation was measured together with high-density surface electromyography (HDsEMG) from the vastus lateralis and medialis muscles. Root mean square (RMS) and muscle fiber conduction velocity (MFCV) were normalised to M-wave peak-to-peak amplitude and MFCV, respectively, to compensate for peripheral properties changes.

We found a decrease in early RFD ($d = 0.56$, $P < 0.001$) and an increase in time to peak force ($d = 0.90$, $P < 0.001$) and time to peak RFD ($d = 0.56$, $P = 0.034$). While we did not find clear signs of peripheral fatigue, there was a substantial decrease in neural efficacy, i.e. voluntary/octet force ratio ($d = 1.50$, $P < 0.001$). Relative RMS ($d = 1.1$, $P = 0.006$) and MFCV ($d = 0.53$, $P = 0.007$) also decreased.

We isolated the fatiguing impact of contraction explosiveness, and we found that the high level of neural drive required to repeat purely explosive contractions resulted in central fatigue that caused a slowing in voluntary force production.

4.2 Introduction

Human locomotion is generated by a coordinated succession of impulsive (burst-like) excitation of muscle groups (Sartori et al., 2013). The activation profiles are brief (i.e. around 200 ms or less) Gaussian-shaped curves (Ivanenko et al., 2006, Gizzi et al., 2011). Most sports are based on short rapid contractions, including shot put (Zaras et al., 2016), vertical jumps (McLellan et al., 2011), sprint kayaking (Lum and Aziz, 2020), sprint cycling (Stone et al., 2004, Connolly et al., 2022), sprint running (Tomazin et al., 2012) and also endurance running (Lieberman et al., 2010). Previous studies adopted explosive/ballistic burst-like contractions under isometric conditions to mimic such muscle excitation in laboratory settings. The isometric protocols based on such purely explosive contractions (i.e. without any holding phase) have been proven to be sensitive to neuromuscular training (Bellumori et al., 2017), ageing (Bellumori et al., 2013, Klass et al., 2008), neuromotor pathologies (Uygur et al., 2022), and muscle asymmetries (Boccia et al., 2018a). However, when it came to studying the fatiguing effect of such a natural way of muscle contraction the laboratory adaptation somewhat lacked of specificity.

Because explosive contractions are considered relevant in real-life conditions (Maffiuletti 2016), some studies adopted explosive contractions to induce fatigue and study the underlying mechanisms (Viitasalo and Komi, 1981b, Buckthorpe et al., 2014, Hannah et al., 2012). However, those protocols adopted a series of short muscle contractions constituted by a first phase of explosiveness phases followed by a holding phase of 1 to 3 s (Viitasalo and Komi, 1981b, Buckthorpe et al., 2014, Hannah et al., 2012). While being valuable attempts, those studies couldn’t distinguish the peculiar way the rapidity/explosiveness induces fatigue. Indeed, while the explosive phase of a contraction lasts 200 ms maximum, adding even just 1 s of holding phase makes most of the contraction a holding maximum contraction (200 ms of explosive phase vs 1 s of holding phase). Therefore the fatigue induced by those protocols are mostly dependent on the holding than the explosive phase. The neuromuscular mechanisms underlying explosive and plateau phases of contraction are critically different. Therefore so far we don’t know the fatiguing effect of the contraction explosiveness *per se* beyond the influence of any holding phase. Even more important, it is unknown what physiological mechanisms are involved in the generation of fatigue induced by explosiveness.

When analysing the specific effect of neuromuscular on contraction explosiveness, previous studies compared the decrement between maximal voluntary force (MVF) and rate of force development (RFD) which is ascending part of the force-time curve of an explosive contraction (for a review see D’Emanuele et al., 2022). For example, Viitasalo and Komi (1981a) found that 100 explosive contractions lasting 3 s of the knee extensor muscles decreased RFD more than MVF (36% vs 24%, respectively). The greater decrement of RFD compared to MVF was explained by the fact that the explosive phase specifically impaired the RFD. Buckthorpe reported that 50 voluntary maximal explosive contractions lasting 3 s exerted a more pronounced effect on RFD (47 – 52%) than on MVF (42%). They also measured the neural efficacy in the first 50 ms of contraction, which is the ratio between voluntary and electrically evoked octects (eight stimuli at 300 Hz; (de Ruiter et al., 1999, de Ruiter et al., 2007)). The 34% decrease in neural efficacy has been interpreted as a sign that repeated explosive contractions caused central fatigue. However, the fatiguing effect of the protocols mentioned above can be attributed to explosive contractions only in a minimal portion because most of the fatiguing effect was induced by holding the maximal contraction for 1 to 3 s.

In the present study, we adopted a set of 100 purely explosive contractions (pulses) without any holding phase to specifically address the fatiguing effect of contraction explosiveness. Of note, when the rising phase of the excitation is highest (i.e. in the first 50 – 100 ms of contraction), the actual force production is still relatively low. In such a way, we avoided any influence of maximal force production (holding phase) on fatigue and isolated the effect of explosiveness. We hypothesised that repeated purely explosive contractions mainly cause a decrease in RFD compared to MVF. Furthermore, as the force production in the first 50 ms of contraction is primarily dependent on neural excitation, we hypothesised that repeated purely explosive contractions mostly induced a decrement in the net neural drive (central fatigue).

4.3 Methods

4.3.1 Overview

Participants visited the laboratory once for ≈60 min. First they performed a warm-up and familiarisation session with real-time visual feedback, which continued until the subject was able to perform the required explosive task. Then they executed the fatiguing task including 100 purely explosive voluntary contractions of the knee extensors. The session involved isometric measurements of voluntary force and electrically evoked (twitch and octets) contractions of the right knee extensors before and immediately after the fatiguing task.

4.3.2 Participants

Seventeen healthy adults (mean ± SD: 26 ± 2 years; 170 ± 7 cm; 70 ± 9 kg) of similar low to-moderate levels of habitual physical activity were recruited for the study. None had any previous history of neuromuscular disorders. All the participants were informed about the testing procedure and provided written informed consent prior to their participation in this study, which was approved by the Ethical Advisory Committee (University of Torino – approval no: 510190) and performed in accordance with the Helsinki Declaration. Participants were instructed to avoid strenuous exercise for 24h and caffeine for 6h before their visit to the laboratory.

4.3.3 Force Measurements

Participants were seated and firmly secured with a seat belt on a custom-made chair that allowed the assessment of isometric force for the right knee extensors (D'Emanuele et al., 2022). The participants' knee and hip were flexed at 90° from full extension. An ankle strap was placed 2 cm above the malleolus consistent with the strain gauge load cell (546QD- 220 kg; DSEurope, Milan, Italy) positioned perpendicular to the tibial alignment. To avoid pain and maintain stiffness during the contractions it was placed between the thrust surface and the tibia a standard hard shin protector as used during soccer (de Ruiter et al., 2007).

The analog force signal was amplified and sampled at 2048 Hz with an external analog-to-digital (A/D) converter (QUATTROCENTO; OT Bioelettronica, Turin, Italy) and the data were recorded the data with the software OTBioLab+ (OT Bioelettronica, Turin, Italy). The force signal was displayed for visual feedback during the tests.

4.3.4 Electrically evoked twitch and octet contractions

The femoral nerve was electrically stimulated (via a constant-current, variable-voltage stimulator; DS7AH; Digitimer Ltd, Welwyn Garden City, UK) with square-wave pulses (0.2 ms in duration) (Giroux et al., 2018) with maximal voltage of 400V to elicit either single-twitch contractions or octet contractions (eight pulses at 300 Hz) to determine the maximal capacity of the muscle–tendon unit for explosive force production (de Ruiter et al., 2004). The anode (50 x 90 mm) was placed over the greater trochanter and the cathode (Ø = 32 mm) was placed within the femoral triangle, above the femoral nerve. During all stimulations, the experimenter pressed with his hand on the anode to bring it closer to the cathode to obtain a better response to the stimulation.

A series of incremental (starting from 20mA and increasing by 20mA at each step) single or octet stimuli were delivered until there was a plateau in the M-Wave amplitude response, which was visually evaluated. After the ramps to find the optimum intensity for both twitch and octets, the stimulation intensity (range: 120–400 mA) was then increased by 20% to reach a supramaximal stimulus (Folland et al., 2014). Two single twitches and two octet contractions, interspersed by 5 s, were delivered pre and immediately post (≈4s) the fatiguing task.

4.3.5 High-Density surface Electromyography

Two bidimensional HDsEMG matrices of 64 electrodes each (13 rows x 5 columns, 8 mm inter-electrode distance, gold-coated; model: GR08MM1305, OT Bioelettronica, Turin, Italy) were placed over the right limb. The first was placed over vastus lateralis (VA) and the second over the vastus medialis (VM). Two more pairs of electrodes were placed over the muscle belly on the biceps femoris and semitendinosus in accordance with the SENIAM guidelines (Hermens et al., 2000). The reference electrode (24 mm, model: CDE-S. OT Bioelettronica, Turin, Italy) was placed on the patella of the same limb. Before the array application, the skin was prepared removing any body hair, slightly abraded with abrasive paste, and finally cleaned with water (Merletti and Muceli, 2019).

To ensure proper electrode-skin contact, the electrode cavities of the matrices were filled with 20–30 lL of conductive paste (Spes-Medica, Battipaglia, Italy). The electrode arrays were fixed with an extensible dressing. The EMG signals were amplified (gain 150), sampled at 2048 Hz, bandpass filtered (3-dB bandwidth, 20–450 Hz, 12 dB/oct slope on each side) and converted to digital data with a 16-bit A/D converter (QUATTROCENTO; OT Bioelettronica, Turin, Italy). Signals, in single-differential configuration, were visualised during acquisition and then stored on a personal computer using OT BioLab+ software version 1.5.5.0 (OT Bioelettronica, Turin, Italy) for further analysis.

4.3.6 Protocol

Following skin preparation, matrices and electrodes placement and chair setting, the volunteers performed an isometric warm-up which consisted of four contractions at 50%, four at ~75%, and one submaximal ~90% contraction of their perceived MVF. The last contraction was recorded to allow to set up real time visual feedback on a computer screen and proceed with task familiarisation. Familiarisation continued until the participant was able to perform five consecutives purely explosive contractions without countermovement and/or holding phase (Figure 15A). Next, through an electrically evoked twitch and octets we determined the maximal M-Wave response and maximal evoked explosive contraction (Figure 15B).

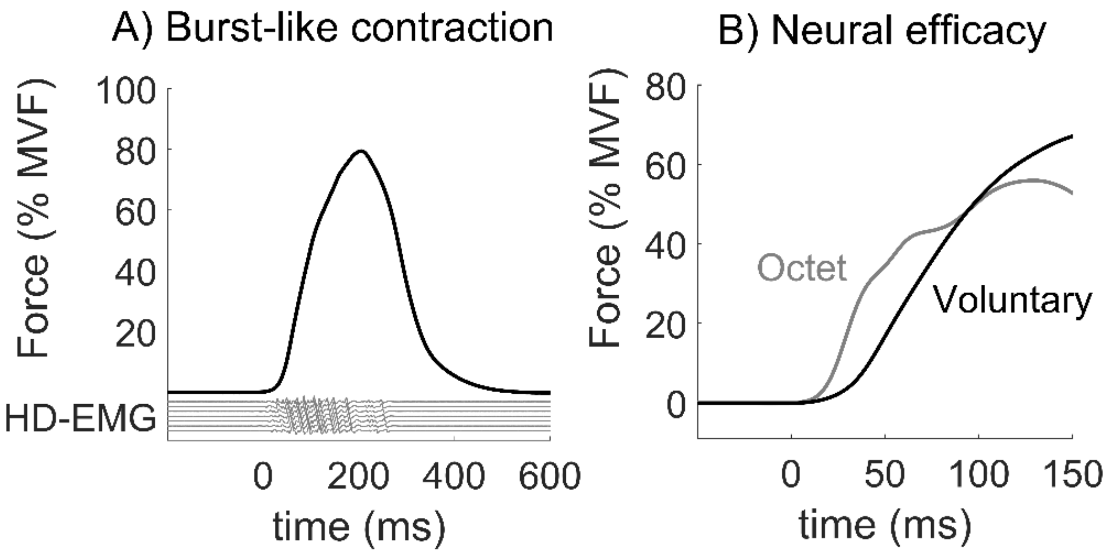

Figure 15. A) Representative example of the force and High-Density EMG (HDsEMG) signals recorded during one of the purely explosive, Gaussian-shaped contractions. The contraction is a brief pulse characterised by the fact that the active phase lasts ≈200 ms, and there is no holding phase. From HDsEMG the average action potential velocity propagation was normalised to the M-wave propagation velocity (here not shown). B) Representative example of the first 150 ms of voluntary (black) and electrically evoked octet (grey) force signals. The Neural efficacy has been calculated as the ratio between the evoked and voluntary at 50 ms from contraction onset. MVF, maximal voluntary force.

To assess MVF, two 5-s maximal voluntary contractions were performed interspersed by 2 min of rest. Standardised verbal encouragements were provided to the participants during the execution of maximal contractions. After that, subjects received two single stimulations and two octets interspaced by 5 s.

The fatiguing protocol comprised 100 maximal purely explosive contractions each lasting ≈200 ms and separated by 2 s of rest with a visual rhythmic cadence feedback on a screen (Figure 16). The participants were encouraged to “push fast and hard as possible” (Sahaly et al., 2001), to reach at least 70% of their MVF, and to relax quickly after each pulse. Throughout the protocol, the subjects were encouraged with strong verbal feedback to avoid loss of attention and to encourage to give their best in the “fastest and strongest” way possible and demanded to avoid countermovement or pre-tension. Immediately after the fatiguing protocol (which lasted 5 min) subjects received two octets, and two single twitches and concluded with a 5-s maximal voluntary contraction.

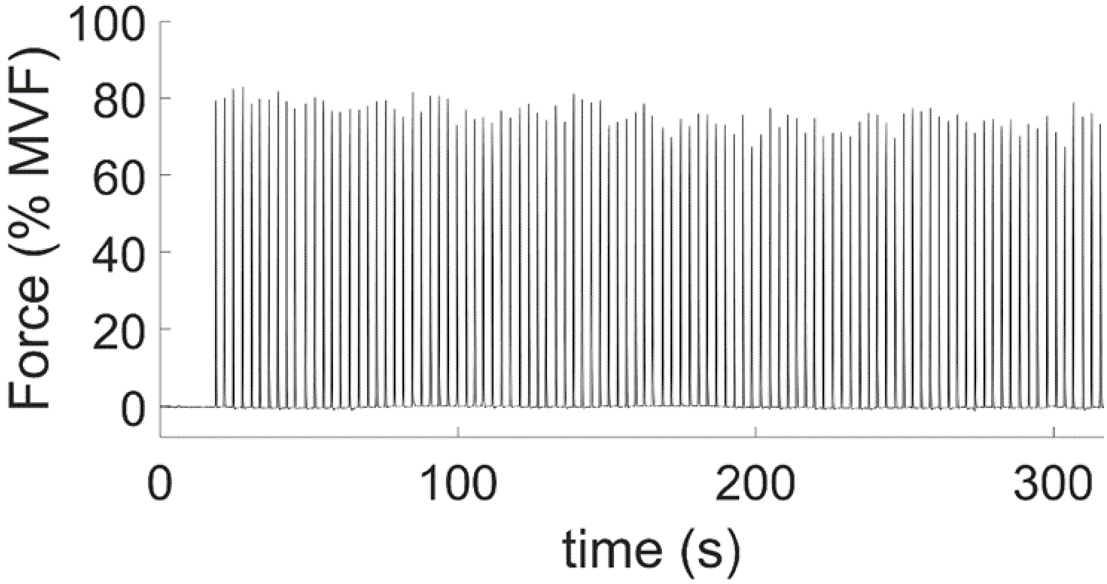

Figure 16. Representative example of the fatiguing protocol composed of 100 purely explosive contractions. As can be seen the peak force reached in each contraction was kept around the 70 – 80 % of maximal voluntary force (MVF).

4.4 Data Analysis

4.4.1 Force signals

The force signals were low-pass-filtered at 50 Hz using a fourth zero-lag Butterworth. MVF was defined as the highest force over the two maximal voluntary contractions. RFD (ΔForce/ΔTime) were measured at 50, 100, 150 ms and peak from onset (defined as RFD_{50}, RFD_{100}, RFD_{150} and RFD_{peak}). The time to peak force, time to peak RFD, and the rate of force relaxation (RFR) were also measured. The onset was visually selected (Tillin et al., 2010) by the same researcher through a hand-customised MATLAB code both for voluntary and evoked contractions. In case some contraction presented countermovement, it was removed and not counted.

4.4.2 High-Density surface Electromyography

The sEMG signals were band-pass filtered at 30-450 Hz using a fourth-order zero-lag Butterworth filter prior to analysis. After removing bad channels with excessive noise or artefacts through visual analysis, the onset of each EMG signal of each contraction was assessed visually (Crotty et al., 2021) by the same researcher through a hand-customised MATLAB code. The amplitude of sEMG signals was assessed as the RMS across all available channels, divided by the M-wave amplitude assessed through single twitch calculated over the same electrodes. RMS was then averaged across VL and VM channels to obtain a single value at 50, 100, 150 ms and from EMG onset (defined as RMS_{50}, RMS_{100}, RMS_{150}).

MFCV was assessed using an algorithm that allows the estimation of conduction velocity from multichannel EMG signals in explosive burst-like contractions (Pozzo et al., 2004) from VM and VL, and then averaged, at 50, 100 and 150 from EMG onset (defined as $MFCV_{50}$, $MFCV_{100}$, $MFCV_{150}$). Then, MFCV was normalised to the M-wave conduction velocity (defined as $MFCV_{rel\_50}$, $MFCV_{rel\_100}$, $MFCV_{rel\_150}$).

The time between the earliest EMG onset and the onset of force was determined as the maximal electromechanical delay (EMD).

4.4.3 Statistical analysis

The first (PRE) and the last (POST) 10 contractions were compared for the analysis of fatigue. To calculate the most stable indices, the 10 estimates of each parameter were averaged after having removed the highest and the lowest values. The two repetitions of electrically evoked contractions were averaged. Then, a series of repeated measure ANOVA were performed to detect the changes in mechanical and EMG parameters calculated over three temporal periods (50, 100, 150 ms) and two times (PRE, POST). The other parameters were analysed with paired Student' T-test.

Kolmogorov–Smirnov normality test was used to assess distributions normality. If the data were not normally distributed, they were log-transformed before statistical analysis. Paired, two-tailed Student' *t*-tests were used to compare the other parameters between PRE vs. POST. The level of statistical significance was set to $P < 0.05$. Differences between PRE vs. POST were reported in absolute and percent values, the precision of estimates for absolute values was indicated with 90% confidence interval (CI). The magnitude of the difference between PRE vs. POST was calculated as Cohen's *d* effect size with 95% Confidence Interval (CI). Threshold values for effect size statistics were: <0.2, trivial; >0.2, small; >0.5, moderate; >0.8 large; >1.4, very large.

4.5 Results

The descriptive statistics and effect size differences with 95% CI between PRE and POST are reported in Table 7

	Time interval (ms)	PRE	POST	Cohen's d (95% Confidence Intervals)
RFD_{peak} (N/s)		9684 ± 2062	8969 ± 1914	-0.886 (-1.441, -0.312)
Time to peak RFD (ms)		55 ± 13	60 ± 21	0.561 (0.040, 1.066)
Time to peak force (ms)		178 ± 29	198 ± 33	0.900 (0.323, 1.458)
RFD (N/s)	50	3243 ± 1000	2664 ± 1071	-0.569 (-1.016, -0.123)
	100	4688 ± 939	4270 ± 1171	-0.411 (-0.797, -0.025)
	150	3956 ± 911	3807 ± 990	-0.147 (-0.465, 0.171)
Normalized RMS	50	0.036 ± 0.013	0.027 ± 0.012	-1.127 (-2.241, -0.013)
	100	0.059 ± 0.009	0.045 ± 0.008	-1.436 (-2.651, -0.220)
	150	0.059 ± 0.011	0.048 ± 0.009	-1.233 (-2.380, -0.086)
Relative MFCV	50	1.053 ± 0.06	1.015 ± 0.06	-0.537 (-1.092, -0.017)
	100	1.097 ± 0.07	1.049 ± 0.07	-0.678 (-1.28, -0.076)
	150	1.162 ± 0.09	1.11 ± 0.08	-0.717 (-1.334, -0.101)
Absolute MFCV (m/s)	50	4.65 ± 0.62	4.8 ± 0.65	0.203 (0.001, 0.405)
	100	4.80 ± 0.73	4.96 ± 0.72	0.219 (0.010, 0.428)
	150	5.14 ± 0.85	5.26 ± 0.91	0.164 (0.353, 0.026)
M-wave CV (m/s)		4.43 ± 0.63	4.75 ± 0.75	1.751 (0.980, 2.477)
M-wave amplitude (µV)		4.01 ± 0.95	4.34 ± 1.03	0.775 (0.229, 1.315)
RFD Octet (N/s)	50	5657 ± 1330	5916 ± 1413	0.628 (0.098, 1.142)
Octet peak force (N)		4235 ± 1232	4165 ± 1175	-1.099 (-1.696, -0.482)
Neural Efficacy	50	59.5 ± 21.8	46.5 ± 21.3	-1.535 (-2.233, -0.814)
MVF (N)		831 ± 178	783 ± 168	-0.784 (-1.321, -0.228)
RFR (N/s)		6071 ± 1620	5541 ± 1726	-0.602 (-1.112, -0.076)

Table 7. Descriptive statistics and effect size differences with 95% CI between PRE and POST

4.5.1 Voluntary force

The peak force reached in the explosive contractions did not vary with time ($P = 0.753$), meaning participants maintained the capacity of reaching around 70% of MVF.

The cumulative RFD showed a time × interval interaction $F(2,32) = 9.7$, $P < 0.001$, $\mu^2 = 0.379$. Indeed, RFD_{50} showed a moderate decrement ($d = 0.56$, $P < 0.001$), RFD_{100} showed a small decrement ($d = 0.41$, $P < 0.001$) with fatigue, while RFD_{150} remained stable ($d = 0.14$, $P = 0.266$).

Both MVF ($d = 0.78$, $P = 0.005$) and RFD_{peak} largely decreased with fatigue ($d = 0.88$, $P = 0.002$). In addition, time to peak force largely decreased ($d = 0.90$, $P < 0.001$) and time to peak RFD moderately increased with fatigue ($d = 0.56$, $P = 0.034$).

4.5.2 EMG in voluntary contractions

Relative ARV decreased with fatigue ($F(1,16) = 20.0$, $P < 0.001$, $\mu^2 = 0.556$) without any time × interval interaction ($F(2,32) = 1.5$, $P = 0.227$, $\mu^2 = 0.089$). In particular, ARV_{50} (d

= 1.1, P = 0.006), ARV_{100} (d = 1.4, P = 0.001), and ARV_{150} (d = 1.2, P = 0.003) decreased with similar very large effect size.

Absolute MFCV increased with fatigue ($F(1,16) = 21.1$, $P < 0.001$, $\mu^2 = 0.569$) without any time × interval interaction ($F(2,32) = 1.0$, $P = 0.346$, $\mu^2 = 0.064$). In particular, $MFCV_{50}$ (d = 0.20, P = 0.004), $MFCV_{100}$ (d = 0.21, P = 0.002), and $MFCV_{150}$ (d = 0.16, P = 0.033) increased with similar small effect size. Conversely, relative MFCV decreased with fatigue ($F(1,16) = 28.3$, $P < 0.001$, $\mu^2 = 0.639$) without any time × interval interaction ($F(2,32) = 0.9$, $P = 0.397$, $\mu^2 = 0.056$). Indeed, $MFCV_{50}$ (d = 0.53, P = 0.007), $MFCV_{100}$ (d = 0.67, P < 0.001), and $MFCV_{150}$ (d = 0.71, P < 0.001) decreased with similar moderate effect size.

4.5.3 Evoked contractions

Octet RFD increased with time (d = 0.62, P = 0.020), while octet peak force decreased with time (d = 1.0, P < 0.001). Neural efficacy largely decreased with fatigue (d = 1.5, P < 0.001). The rate of force relaxation moderately decreased (d = 0.60, P = 0.025).

MFCV of M-wave (d = 0.44, P < 0.001) and peak-to-peak amplitude of M-Wave showed a small increase with time (d = 0.31, P < 0.001).

Stimulated EMD moderately increased with time (d = 0.71, P = 0.009) while voluntary EMD moderately decreased with time (d = 0.69; P = 0.011).

4.6 Discussion

To isolate the fatiguing effect of contraction explosiveness, we adopted a protocol constituted by 100 purely explosive contractions, i.e. brief force pulses without any holding phase. We found an overall slowing in voluntary force production evidenced by a decrease in RFD_{peak}, and an increase in time to peak force and time to peak RFD. Early RFD (0-50 ms) showed the largest decline in the time-locked analysis compared to late RFD (100 ms). While we did not find any clear sign of peripheral fatigue, there was a very large decrease in neural efficacy, meaning that the protocol induced substantial central fatigue.

The nervous system can produce explosive muscle contraction by compressing the motor unit recruitment and abruptly increasing the discharge rate (Del Vecchio, 2023). These mechanisms are associated with the neural drive to the muscle, which is the primary determinant of RFD (Del Vecchio et al., 2019). As the activation of the central nervous system is crucial in performing explosive contractions, it is possible to hypothesise that repeated explosive contractions would induce central fatigue by decreasing the net neural drive to the muscles. Previous studies failed to isolate the role of contraction explosiveness on neuromuscular fatigue even when they adopted explosive muscle contractions. By adopting contractions longer than ≈200 ms they included the production of high force levels as a confounding factor. Producing high muscle force levels is known to induce peripheral fatigue (Carroll et al., 2017, Taylor and Gandevia, 2008). Therefore, the concurrent central and peripheral fatigue found in previous studies is likely the combined effect of explosiveness and a high level of force production. To isolate the impact of explosiveness, we required participants to perform purely explosive contractions, i.e. brief and fast pulses (targeting around 70% of MVF to assure maximal explosiveness (Folland et al., 2014), without holding the maximal contraction (Figure 15). As such, participants concentrated on performing the early explosive phase of contractions, activated their muscles for a short duration (200 ms), and never produced forces higher than 70 – 80 % of MVF. Moreover, the such motor task is somewhat ecological because it reflects the muscle activation profiles of locomotion (Ivanenko et al., 2006, Gizzi et al., 2011).

We found a fatigue-induced shifting of the force-time curve towards the right resulting in a wider Gaussian-shaped force curve (Figure 17). Indeed, the time to peak force (d = 0.90) and the time to peak RFD (d = 0.56) shifted towards the right, and those changes were accompanied by a large decrease in RFD_{peak} (d = 0.88). Fatigue slowed the voluntary force production even when the force target could already be reached, as the peak force of each pulse did not change throughout the 100 contractions. The slowing in voluntary force production due to repetitive explosive contractions can profoundly affect sports and work-related tasks. As the task adopted here reflects the muscle activation profiles of locomotion (Gizzi et al., 2011, Ivanenko et al., 2006) the present results can be related to what happens under fatigue induced by running/cycling. For example, it can explain why runners increase their foot contact time with fatigue while maintaining their running velocity (Möhler et al., 2021, Möhler et al., 2022).

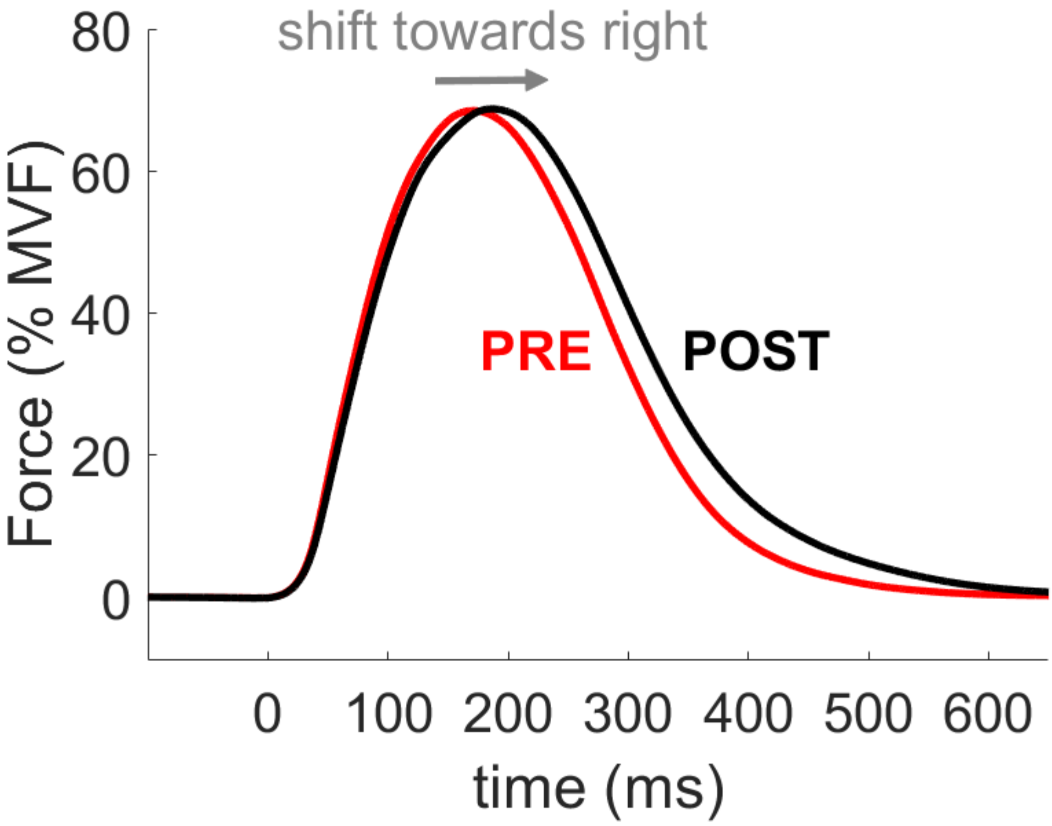

Figure 17. The figure represents the force signals of the average first 10 (PRE) and the average last 10 (POST) burst-like explosive contractions averaged across 17 participants. It can be seen that the force-time curve is shifted towards the right as there was an overall slowing of the voluntary force production.

Performing 100 purely explosive contractions induced a significant amount of central fatigue, as evidenced by the very large decrement (d = 1.50) in neural efficacy. Neural efficacy is the most specific parameter to quantify the voluntary activation in the first 50 ms of contractions(de Ruiter et al., 2004). It is calculated as the ratio between evoked octets and voluntary force at 50 ms from the contraction onsets (Figure 16): its drop showed a decrease in the net neural drive to the muscles at the beginning of the contraction. It is not surprising that repetitive explosive contractions elicit central fatigue as the neural drive is the main determinant of explosive contractions (Del Vecchio, 2023). Central fatigue occurrence could also be found in the significant drop of ARV ($d \approx 1.0$) and MFCV ($d \approx 0.6$) over the first 50 – 100 ms of contractions. To remove the effect of peripheral changes, we normalised each ARV estimate to the corresponding M-wave peak-to-peak amplitude and the MFCV estimate by the M-wave MFCV. As such, those normalised ARV and MFCV estimates can be considered markers of central fatigue and are very robust as they are calculated over numerous (columns of) electrodes.We did not find any clear evidence of peripheral fatigue following 100 explosive contractions. Evoked octets showed an increase at 50 ms and a decrease at 100 ms. Absolute estimates of MFCV also showed an increase after the protocol. This was not surprising as MFCV have already been demonstrated to increase after intermitting contractions in response to altered membrane properties, muscle fibre swelling, and temperature increase (Van der Hoeven and Lange, 1994). Nevertheless, we found a moderate decrease in the rate of force relaxation, which is a sign of peripheral fatigue related to calcium handling in the sarcolemma (Bigland-Ritchie et al., 1983). As mentioned above, peripheral fatigue is typically induced by prolonged high-intensity muscle contractions, while for most of the contraction duration in the present protocol, the force production is not very high and is always lower than 70 – 80% of MVF. We did not find an unequivocal sign of peripheral fatigue and even possible evidence of potentiation induced by intermittent explosive contraction. Therefore, the decrease in RFD, particularly when calculated in the first 50 ms of muscle contraction can only be explained by a decrease in the neural drive.

4.7 Conclusions

In the present study, we first isolated the fatiguing effect of contraction explosiveness without the interference of prolonged maximal force production. Repeating 100 purely explosive contractions induces a slowing in the force production i.e. shifts towards the right in the force-time curve. This slowing was more evident in the first 50 ms of contraction (early RFD) and was mainly due to central fatigue. As the neural drive to the muscles is the primary determinant of early RFD, we can now clearly associate central fatigue induced by repetitive explosive contractions with their high neural drive requirements. Therefore, the high neural drive requirement for repeating explosive contractions resulted in central fatigue

Chapter 5 - Strength Asymmetries Are Muscle-Specific and Metric-Dependent

5.1 Abstract

We investigated if dominance affected upper limbs muscle function, and we calculated the level of agreement in asymmetry direction across various muscle-function metrics of two heterologous muscle groups. We recorded elbow flexors and extensors isometric strength of the dominant and non-dominant limb of 55 healthy adults. Participants performed a series of explosive contractions of maximal and submaximal amplitudes to record three metrics of muscle performance: maximal voluntary force (MVF), rate of force development (RFD_{peak}), and RFD-Scaling Factor (RFD-SF). At the population level, the MVF was the only muscle function that showed a difference between the dominant and non-dominant sides, being on average slightly (3–6%) higher on the non-dominant side. At the individual level, the direction agreement among heterologous muscles was poor for all metrics (Kappa values ≤ 0.15). When considering the homologous muscles, the direction agreement was moderate between MVF and RFD_{peak} (Kappa = 0.37) and low between MVF and RFD-SF (Kappa = 0.01). The asymmetries are muscle-specific and rarely favour the same side across different muscle-performance metrics. At the individual level, no one side is more performative than the other: each limb is favoured depending on muscle group and performance metric. The present findings can be used by practitioners that want to decrease the asymmetry levels as they should prescribe specific exercise training for each muscle.

5.2 Introduction

According to the dynamic dominance models (MacNeilage et al., 2009), the dominant limb might be specialized for controlling movements through predictive mechanisms that are most effective under stable mechanical conditions, while the non-dominant limb might be specialized for impedance control, which imparts stability when mechanical conditions are unpredictable (Sainburg, 2014). Although this model does not mention muscle strength or power as critical factors in dominance differentiation, many studies investigated the effect of limb dominance on such muscle performance.

Handgrip muscles are the only ones that present a clear trend (at least in right-handed individuals) of 8–16% towards a stronger dominant than non-dominant side (Bohannon, 2003). The effects of limb dominance on other strength tests are not as noticeable. In a recent systematic review, including 19 studies (1880 healthy non-athletes subjects), Kotte et al. (Kotte et al., 2018) reported no difference between the dominant and non-dominant side in elbow flexors and extensors. Ditroilo et al. (2010) did not find any difference in maximal voluntary force (MVF) and rate of force development (RFD) between dominant and non-dominant knee extensors in a sample of 152 people of various ages. In sports, two meta-analyses found that lower limb dominance did not influence isometric and dynamic muscle strength (DeLang et al., 2019, McGrath et al., 2016).

The fact that the dominant limb is not stronger or weaker than the non-dominant one at the population level does not imply that one side would be stronger than the contralateral one at the individual level. Regardless of dominance, the interlimb asymmetry varies depending on the test selected, and, thus, the level of asymmetry may strongly depend on tasks (Virgile and Bishop, 2021). Numerous recent studies found that the direction of interlimb asymmetry is rarely consistent across tests (Bishop et al., 2018, Virgile and Bishop, 2021). For example, by comparing the lower limb asymmetry during three jump tests, Bishop et al. (Bishop et al., 2020) found that the levels of agreement across jump tests (considering peak torque and other metrics) were poor. While a metric may favour the dominant limb at an individual level, others may favour the non-dominant one. Those studies reinforce that limb dominance does not represent a strong predictor of strength and quickness produced by a muscle group. However, previous studies investigating the consistency of asymmetry direction focused only on one muscle group/kinetic chain (Bishop et al., 2020). So far, it is unclear if asymmetry direction is consistent among heterologous muscles. Considering the impact of interlimb asymmetry on sports performance (Bishop et al., 2018) it would be essential to understand if, in the presence of an asymmetry, all muscles of one limb are more performative than the contralateral ones.

Measuring the MVF is the most straightforward assessment to detect interlimb strength asymmetry (Nuzzo et al., 2019). Since RFD represents a valid alternative to the classical evaluation of MVF (Maffiuletti et al., 2016), RFD is emerging as a meaningful indicator of interlimb asymmetry (Boccia et al., 2018a, Sarabon et al., 2020). RFD represents the derivative of force with respect to time (Lin et al., 2019) and quantifies a muscle contraction's explosiveness (Maffiuletti et al., 2016). RFD is an important neuromuscular variable in time-constrained activities (Maffiuletti et al., 2016, Lin et al., 2019). Its relevance has been repeatedly demonstrated in sports (Tillin et al., 2013a), ageing (Caserotti et al., 2008), and disease contexts (Rose et al., 2013). The RFD and MVF rely on partially different physiological determinants; for example, MVF is more related to muscle volume (Folland et al., 2014, Andersen et al., 2010), while RFD is more related to the rate of motor unit recruitments (Del Vecchio et al., 2019). For these reasons, MVF and RFD are weakly correlated (Andersen et al., 2010, Del Vecchio et al., 2019), while RFD is more related to the rate of motor unit recruitments (Del Vecchio et al., 2019). For these reasons, MVF and RFD are weakly correlated (Andersen et al., 2010, Del Vecchio et al., 2019), especially when RFD is measured in the early phase of a muscle contraction (Maffiuletti et al., 2016). Nevertheless, RFD and MVF have in common the fact that they are assessed performing maximal-effort contractions. However, not all daily activities and sports gestures are based on maximal-effort contractions. Most actions are likely based on quick contractions of submaximal intensities: for example, walking, running, passing a ball in soccer, or shooting a free shot in basketball. In this context, the adoption of RFD-Scaling Factor (RFD-SF) has emerged as an informative measure to quantify the neuromuscular quickness of submaximal contractions (Bellumori et al., 2011, Bellumori et al., 2013, Corrêa et al., 2020, Djordjevic and Uygur, 2017). Interestingly, RFD-SF is weakly correlated to MVF and also to maximal RFD (Brustio et al., 2019). The interest in this capacity has increased over the last years (Kozinc et al., 2022), and RFD-SF has been widely used to identify interlimb asymmetry (Boccia et al., 2018a, Kozinc and Šarabon, 2020, Smajla et al., 2021a). Together these studies suggest that MVF, RFD, and RFD-SF might provide different and complementary outcomes in the assessment of interlimb asymmetry.

In the present study, we focused on upper limbs (elbow flexors and extensors) because they play a critical role in everyday living and sports context in non-disabled, amputee, and wheelchair users. We firstly aimed to examine if dominance affected muscle function. Secondly, we investigated if muscle function asymmetries are muscle-specific or, conversely, if one side is overall more performative than the other independently of the muscle group. Thirdly, we aimed to investigate if, within each muscle group, asymmetry direction is consistent among various muscle performance metrics (MVF, RFD, and RFD-SF).

To answer the first experimental question, we adopted a linear mixed-effects model analysis, while to answer the second and third experimental questions, we tested the agreement between asymmetry direction among heterologous muscle groups and various performance metrics. We hypothesized that: (1) the dominance did not affect muscle functions (MVF, RFD, and RFD-SF); (2) the asymmetry direction agreement among heterologous muscles (i.e., elbow flexors and extensors) was low; and (3) the asymmetry direction agreement among the metrics adopted (MVF, RFD, and RFD-SF) in homologous muscles was low. Finally, we tested the inter-day repeatability of the custom-made isometric dynamometer adopted in the present study as a secondary objective.

5.3 Methods

5.3.1 Participants

A total of 55 young (31 males and 24 females, mean age = 30 ± 7 years;) physically active healthy individuals (body mass = 70 ± 9 kg, body height = 1.74 ± 0.17 m, body mass index 23.3 ± 1.6) were recruited for the study. Five of them were left-handed. Inclusion criteria were: being adults (≥18 years of age); and being physically active, i.e., participating in moderate-intensity physical activity at least 150 min/week or vigorous-intensity physical activity at least 75 min/week or an equivalent combination of both moderate and vigorous physical activity. Exclusion criteria were: any upper-limb complaints and general illness in the past six months; any clinical evidence of cardiovascular, neuromuscular, or neurological disorders; and participation in any sports that require extensive asymmetric involvement of the upper limbs (such as tennis, badminton, fencing, etc.). All the participants were informed about the testing procedure and provided their written informed consent before participation in the experiments. Participants were instructed to refrain from performing strenuous physical exercise and consuming caffeine 24 h before the experimental session and completed a socio-demographic questionnaire before the experimental sessions. The study was approved by the

Ethical Committee (University of Torino—approval no: 510190) and performed in accordance with the Helsinki Declaration.

5.3.2 Experimental Setup

A picture of the experimental setup is reported in Figure 18A. During the testing, participants were comfortably seated on a bench (seat height = 44 cm) with the left or right upper arm vertically and slightly abducted from the trunk (~15° degree). Each participant's elbow was flexed at 90° from full extension. Furthermore, the elbow leaned over adjustable support to avoid the force exerted with the shoulder and trunk would transmit through the force sensor. The hand and forearm were oriented in a neutral position. The wrist was aligned with custom-built telescopic support (see Figure 18A) and fixed with nonelastic straps to the arm. The custom-built support was rigidly connected to a strain gauge load cell (Model TF 022, cct transducers, Torino, Italy) to record compression/extension forces. Real-time visual feedback of elbow flexor/extensor forces was provided on a computer screen (size screen 48 cm × 27 cm). The force signals were sampled at 100 Hz and converted to digital data with a 16-bit A/D converter (Forza, OT Bioelettronica, Turin, Italy).

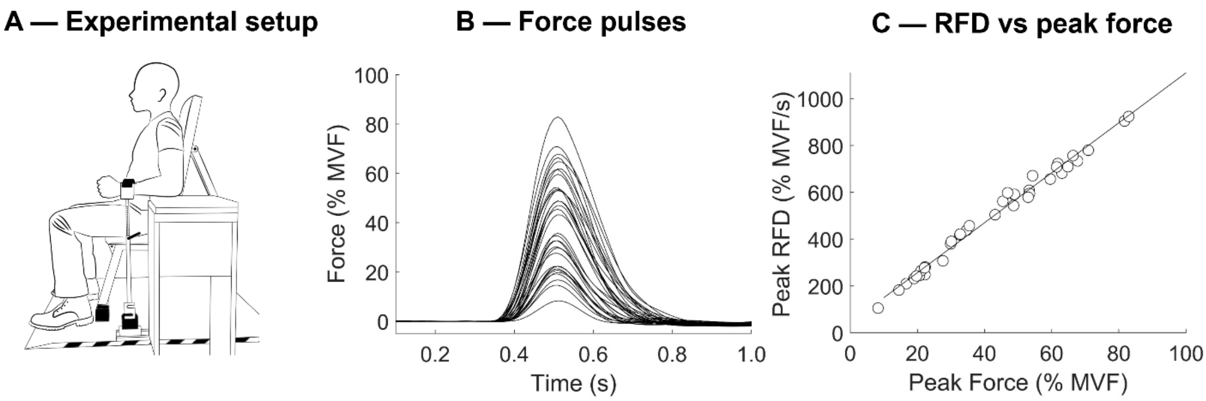

*Figure 18. (**A**) The experimental setup adopted to test the elbow flexors and extensors. The arm was maintained in a neutral position. The load cell, which was rigidly attached to the height-adjustable support, allowed mechanical recording in both traction and compression. (**B**) Traces recorded during the execution of the RFD-SF (rate of force development scaling factor) protocol for a representative participant. Left panel: superimposed force traces are reported for each rapid muscle contraction executed at various submaximal amplitudes compared to the maximal voluntary force (MVF). (**C**) Scatterplot representing the peak force and peak RFD of each muscle contraction reported in the right panel. The slope of the linear regression represents the RFD-SF.*

5.3.3 Procedure

All participants completed one experimental session during which the muscle-function assessment was performed for elbow flexion and extension of the dominant and non-dominant limb in randomized, counterbalanced order. The experimental protocol was re-administered to a sub-sample of 15 participants to check its test–retest reliability. The experimenters placed particular attention on avoiding torso and shoulder movement during contractions execution. In addition, participants were instructed to avoid trapezius activation during the elbow flexion and body leaning forward during elbow extension. The same investigators conducted all test sessions. A rest of 5 min was observed between testing each muscle group. For each muscle group and limb, the protocol comprised: (1) a warm-up consisting of 10 submaximal isometric contractions (at intensities from 20 to 80% of the perceived maximum force); (2) familiarisation to ballistic contractions (see later); (3) two maximal voluntary isometric contractions; and (4) RFD-SF protocol.

Two 5 s maximal voluntary contractions, interspersed by 2 min of rest, were performed to measure MVF. A third maximal voluntary contraction was performed when the MVF difference between the two trials was higher than 5%. Participants received standardized verbal encouragements during the execution of maximal voluntary contractions.

The RFD-SF protocol started 2 min after the last maximal voluntary contractions. The original RFD-SF protocol requires the performance of 125 ballistic isometric contractions across a full range of submaximal amplitudes (Bellumori et al., 2013). As a reduced form of the original protocol consisting of at least 36 contractions showed reliable results (Smajla et al., 2021b), participants were instructed to perform 12 ballistic isometric contractions (interspersed by 5 s) at 80%, 60%, 40%, and 20% of their MVF for a total of 48 contractions (see Figure 18B). They were asked to produce rapid contractions with peak forces reaching approximately ±10% range of the target force. Each pulse was controlled by standardized acoustic cues. When it was obvious that a ballistic isometric contraction had not been performed properly, the same was repeated. The range force was displayed on the computer screen as a horizontal band of 20% MVF width. Participants were explicitly instructed to produce each isometric torque pulse as quickly as possible and then relax instantly. The emphasis was on the quickness of the contraction rather than the accuracy.

5.3.4 Mechanical Signals

Signal processing was conducted using a custom-written software in MATLAB R2020b (The MathWorks Inc., Natick, MA, USA). MVF and RFD_{peak} were calculated over the raw force signal. MVF was computed as the 0.5 s epoch with the highest value of the force signal. To obtain the RFD_{peak}, we averaged the three contractions showing the highest maximal RFD (calculated as the peak of the first derivative of force signal among the explosive contractions of the RFD-SF protocol).

To calculate the RFD-SF, the force signal was firstly pre-processed using an overlapping moving window of 0.1 s (Bellumori et al., 2011, Boccia et al., 2018a, Ditroilo et al., 2010). The adoption of a moving window was preferred to a 5 Hz low-pass filter because it does not introduce aberration in the signals (typically evident as a force signal below zero just before the contraction onset). If any countermovement was evident (i.e., a drop in force greater than 0.25 kg in the 250 ms before the contraction onset), the contraction was rejected from the analysis. Then, the first derivative of the force signal was computed to obtain the RFD signal. For each ballistic contraction, peak force and RFD_{peak} (which is the local maximum of the RFD signal) were calculated.

The RFD-SF was calculated as the slope of the linear regression between peak force and peak RFD obtained in each contraction (Figure 18C). RFD-SF represents how RFD scales with force in a range of submaximal contraction and, thus, quantify the quickness across a span of intensities. The R^2 was also quantified as it reveals the consistency and linearity of the linear regression. Outliers were detected and removed using the Cook distance methodology to improve the fit of the linear regression (Cook, 1977).

5.3.5 Statistical Analysis

Descriptive data of the dependent variables are presented as mean and standard deviation (SD). The bilateral asymmetry index was calculated for each parameter according to the following formula (Kobayashi et al., 2013):

$$\frac{\text{Dominant limb} - \text{Nondominant limb}}{\text{Dominant limb} + \text{Nondominant limb}} \times 100$$

We calculated the smallest worthwhile change (SWC, 0.2 × pooled SD (McCubbine et al., 2018) to interpret interlimb difference that exceeded this threshold as a true difference (Hopkins et al., 2009). Participants were considered symmetric when the interlimb difference was less than SWC (Exell et al., 2012). Otherwise, they were considered asymmetric, favouring either the dominant or the non-dominant side. Then, Kappa coefficients were calculated to determine the levels of agreement for the direction of asymmetry among muscle groups and performance metrics at the individual level (Bishop et al., 2018). The Kappa coefficient describes the proportion of agreement between two methods after any agreement may have occurred by chance (Cohen, 1960). We adopted linear weighting kappa (Landis and Koch, 1977) to account for how far apart two categories might be (e.g., “asymmetry favouring the dominant limb” is a category closer to “symmetry” than to “asymmetry favouring the non-dominant limb”). Kappa values were interpreted as follows (Viera and Garrett, 2005): 0.01–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; and 0.81–0.99 = nearly perfect. High Kappa values would mean that the direction of asymmetry tends to be the same for different muscle groups or metrics. Therefore, Kappa statistics were applied to test the dominant vs. non-dominant advantage across muscle groups (considering the same performance metric) and across metrics (considering the same muscle group).

To check if dominance affected muscle function at the sample level (i.e., collectively considering all participants), we performed multilevel mixed-effect linear regression analysis (Bates et al., 2014). The adoption of mixed-effects models is essential to account for the fact that each subject was measured four times (i.e., two muscle groups of two sides). Therefore, we considered the dominance and muscle group over participants as random factors. Then we considered dominance, muscle group, and gender as fixed effects.

For each muscle function metric (MVF, RFD_{peak}, and RFD-SF), intraclass correlation coefficient (ICC), standard error of measurement (SEM), and coefficient of variation (COV) were calculated to assess the interday reliability (Weir, 2005). According to Koo and Li (2016), ICC reliability were interpreted as: >0.90 = excellent, 0.75–0.90 = good, 0.50–0.75 moderate and < 0.50 poor. COV values < 10% were deemed acceptable.

Statistical analysis was performed in R (ver 4.1.1, R Core Team, Vienna, Austria, 2021), the figures were produced using the package ggplot2 (Wickham, 2016) and MATLAB R2020b (The MathWorks inc., Natick, MA, USA). The threshold for statistical significance was set at $p < 0.05$.

5.4 Results

The descriptive statistics of the three-performance metrics across muscle groups and limb dominance are reported in Table 8. When controlling for gender, the dominant side showed higher MVF ($F = 19.2$, $p < 0.001$) both in extensors ($p = 0.010$) and flexors ($p = 0.001$) compared to the non-dominant side. The RFD_{peak} was similar on both sides ($F = 3.2$, $p = 0.077$), while the RFD-SF was higher in the non-dominant side compared to the dominant side in the elbow extensors ($p = 0.016$) but not in the elbow flexors ($p = 0.409$). Based on SWC analysis (see Table 8), on average more than 65% of individuals were asymmetric.

	Flexors				Extensors			
	Dominant	**Non-Dominant**	**Bilateral Asymmetry Index (%)**	**Participant Favouring Non-Dominant/Symmetric/Favouring Dominant (%)**	**Dominant**	**Non-Dominant**	**Bilateral Asymmetry Index (%)**	**Participant Favouring Non-Dominant/Symmetric/Favouring Dominant (%)**
MVF (N)	311 ± 118	346 ± 135	−4 ± 11	56/26/19	229 ± 69	258 ± 91	−6 ± 12	41/41/19
RFDpeak (N/s)	4419 ± 1530	4664 ± 1782	−1 ± 10	39/25/37	2970 ± 1019	3050 ± 974	−2 ± 10	9/82/9
RFD-SF (1/s)	9.1 ± 1.4	8.7 ± 1.4	2 ± 8	29/18/54	9.2 ± 1.5	9.8 ± 1.5	−3 ± 9	57/16/27

Table 8. The asymmetry index was calculated as ((dominant limb − non-dominant limb)/(dominant limb + non-dominant limb)) × 100 according to previously published studies (Kobayashi et al., 2013). Therefore, negative values indicate a favour of non-dominant limb. The percentage of participants favouring non-dominant/symmetric/favouring dominant are computed based on the smallest worthwhile change (SWC).

The distribution of bilateral asymmetry indices is reported in Figure 19A. As can be seen, the distributions are widely distributed both towards the dominant and non-dominant sides. The Figure 19B reports the data of eight representative participants: most individuals show some performance metrics favouring the dominant and some others favouring the non-dominant side. The agreement analysis confirmed this scenario. Indeed, the asymmetry direction agreement between heterologous muscle groups was slight for all metrics: MVF Kappa = 0.13; RFD_{peak} Kappa = 0.14; and RFD-SF Kappa = 0.16.

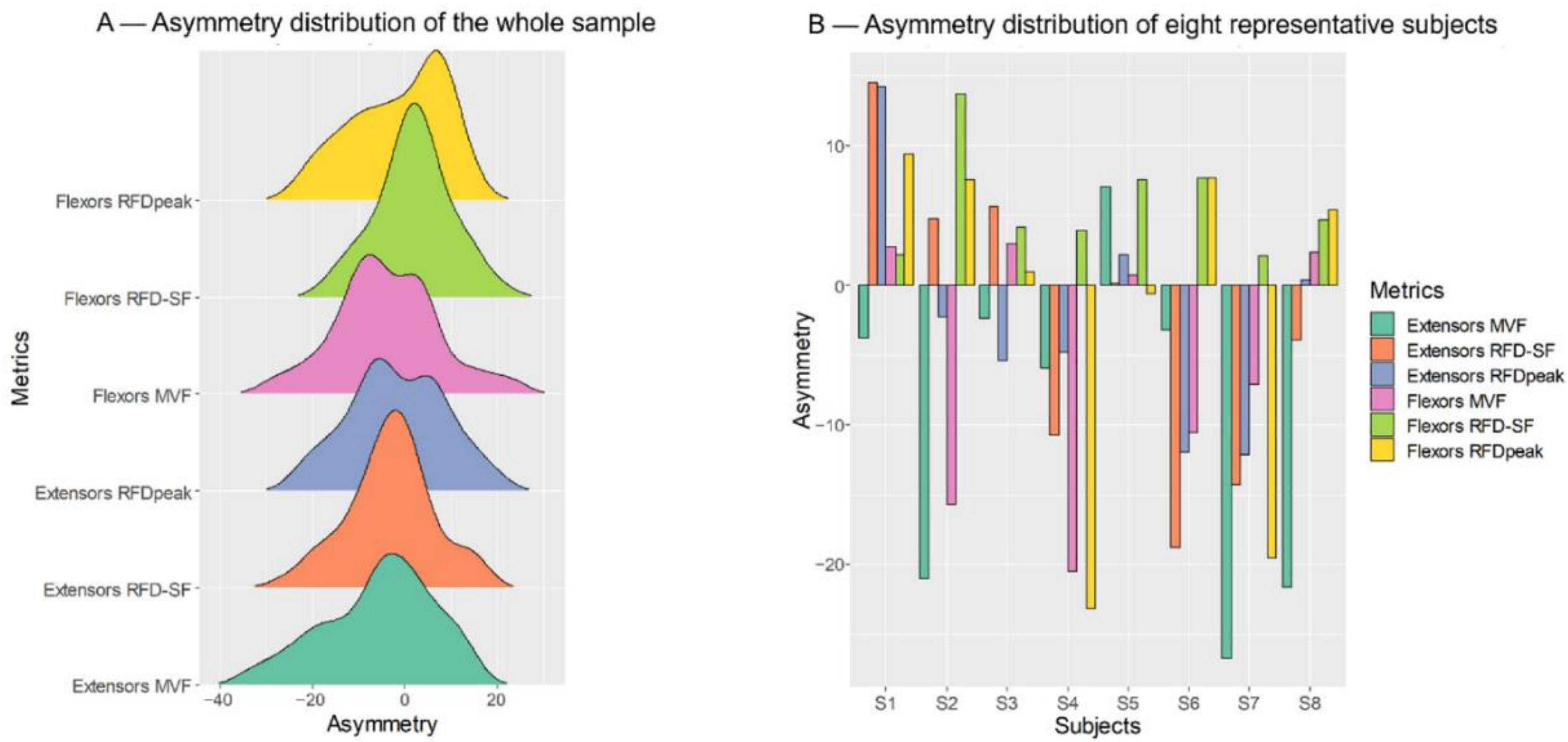

Figure 19. (A) Distributions of each performance metric for elbow flexors and extensors. Positive values denote the favour of the dominant limb. As can be seen, the distributions are widely distributed both towards the dominant and non-dominant sides. (B) Individual values of bilateral asymmetry indices are reported for each performance metric of the first eight subjects of the sample group. MVF, maximal voluntary force; RFD peak, peak rate of force development; and RFD-SF (rate of force development scaling factor).

The asymmetry direction agreement between muscle performance metrics (among homologous muscle groups) was fair for the agreement between MVF and RFD_{peak} (Kappa = 0.37), slight for the agreement between RFD_{peak} and RFD-SF (Kappa = 0.14), and null when comparing MVF with RFD-SF (Kappa = 0.01).

The two most commonly adopted muscle performance metrics, MVF (ICC = 0.93) and RFD_{peak} (ICC = 0.92), showed excellent reliability, while the RFD-SF showed lower but still acceptable reliability (ICC = 0.69). The coefficient of variation of all variables was <10% (MVF = 7.0%; RFD_{peak} 6.5%; and RFD-SF 6.9%). The R^2 of the RFD-SF protocol was on average ≈0.96 for both elbow flexors and extensors.

5.5 Discussion

We measured three muscle-performance metrics (i.e., MVF, RFD_{peak}, and RFD-SF) in two muscle groups of the upper limbs (i.e., elbow flexors and extensors) of the dominant and non-dominant sides. The main findings were that (1) at the population level, the difference between the dominant and non-dominant side was trivial, when present, and it was favouring the non-dominant side; (2) the asymmetry direction agreement between heterologous muscle groups were relatively poor for all metrics (all Kappa values ≤ 0.16); and (3) the asymmetry direction agreement between muscle performance metrics (among homologous muscles) was moderate between MVF and RFD_{peak} (Kappa = 0.37) and low between MVF and RFD-SF (Kappa values = 0.01). Overall, the present findings suggest that no one side is more performative than the other: the objectively better side depends on muscle group and performance metrics adopted.

At the sample level (i.e., collectively considering all participants), the MVF was the only metric that showed a clear trend favouring one side compared to the other one. Indeed, in our sample, the MVF was higher on the non-dominant compared to the dominant side (Table 8). This is partially in conflict with previous data showing slightly higher strength on the dominant compared to the non-dominant side (Kotte et al., 2018). As we did not record any physiological measures of muscle activation or contractile properties, it is impossible to ascribe the side-by-side difference to central or peripheral properties. However, the relatively small sample size of our study (55 subjects) does not allow for inferring the present finding to the general population. Furthermore, the magnitude of difference between the sides was negligible as it ranged from 3 to 6%. A symmetry index lower than 10% is usually considered negligible

(DeLang et al., 2019, McGrath et al., 2016). Nevertheless, the asymmetries directions were sparse at the individual level (see Figure 19). Therefore, the most important findings of the present study regard the analysis of asymmetry direction agreement at the individual level.

For each performance metric, the bilateral asymmetry index at the individual level was muscle specific. The low Kappa values (all Kappa coefficients were ≤0.16) showed that the between-muscle agreement of asymmetry direction was poor for each metric. Kappa values close to 0 suggest that the direction agreement between the two heterologous muscles was due mainly to chance. Therefore, if one metric favoured the dominant limb in one muscle group (e.g., elbow flexors), this does not necessarily occur for the heterologous muscle (i.e., elbow extensors). As a consequence, it is possible to suggest that participants do not have an overall stronger or quicker side. They have a muscle-specific level of strength and quickness instead. This may be due to differences in morphological (muscle size and architecture) (Cossich et al., 2021) and neural activation features (Maffiuletti et al., 2016) across muscles. Bishop and colleagues (Bishop et al., 2018) highlighted the importance of reporting the agreement between asymmetry direction, as they noted that most previous studies did not mention the direction agreement among asymmetry metrics. Here we expand previous literature demonstrating that, even when assessing the same performance metric, the upper limb's heterologous muscles do not share the same asymmetry direction.

Asymmetries rarely favoured the same side when considering different performance metrics of homologous (contralateral) muscles. Except for the agreement between MVF and RFD_{peak} (which was moderate), all other Kappa values were low (≤ 0.14). RFD_{peak} has been previously reported to be more sensitive to detect asymmetry than MVF (Sarabon et al., 2020). Here we expand previous literature by demonstrating that RFD and MVF do not point necessarily in the same direction. Furthermore, when comparing MVF with quickness metrics (i.e., RFD-SF), the asymmetry agreement was null (Kappa values = 0.01). RFD-SF is believed to quantify contraction quickness independently by maximal strength (Bellumori et al., 2011). The present findings suggest that at the individual level, maximal strength asymmetry is unrelated to quickness asymmetry. The differences in underlying physiological mechanisms could be responsible for the observed poor agreement (Folland et al., 2014, Andersen and Aagaard, 2006). From a practical point of view, this finding advocate that practitioners should include muscle-performance tests and metric specifically oriented to muscle quickness, such as relative RFD-SF (Smajla et al., 2020).

The task-specific nature of interlimb differences has been clearly demonstrated by previous studies by Bishop and colleagues (Bishop et al., 2020, Bishop et al., 2018, Bishop et al., 2021b). Here we expand previous literature demonstrating that, even when the mechanical constraints and contraction modality are the same, i.e., in isometric conditions, analysing different muscle performance metrics may favour one side or the other. This can be clearly seen in the Figure 19B, which shows the individual pattern of the first eight participants of the sample. In most participants, interlimb asymmetry favours either the dominant or non-dominant limb depending on muscle group and performance metric. Indeed, the asymmetry indices are sparse below and above the zero line, which would indicate perfect symmetry (Figure 19B). These results suggest that most people do not present one limb overall more performative than the other. Conversely, each limb is more performative in one performance metric, independent of dominance.

From a practical point of view, the present findings suggest that to determine strength asymmetries, practitioners should adopt that specific test for each relevant muscle group. Even more importantly, the current study may inform the practitioners when they try to treat strength asymmetries, i.e., when they prescribe physical training to diminish the asymmetry level of a person. The strength asymmetry should not be treated just by performing more exercise on one side (the weakest limb) compared to the other (the strongest limb). Each side may need more specific training for the physical characteristic where it is less proficient. For example, one side may need more maximal strength training while the contralateral side may need more explosive training.

The novel findings of the present study do not come without limitations. First, we measured only two of the many muscle groups of the upper limb (elbow flexors and extensors). Therefore, our results may not translate to shoulder or wrist muscle groups. Second, we only adopted isometric contractions; thus, the asymmetry agreement among other contraction modalities remains unexplored. Third, we only included physically active individuals, therefore, our results do not necessarily transfer to sedentary people or highly trained athletes. Even more importantly, our results do not relate to people participating in highly asymmetric sports such as tennis, badminton, or fencing. Indeed, we expect that the asymmetry levels in asymmetric sports would be much broader than the those reported in the present study. Lastly, we could not compare left- vs. right-handed individuals because we only recruited five left-handed individuals; therefore, this comparison’s statistical power would be too low. However, investigating whether left-hand individuals would show different asymmetry agreements would be attractive.

Future studies should address two main questions that remain open from the present study. First, the neuromuscular determinants of the asymmetry should be elucidated: it is unknown if MVF and RFD asymmetries were more related to central (i.e., neural activation) or peripheral (i.e., muscle size and architecture) characteristics. Second, as we determined the asymmetry only once for each subject, we do not know if those asymmetries fluctuate with time or if they remain stable over long periods.

5.6 Conclusions

At the individual level, the asymmetries are muscle-specific and rarely favour the same limb across different muscle groups. When adopting various performance metrics, there is no one limb more performative than the other in general: each limb is favoured depending on muscle group and performance metric, independent of dominance.

Chapter 6 – General Discussion

6.1 Recap

In this chapter, the main findings of the four studies are briefly summarized and some general conclusions are drawn along with some considerations about future perspectives.

The present dissertation aimed to enhance our knowledge about the RFD, assessed through purely explosive contractions, and give new insights into its determinants and possible usefulness as an indicator of neuromuscular fatigue or as a method to assess the asymmetry in upper limbs.

We have extensively discussed the use and utility of RFD as a parameter to evaluate the acute effects induced by fatiguing exercises/tasks, the effect of ageing, training or as a parameter to highlight the differences between limbs and muscles at the level of asymmetries (Chapter 1 – Background, aims and hypotheses). Then to provide some potential answers to the above questions, we investigated the contractile and neural determinants by purely explosive isometric contractions of the quadriceps, using peripheral nerve stimulation (octet, 8 stimuli at 300 Hz) and HDsEMG (Chapter 2 - Neural and contractile determinants of burst-like explosive isometric contractions of the knee extensors), demonstrating that the force production of burst-like explosive contractions was regulated by a different neuromuscular factor that changed throughout the contraction duration.

To follow, a scoping review (see Chapter 3 - Rate of Force Development as an Indicator of Neuromuscular Fatigue: A Scoping Review) was carried out to sound out the existing literature about the possibility of using the RFD as an indicator of neuromuscular fatigue demonstrating that it could be considered as a valid alternative to the more classic MVF and that the early RFD (<100 ms) is a more sensitive parameter than the late RFD (>100 ms).

After investigating the lack of information regarding purely explosive (without holding phase; see 1.3.3 Methods to assess and induced fatigue through different types of contraction) contractions and fatigue, we investigated the effect of one hundred purely explosive isometric contractions of the knee extensors in terms of central and peripheral fatigue (see Chapter 4 - Repeated purely explosive contractions induce central fatigue). For this work, the same setup of D'Emanuele et al. (2022) was used (see 2.3 Material and Methods) with HDsEMG and electrically evoked contractions (twitch and octets). This chapter demonstrates that repeating one hundred purely explosive contractions induces a slowing in the force production i.e. shifts towards the right in the force-time curve. This slowing was more evident in the first 50 ms of contraction (early RFD) and was mainly due to central fatigue. As the neural drive to the muscles is the primary determinant of early RFD, we can now clearly associate central fatigue induced by repetitive explosive contractions with their high neural drive requirements.

The last aim, about asymmetry direction among various muscle performance metrics (MVF, RFD, and RFD-SF; see Chapter 5 - Strength Asymmetries Are Muscle-Specific and Metric-Dependent) was carried out through the use of an RFD-SF protocol reduced in both extension and flexion in both upper limbs, demonstrating that the asymmetries are muscle-specific and rarely favour the same limb across different muscle groups. Furthermore, no one side performs better than the other as each limb is favoured according to the muscle group and/or the performance metric investigated, regardless of dominance.

6.2 Summary of main findings

The results of each study (detailed discussed in respective chapters) can be summarized as follows:

Study I - Neural and contractile determinants of burst-like explosive isometric contractions of the knee extensors

For the first time, HDsEMG and electrically evoked contractions by octets (8 stimuli at 300 Hz) were used together with the purpose to assess the determinants of burst-like explosive isometric contractions of knee extensors. It was demonstrated that the force production was related to different neuromuscular determinants that changed through the contraction timing, in line with what was shown by other authors (Andersen and Aagaard, 2006, Folland et al., 2014). Indeed, the multiple regression analysis showed that 36% of the variance of force assessed at 50 ms from the onset was explained by RMS (always assessed at 50 ms from the onset; $R^2 = 0.361$, $p = 0.001$), in line with Magrini et al. (2022); regarding the force assessed at 100 ms, the 65% of the variance was explained by the octet force (assessed at 50 ms from the onset; $R^2 = 0.646$, $p < 0.001$); the force assessed at 150 ms instead was explained for 71% by MVF ($R^2 = 0.711$, $p < 0.001$) and for 6% by the octet force (assessed at 50 ms from the onset; $R^2 = 0.061$, $p = 0.016$); at last, peak RFD that occurred after $\approx$ 60 ms from the force onset, was explained for 52% of variance by MVF ($R^2 = 0.518$, $p < 0.001$) and for 6% by RMS (assessed at 50 ms from the onset; $R^2 = 0.074$, $p = 0.036$). Unexpectedly, MFCV did not contribute to explaining anything in any variable considered, despite the results shown by Del Vecchio et al. (2018), not corroborating the usefulness of analysing MFCV in purely explosive contractions.

To summarize the results, the main determinant of early RFD was muscle excitation while the late RFD was determined by both contractile properties and MVF; peak RFD, surprisingly, was determined in larger part by MVF and therefore may provide similar information showing that may not be adequate as an index to assess the explosive contractions.

Study II - Rate of Force Development as an Indicator of Neuromuscular Fatigue: A Scoping Review

It was demonstrated, by the analysis of 70 studies, that the classic acute decline in MVF induced by different types of fatiguing exercise was accompanied by a consequent decline in RFD. In detail, peak RFD appeared more sensitive than MVF to detecting neuromuscular fatigue (−25% and −19% respectively). This trend was also observed when the fatiguing tasks were divided between strength exercises and "others" (i.e., endurance tasks). Indeed, peak RFD showed greater decreases than MVF both following strength exercises (−30 and −23% respectively) and following "other exercises" (−20% and −14% respectively). Moreover, the early RFD phase (< 100 ms) appeared more sensitive than the late RFD phase (> 100 ms) to determine the presence of neuromuscular fatigue (−23% and –19% respectively). And again, this trend is consistent with the division among strength and “other exercises”. Sure enough, early RFD showed more decline compared to late RFD both in strength exercises (–28% and –25% respectively) and other exercises (–19% and –13% respectively). This review showed also corroborates the indications expressed in other works (Maffiuletti et al., 2016, Rodríguez-Rosell et al., 2018) regarding the importance of the choice of the evaluation task. In fact, when the fatiguing and assessment tasks were equal (in 50% of the studies analysed), both the decline in MVF and peak RFD were greater (–27% and –33% respectively) than when the fatigue and assessment tasks were different (–15% and –23% respectively). To summarize the results, peak RFD and early RFD seems to be more sensitive to detect changes after fatiguing task compared to MVF and late RFD. Indeed, based on the available data, we suggest adding the analysis of early RFD inasmuch would add meaningful insight to neuromuscular fatigue assessment while late RFD may be redundant compared to MVF.

Study III - Repeated purely explosive contractions induce central fatigue

This work aimed to investigate the effects of one hundred purely explosive contractions (pulses) of knee extensors without any holding phase to specifically address the fatiguing effect of contraction explosiveness through HDsEMG and electrically evoked contractions (twitch and octets). The analysis of force signals showed that the peak force reached in the explosive contractions did not vary with time ($P = 0.753$). In terms of RFD, the cumulative RFD showed a time × interval interaction $F(2,32) = 9.7$, $P < 0.001$, $\mu^2 = 0.379$. Indeed RFD_{50} showed a moderate decrement ($d = 0.56$, $P < 0.001$), RFD_{100} showed a small decrement ($d = 0.41$, $P < 0.001$) with fatigue, while RFD_{150} remained stable ($d = 0.14$, $P = 0.266$). Both MVF ($d = 0.78$, $P = 0.005$) and RFD_{peak} largely decreased with fatigue ($d = 0.88$, $P = 0.002$). In addition, time-to-peak force largely decreased ($d = 0.90$, $P < 0.001$) and time-to-peak RFD moderately increased with fatigue ($d = 0.56$, $P = 0.034$).

Regarding the EMG signals, relative ARV decreased with fatigue ($F(1,16) = 20.0$, $P < 0.001$, $\mu^2 = 0.556$) without any time × interval interaction ($F(2,32) = 1.5$, $P = 0.227$, $\mu^2 = 0.089$). In particular, ARV_{50} ($d = 1.1$, $P = 0.006$), ARV_{100} ($d = 1.4$, $P = 0.001$), and ARV_{150} ($d = 1.2$, $P = 0.003$) decreased with similar very large effect size.
Absolute MFCV increased with fatigue ($F(1,16) = 21.1$, $P < 0.001$, $\mu^2 = 0.569$) without any time × interval interaction ($F(2,32) = 1.0$, $P = 0.346$, $\mu^2 = 0.064$). In particular, $MFCV_{50}$ ($d = 0.20$, $P = 0.004$), $MFCV_{100}$ ($d = 0.21$, $P = 0.002$), and $MFCV_{150}$ ($d = 0.16$, $P = 0.033$) increased with similar small effect size. Conversely, relative MFCV decreased with fatigue ($F(1,16) = 28.3$, $P < 0.001$, $\mu^2 = 0.639$) without any time × interval interaction ($F(2,32) = 0.9$, $P = 0.397$, $\mu^2 = 0.056$). Indeed, $MFCV_{50}$ ($d = 0.53$, $P = 0.007$), $MFCV_{100}$ ($d = 0.67$, $P < 0.001$), and $MFCV_{150}$ ($d = 0.71$, $P < 0.001$) decreased with similar moderate effect size.

The electrically evoked contractions showed that the octet RFD increased with time ($d = 0.62$, $P = 0.020$), while the octet peak force decreased with time ($d = 1.0$, $P < 0.001$). Neural efficacy largely decreased with fatigue ($d = 1.5$, $P < 0.001$). The rate of force relaxation moderately decreased ($d = 0.60$, $P = 0.025$). MFCV of M-wave ($d = 0.44$, $P < 0.001$) and peak-to-peak amplitude of M-Wave showed a small increase with time ($d = 0.31$, $P < 0.001$). Stimulated EMD moderately increased with time ($d = 0.71$, $P = 0.009$) while voluntary EMD moderately decreased with time ($d = 0.69$; $P = 0.011$).

To sum up, we found a fatigue-induced shifting of the force-time curve towards the right resulting in a wider Gaussian-shaped force curve. Indeed, the time-to-peak force ($d = 0.90$) and the time-to-peak RFD ($d = 0.56$) shifted towards the right, and those changes were accompanied by a large decrease in RFD_{peak} ($d = 0.88$). Fatigue slowed the voluntary force production even when the force target could already be reached, as the peak force of each pulse did not change throughout the 100 contractions. Then, the performed task induced a significant amount of central fatigue, as evidenced by the very large decrement ($d = 1.50$) in neural efficacy while we did not find any clear signs of peripheral fatigue. This central fatigue is also supported by the significant drop of ARV ($d \approx 1.0$) and MFCV ($d \approx 0.6$) over the first 50 – 100 ms of contractions.

Study IV - Strength Asymmetries Are Muscle-Specific and Metric-Dependent

This work aimed to investigate if dominance affects upper limbs muscle function and then calculated the level of agreement in asymmetry direction across various muscle-function metrics (MVF, RFD, RFD-SF) of elbow flexors and extensors through purely explosive isometric contractions at various levels of submaximal (%MVF) intensities (20, 40, 60, 80%). Then we calculated the smallest worthwhile change (SWC) and Kappa coefficient to interpret interlimb difference and to determine the levels of agreement for the direction of asymmetry among muscle groups and performance metrics at the individual level. Then, to check if dominance affects muscle function at the sample level a multilevel mixed-effect linear regression analysis was performed.

The SWC analysis showed that more than 65% of individuals were asymmetric and the distributions of bilateral asymmetries were widely distributed both towards the dominant and non-dominant sides. Regarding the asymmetry direction agreement between heterologous muscle groups, the Kappa coefficient highlighted was slight for all metrics (MVF Kappa = 0.13; peak RFD Kappa = 0.14; and RFD-SF Kappa = 0.16). Moreover, the two most commonly adopted muscle performance metrics, MVF (ICC = 0.93) and peak RFD (ICC = 0.92), showed excellent reliability, while the RFD-SF showed lower but still acceptable reliability (ICC = 0.69). Indeed, the asymmetry direction agreement between muscle performance metrics supports the aforementioned result since was fair for the agreement between MVF and peak RFD (Kappa = 0.37), slight for the agreement between peak RFD and RFD-SF (Kappa = 0.14), and null when comparing MVF with RFD-SF (Kappa = 0.01). Nevertheless, the coefficient of variation of all metrics analysed was < 10% and the R^2 of the RFD-SF protocol was on average ≈ 0.96 for both elbow flexors and extensors. Furthermore, when comparing MVF with RFD-SF, the asymmetry agreement was null (Kappa = 0.01). Is commonly accepted that RFD-SF can quantify contraction quickness independently by maximal strength (Bellumori et al., 2011). Indeed, the present results suggest that at the individual level, maximal strength asymmetry is unrelated to quickness asymmetry. Since Study 1 (D'Emanuele et al., 2022) highlighted the differences in underlying physiological mechanisms about rapid contractions these could be responsible for the observed poor agreement between MVF and RFD-SF. To summarize, the present results considered overall suggest that no one side is more performative than the other because the objectively better side depends on muscle group and performance metrics adopted and from a practical point of view, this finding advocate that practitioners should include muscle performance tests and metric specifically oriented to muscle quickness.

6.3 Limits and future perspectives

The number of studies regarding purely explosive/ballistic contractions is certainly minor compared to other types of contractions (i.e., holding contractions). However, recent works about the RFD and RFD-SF have shown a field that can be widely explored from multiple points of view (e.g., asymmetries, fatigue, pathological conditions, training etc...).

The works contained in this thesis are not without limitations. Starting from the scoping review (study II), there is an intrinsic limit precisely in choosing a scoping and not a meta-analysis. Indeed, we did not perform a meta-analysis because the study design and the RFD assessment (and sometimes lack of rationale to assess the RFD) are too heterogeneous among the studies. This highlights the prospect of creating and following guidelines (partly already published by Maffiuletti et al., 2016) in agreement with all researchers dealing with RFD in all its aspects.

About study I, the use of isometric contractions of the quadriceps could invalidate the results in dynamic conditions or on other muscle groups (e.g., upper limb). The same consideration applies to study III and for both aforementioned studies both male and female adults were included; these results may again not be transferable to other age targets (e.g., elderly subjects). Study IV again was conducted with adult subjects (both males and females) and only on elbow flexors and extensors through isometric contractions. Again, the results can not be applied to other muscle groups or categories, However, these limitations pave the way for future studies on categories, muscle groups and types of contractions (e.g., dynamics) different from those already investigated but always through the analysis of explosive contractions, the evaluation of the RFD and/or the using a protocol like RFD-SF.

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Appendices

Example of participation sheet and consent form

Informativa e manifestazione del consenso al trattamento dei dati personali

1. **Identificazione della Ricerca**

Rate of Force Development and Fatigue (Tasso di Sviluppo della Forza e Fatica)

2. **Identificazione del titolare del trattamento dei dati**

Ai sensi dell'articolo 13 del Regolamento (UE) 2016/679 il Titolare del trattamento è l'Università degli Studi di Verona, con sede in Via dell'Artigliere n. 8, 37129, Verona (e-mail: privacy@ateneo.univr.it, PEC: ufficio.protocollo@pec.univr.it, tel. +39 045.8028777).

3. **Identificazione del soggetto presso cui sono raccolti i dati**

I dati personali sono raccolti presso l'interessato e sono trattati dal titolare e dal gruppo di ricerca nell'esecuzione dei propri compiti di interesse pubblico o scientifico o comunque connessi all'esercizio dei propri pubblici poteri nell'ambito della ricerca scientifica.

4. **Identificazione del tipo di dati trattati e delle finalità del trattamento**

I dati che verranno trattati sono inquadrati nelle seguenti tipologie:

- dati anagrafici, personali e di contatto;
- dati sanitari e biometrici.

I dati sono raccolti e trattati per consentire lo svolgimento delle attività di ricerca scientifica e di tutte le operazioni connesse, compresi i procedimenti amministrativi.

Il conferimento da parte dell'interessato o del suo rappresentante legale dei dati personali per le finalità del progetto o per l'adempimento di obblighi legge o per il perseguimento di interessi generali è facoltativo, ma necessario per la realizzazione del progetto o per fruizione dei servizi da parte dell'interessato.

5. **Identificazione dei destinatari dei dati**

I dati trattati per le finalità di cui sopra verranno comunicati o saranno comunque accessibili ai dipendenti e collaboratori assegnati al progetto o ai competenti uffici dell'Università, ovvero a persone fisiche o giuridiche che prestano attività di consulenza o di servizio verso l'Università o il team di ricerca ai fini dell'erogazione dei servizi richiesti. L'elenco completo ed aggiornato dei responsabili del trattamento è pubblico e accessibile tramite richiesta al titolare.

I dati non verranno diffusi.

6. **Conservazione dei dati**

I dati verranno salvati e conservati all'interno di apposite cartelle in cloud (es. OneDrive) e protetti da password alfanumeriche all'interno degli account dei ricercatori coinvolti. Anche l'accesso agli account è protetto da password alfanumeriche.

I dati raccolti sono analizzati in forma aggregata e sono diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici.

7. **Diritti degli interessati**

L'interessato ha il diritto di ottenere, l'accesso ai dati personali e la rettifica o la cancellazione degli stessi o la limitazione del trattamento che li riguarda o di opporsi al trattamento (art. 15 e seguenti del regolamento) presentando apposita istanza via mail all'indirizzo samuel.demanuele@univr.it.

8. **Consenso**

Sottoscrivendo tale modulo acconsento al trattamento dei miei dati personali per gli scopi della ricerca nei limiti e con le modalità indicate nell'informativa fornitami con il presente documento.

Nome e Cognome dell'interessato (in stampatello) ______________________

Firma dell'interessato _______________________ Data _ _/_ _/_ _ _ _

UNIVERSITÀ di VERONA
Dipartimento di NEUROSCIENZE, BIOMEDICINA E MOVIMENTO

DICHIARAZIONE DI CONSENSO

Titolo dello Studio

Rate of Force Development and Fatigue (Tasso di Sviluppo della Forza e Fatica)

Scopo della Ricerca

Il presente progetto di ricerca mira a valutare i cambiamenti di forza massima (MVC) e di tasso di sviluppo della forza (RFD) a seguito di differenti task affaticanti dell'arto inferiore (estensori di ginocchio) in adulti sani.

Promotori della ricerca

Questa ricerca è promossa e condotta dalla sezione di Scienze Motorie dell'Università di Verona. Per qualsiasi informazione riguardante le caratteristiche dello studio contattare il Dr. Samuel D'Emanuele (PhD student del corso di dottorato in Neuroscienze, Scienze Psicologiche e Psichiatriche, e Scienze del Movimento – Scuola di Scienze della Vita e della Salute) alla seguente mail: samuel.demanuele@univr.it

Descrizione del Protocollo Sperimentale

Riscaldamento: Sarà chiesto al soggetto di svolgere un riscaldamento specifico dell'arto interessato eseguendo una decina di contrazioni ad intensità crescente.

Preparazione alla prova. Il soggetto verrà posizionato su una Leg Extension Isometrica, la quale verrà regolata in modo da rendere confortevole la posizione e si utilizzeranno delle cinghie di sicurezza per limitare contro-movimenti. Verranno posizionate delle matrici HDsEMG (elettromiografia di superficie ad alta densità) sul quadricipite e relativi elettrodi di riferimento sulla patella. Verrà inoltre posizionato un elettrodo sul grande trocantere ed uno sul nervo femorale all'interno del triangolo femorale per la stimolazione nervosa periferica. Una volta posizionati gli elettrodi si procederà a dare delle stimolazioni ad intensità crescente fino al raggiungimento del plateau di forza raggiungibile attraverso la stimolazione del nervo.

Trovata l'intensità necessaria, la stessa verrà aumentata del 20% per le stimolazioni PRE e POST protocollo affaticante.

Test di valutazione. Al soggetto sarà poi richiesto di esprimere per tre volte la massima forza (massime contrazioni muscolari volontarie). Il recupero tra le due prove sarà di circa 2 minuti. Successivamente al soggetto sarà richiesto di eseguire 3 contrazioni brevi e veloci intervallate da 30s di recupero, per valutare la capacità di esprimere forza velocemente. A seguire verranno date tre stimolazioni del nervo femorale attraverso degli ottetti (otto impulsi a 300Hz). Tra gli ottetti il recupero sarà di 5s. Verranno eseguiti anche dei micro-prelievi (una goccia di sangue) dal lobo dell'orecchio o dalla punta del dito della mano, ad intervalli prestabiliti (immediatamente prima, immediatamente dopo e a 12, 24, 36, 48 e 72h), per la valutazione del danno muscolare (CPK). Tutti questi test verranno effettuati sia PRE che POST protocollo affaticante.

Periodo delle prove. Ogni sessione durerà circa un'ora. Si richiederà di svolgere il protocollo appena descritto in quattro differenti giornate intervallate da almeno tre giorni di recupero evitando attività fisica intensa durante questo lasso di tempo.

Protocollo affaticante. Oltre ad una seduta di familiarizzazione con i protocolli, sono previste tre sedute con differenti prove affaticanti che verranno assegnate in modalità randomizzata.

1. **Potenziali rischi**

Potrebbe in rari casi accadere di percepire un leggero indolenzimento muscolare, che comunque non limita la prestazione e le normali attività di vita di tutti i giorni e che si risolve nell'arco di 48-72 ore.

Si prevede in ogni caso di interrompere le prove in qualsiasi momento se il soggetto vorrà ritirarsi.

2. **Potenziali disagi**

Non si evidenziano potenziali rischi se non, in rarissimi casi, un leggero indolenzimento muscolare nell'arco di 48 ore.

Potrebbe essere percepita una sensazione di fastidio durante la stimolazione del nervo femorale, che comunque si limita al momento stesso degli impulsi.

Potrebbe essere percepita una sensazione di fastidio durante il prelievo di una goccia di sangue dal lobo dell'orecchio o dalla punta del dito della mano per le valutazioni di danno muscolare (CPK), che comunque si limita al momento stesso del prelievo.

3. Potenziali vantaggi

È importante sapere che i risultati di questo studio contribuiranno allo studio della funzione neuromuscolare degli arti inferiori in soggetti sani e permetteranno di comprendere meglio le possibili dinamiche relative al tasso di sviluppo di forza, di massima forza volontaria e di danno muscolare a seguito di differenti protocolli affaticanti. Tali risultati possono avere importanti risvolti in ambito applicativo come durante l'allenamento sportivo.

- La Sua adesione a questa Ricerca è completamente volontaria e Lei potrà ritirare il consenso alla partecipazione in qualsiasi momento
- Ai sensi dell'art. 10 della legge n. 675 del 31/12/1996 sulla tutela delle persone per il trattamento dei dati personali, La informiamo che i Suoi dati personali verranno raccolti ed archiviati protetti per la privacy e saranno utilizzati esclusivamente per scopi di ricerca scientifica.
- Lei ha diritto, se lo vuole, di sapere quali informazioni saranno archiviate ed in quale modo.
- L'accesso a tali dati sarà consentito solo a personale autorizzato. I risultati della Ricerca a cui Lei parteciperà potranno essere oggetto di pubblicazione, ma la Sua identità rimarrà segreta.
- Se Lei lo desidera può informare il Suo medico di famiglia della Sua partecipazione a questa Ricerca per evitare interferenze con eventuali farmaci/procedure.
- Se lo richiederà, alla fine della Ricerca potranno esserLe comunicati i risultati dello studio in generale ed anche in particolare quelli specifici che La riguardano.
- Il Protocollo di Studio che Le viene proposto è stato redatto in conformità con le Norme di Buona Pratica Clinica dell'Unione Europea, in accordo con la dichiarazione di Helsinki.

Io sottoscritto……………………………………………………………………

(Nome e Cognome per esteso del Soggetto)

nato a…………………………………………il……………………

dichiaro di aver ricevuto complete informazioni sulla natura dello Studio e delle sue finalità, nonché delle modalità di esecuzione, degli eventuali rischi dei test e delle analisi che saranno eseguite. Le informazioni ricevute sono state chiare ed esaurienti.

- Dichiaro di aver potuto discutere tali spiegazioni, di aver potuto porre domande e di avere ricevuto risposte in merito soddisfacenti.
- Dichiaro inoltre di avere avuto la possibilità di informarmi in merito ai particolari dello Studio anche con altre persone di Mia fiducia.
- Accetto quindi liberamente di partecipare alla Ricerca, avendo perfettamente compreso tutte le informazioni sopra riportate.
- Sono consapevole che la Mia partecipazione alla ricerca è volontaria e che ho la facoltà di ritirarmi in qualsiasi momento.
- Acconsento inoltre al trattamento dei dati personali e di quelli derivanti dallo Studio, in forma anonima e per i soli scopi di Ricerca (ai sensi dell'art. 10 della legge n. 675 del 31/12/1996 sulla tutela delle persone rispetto al trattamento dei dati personali).

Data,

Firma del Soggetto…………………………………………………………