KU Leuven
Biomedical Sciences Group
Faculty of Movement and Rehabilitation Sciences
Department of Movement Sciences

AGING AND MUSCULAR FUNCTION

SPECIAL EMPHASIS ON RESPONSE TIME, CONTRACTION TYPE, MOVEMENT COMPLEXITY AND ACCELERATION RATE

Stijn VAN DRIESSCHE

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Jury:

Supervisors: Prof. dr. Christophe Delecluse (KU Leuven)

dr. Evelien Van Roie (KU Leuven)

Prof. dr. Benedicte Vanwanseele (KU Leuven)

Chair: Prof. dr. Filip Boen (KU Leuven)

Jury members: Prof. dr. Jos Vanrenterghem (KU Leuven)

Prof. dr. Peter Hespel (KU Leuven)

Prof. dr. Martine Thomis (KU Leuven)

Prof. dr. Sarianna Sipilä (University of Jyväskylä)

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English summary

Life expectancy is rising globally, which is a human success story. However, aging is accompanied by a loss of functional performance capacity and a higher risk of falling, leading to a loss of autonomy. Due to these changes, the rising medical costs and the higher need for primary health care, a major clinical and economic burden for the society exists. Therefore, detection of early declines in muscular function during aging and prevention of the loss in functional performance capacity are of paramount importance. However, the current methodologies used in clinical practice are rather limited to capture the complex functioning of muscles during human movements and hence the age-related decline in muscular function. Factors such as **response time**, **contraction type**, **movement complexity** and **acceleration rate** are shown to have a clear influence on muscular function. However, how these factors are affected by aging is not well understood. Therefore, we aimed to identify age-related changes in muscular function and get more insight into the functional outcomes of the aging process by investigating the effect of aging on muscular function with the focus on response time, contraction type, movement complexity and acceleration rate. In addition, we aimed to gain a better insight into the **underlying mechanisms** of the age-related changes in muscular function, which could help to develop effective strategies to counteract these age-related deteriorations. Generally, this doctoral thesis, which consists of three chapters, aims to create awareness in clinical practice about less known age-related problems that can have a high impact and to bring new insights into the field of aging research to help finding solutions for the loss of functionality.

Chapter 1 focusses on factors such as **response time** and **contraction type**. More specifically, the reliability and the age-related decline of time-dependent measures of knee extensor function obtained through isotonic testing is investigated. In **article 1,** it is shown that maximal and time-dependent measures of muscular function such as pP and RPD are good to highly reliable in older adults. Therefore, pP and RPD can be considered as consistent measures of muscular function. In **article 2,** it is found that RPD differentiates more between young and older adults compared with pP, due to an additional age-related increase in the time to pP. Furthermore, all power-related parameters show a strong relationship with functional performance tests, such as 7.5-meter fast walk, timed-up-and-go and stair climbing, in well-functioning community-dwelling older adults. These results underline the importance of time-dependent measures to detect age-related changes in muscular function, in particular they emphasize the inability to generate power rapidly at older age.

Chapter 2 focusses on **movement complexity**. In **article 3,** the effect of age on power production of the leg extensors in single- versus multi-joint movements is evaluated across the adult life span. In both single- and multi-joint tests, it is shown that the age-related decline in RPD exceeds the decline

in pP. In addition, it is found that RPD declines more in the multi-joint compared with the single-joint test. This phenomenon is true for tests at different velocities. Moreover, it is found that RPD multi-joint is more associated with squat jump height compared with RPD single-joint. Therefore, research and clinical practice should consider focusing on the initial phase of rapid power development and multi-joint testing for the detection of functional disability during aging.

Chapter 3 investigates the effect of aging on power production at different **accelerations** and aims to gain a better insight in the **underlying mechanisms** of the age-related decline in muscular function in terms of neural activation and in vivo fascicle behavior. In **article 4**, it is shown that RPD largely declines with aging with the steepest decline at the highest acceleration. Neuromuscular activation declines more at higher compared to lower acceleration for rectus femoris (RF) and vastus lateralis (VL) muscles. The age-related changes at high relative to lower acceleration in RF and VL activity are associated with the age-related decline in RPD across the sample. These findings emphasize the magnitude of the age-related decline in leg extensor RPD in response to abrupt changes in movement velocity across the adult life span and its association with impairments in neuromuscular activity. In **article 5**, it is shown that VL fascicle shortening and shortening velocity increase significantly with aging with no difference between accelerations. This age-related change is mainly due to a higher shortening during the phase of electromechanical delay. VL fascicle shortening and shortening velocity are positively associated with RPD. These findings demonstrate that the age-related decline in RPD in fast actions is accompanied by an increase in fascicle shortening and shortening velocity. While in vivo fiber shortening velocity seems to be no limiter, specific fiber force may have a bigger influence on rapid power development at advancing age than its capacity to shorten fast. Increased VL fascicle shortening might result in less optimal fiber lengths, which may be due to decreased stiffness of the series elastic element with aging.

All together, the findings of the different papers highlight that time-dependent measures of muscular function could be considered as potential identifiers of muscular aging in research and clinical practice, especially in dynamic, multi-joint testing at high accelerations. Preventive exercise interventions should not only focus on improving muscle mass and maximal strength, but also neural activation, fiber properties and tendon stiffness.

Dutch summary - Samenvatting

De levensverwachting neemt wereldwijd toe en dat is een succesverhaal voor de mensheid. Hoewel, veroudering gaat gepaard met een verlies aan functionaliteit en een hoger valrisico, die leiden tot een verlies aan autonomie. Hierdoor is er een toename in het aantal medische kosten en een hogere nood voor eerstelijnsgezondheidszorg met als gevolg een zware klinische en economische last voor de maatschappij. Daarom is het vroeg detecteren van veranderingen in de functie van spieren tijdens veroudering en preventie van het verlies aan functionaliteit van enorm belang. Echter, de huidige methodes die gebruikt worden in de klinische praktijk om leeftijdsgerelateerde veranderingen in spierfunctie te detecteren zijn eerder beperkt om het complexe functioneren van de spieren tijdens beweging te omvatten. Het is aangetoond dat factoren zoals **responstijd**, **contractietype**, **complexiteit van de beweging** en **mate van versnelling** een duidelijke invloed hebben op spierfunctie. Hoe deze factoren worden beïnvloed door veroudering is echter nog niet helemaal duidelijk. Daarom streven we ernaar om leeftijdsgerelateerde veranderingen in spierfunctie met de focus op respons tijd, contractie type, bewegingscomplexiteit en versnelling op te sporen en meer inzicht te krijgen in de functionele gevolgen van veroudering. Daarnaast willen we meer inzicht krijgen in de **onderliggende mechanismes** van de leeftijdsgerelateerde veranderingen in spierfunctie, wat kan helpen voor de ontwikkeling van effectieve strategieën om deze leeftijdsgerelateerde achteruitgang tegen te gaan. Deze doctoraatsthesis bestaat uit drie hoofdstukken en heeft als algemeen doel om de klinische praktijk bewust te maken over minder bekende leeftijdsgerelateerde veranderingen in spierfunctie die een grote impact kunnen hebben en om nieuwe inzichten te verwerven in het domein van verouderingsonderzoek om gepaste oplossingen te helpen vinden tegen het verlies aan functionaliteit.

Hoofdstuk 1 focust op factoren zoals **responstijd** en **contractietype**. Meer specifiek wordt de betrouwbaarheid en de leeftijdsgerelateerde daling van tijdsafhankelijke parameters van de knie extensoren door middel van isotonische testen onderzocht. In **artikel 1** wordt aangetoond dat maximale en tijdsafhankelijke spierfunctie parameters zoals pP en RPD goed tot erg betrouwbaar zijn bij ouderen. Vandaar dat pP en RPD kunnen beschouwd worden als consistente metingen van spierfunctie. In **artikel 2** wordt gevonden dat RPD meer verschilt tussen jong en oud in vergelijking met pP, dit door een additionele toename van de tijd tot pP bij veroudering. Bovendien zijn alle vermogensgerelateerde parameters bij de ouderen sterk geassocieerd met functionele testen zoals 7.5 meter snelwandelen, timed-up-and-go en traplopen. Deze bevindingen onderstrepen het belang van tijdsafhankelijke parameters om leeftijdsgerelateerde veranderingen in spierfunctie te detecteren. In het bijzonder benadrukken ze het onvermogen bij ouderen om vermogen snel te genereren.

Hoofdstuk 2 focust op **bewegingscomplexiteit**. In **artikel 3** wordt het effect van leeftijd op de vermogensproductie van de knie extensoren geëvalueerd tussen bewegingen in één en in meerdere gewrichten. In zowel bewegingen in één als in meerdere gewrichten wordt aangetoond dat de leeftijdsgerelateerde daling in RPD de daling in pP overtreft. Daarnaast wordt gevonden dat RPD meer daalt in de beweging over meerdere gewrichten in vergelijking met de beweging in één gewricht en dit aan verschillende snelheden. Bovendien wordt aangetoond dat RPD over meerdere gewrichten sterker geassocieerd is met spronghoogte tijdens een squat jump in vergelijking met RPD in één gewricht. Daarom zou onderzoek en de klinische praktijk moeten overwegen om meer te focussen op de initiële fase van snelle vermogensontwikkeling en bewegingen over meerdere gewrichten voor het detecteren van functionele beperkingen tijdens veroudering.

Hoofdstuk 3 onderzoekt het effect van veroudering op vermogensproductie aan verschillende **versnellingen** en streeft ernaar meer inzicht te verwerven in de **onderliggende mechanismes** van de leeftijdsgerelateerde daling in spierfunctie in termen van neurale activatie en in vivo gedrag van spiervezelbundels. In **artikel 4** wordt aangetoond dat RPD sterk daalt tijdens veroudering met de sterkste daling aan de hoogste versnelling. Neuromusculaire activatie daalt meer aan hoge in vergelijking met lagere versnelling voor de rectus femoris (RF) en vastus lateralis (VL) spieren. De leeftijdsgerelateerde veranderingen aan hoge ten opzichte van lagere versnelling in RF en VL spieractiviteit zijn geassocieerd met de leeftijdsgerelateerde daling in RPD over de proefgroep heen. Deze bevindingen benadrukken de omvang van de leeftijdsgerelateerde daling in RPD van de beenstrekkers als reactie op abrupte veranderingen in bewegingssnelheid over de leeftijden heen en het verband met een verslechterende neuromusculaire activiteit. In **artikel 5** wordt aangetoond dat VL vezelverkorting en verkortingssnelheid significant toenemen tijdens veroudering, zonder een verschil te vertonen tussen versnellingen. Deze leeftijdsgerelateerde verandering is vooral te wijten aan een grotere verkorting tijdens de fase van elektromechanische vertraging. VL spiervezel verkorting en verkortingssnelheid zijn positief geassocieerd met RPD. Deze bevindingen tonen aan dat de leeftijdsgerelateerde daling in RPD tijdens snelle spieracties samengaat met een toename in spiervezel verkorting en verkortingssnelheid. Terwijl in vivo vezel verkortingssnelheid geen limiterende factor blijkt, lijkt specifieke vezelsterkte een grotere invloed te hebben op snelle vermogensproductie bij toenemende leeftijd dan de capaciteit van de vezels om snel te verkorten. De toename in VL spiervezel verkorting is mogelijks het gevolg van een verminderde stijfheid van het serie elastische element tijdens veroudering en kan resulteren in minder optimale spiervezel lengtes.

De bevindingen uit de verschillende studies benadrukken dat tijdsafhankelijke parameters van spierfunctie beschouwd kunnen worden als potentiële indicatoren voor veroudering van de spieren in zowel onderzoek als de klinische praktijk en dit vooral in dynamische bewegingen over meerdere gewrichten aan hoge versnellingen. Preventieve trainingsinterventies zouden niet enkel moeten focussen op het verbeteren van spiermassa en maximale kracht, maar ook op het verbeteren van neurale activatie, specifieke vezeleigenschappen en peesstijfheid.

PART 1

GENERAL INTRODUCTION AND OUTLINE

1 Aging: birth of a health-related problem

1.1 An aging and graying society

Life expectancy is rising globally thanks to the medical and scientific progress, a better health care system, improved working and living conditions, a better education and a lower infant mortality rate (World_Health_Organisation 2015). In addition, the number of older people aged above 60 years is increasing substantially since recent years resulting in 'graying' of the society (Fig. 1)(United_Nations 2015). According to the World Health Organization, one in five people will be 60 years or older by 2050 (World_Health_Organisation 2015). This proportion of people over 60 years will almost double from 900 million in 2015 up to an estimated two billion in 2050 (Fig. 2).

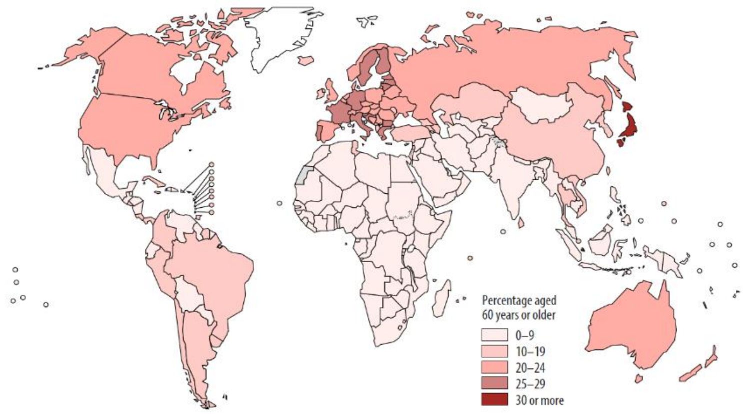

Fig. 1 Proportion of population aged 60 years or older, by country, 2015. Adapted from (World_Health_Organisation 2015).

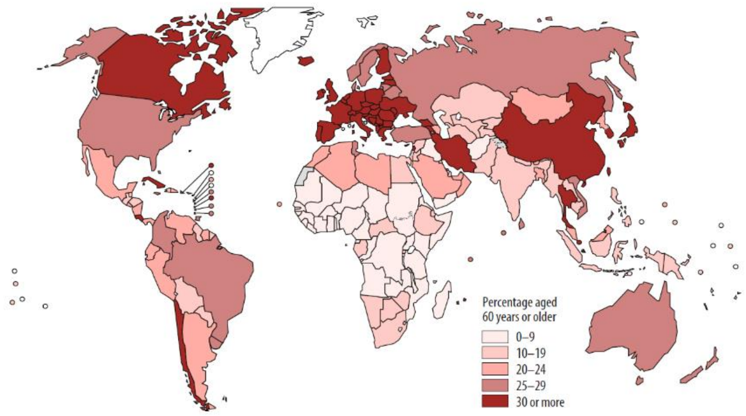

Fig. 2 Proportion of population aged 60 years or older, by country, 2050 projections. Adapted from (World_Health_Organisation 2015).

Next to the growing number of older people aged above 60, there is a rapid increase in the number of very old people aged above 80 (i.e. the oldest-old)(Eurostat 2017). This phenomenon, called ‘silvering’, is expected to result in a three-fold increase of the oldest-old towards 2050 (United_Nations 2015).

1.2 Functional disability and fall risk

Aging of the population indicates that health conditions are improved, which is a human success story. However, aging will increase the likelihood to suffer from disabilities. Disability can be defined as the experienced difficulty doing activities in any domain of life due to a health or physical problem (Verbrugge and Jette 1994). These problems originate from a certain pathology that refers to biochemical and physiological abnormalities that are detected and medically labeled as diseases, injury, congenital or developmental conditions (Verbrugge and Jette 1994). Older people are more vulnerable to develop chronic pathologies like cardiovascular, respiratory, endocrine or metabolic diseases, mental health problems and musculoskeletal disorders (World_Health_Organisation 2015). The National Council of Aging indicates that about 80% of older people have at least one chronic pathology (National_Council_on_Aging 2018). Physiological function progressively deteriorates from middle age onwards, can evolve into impairments and functional limitations and eventually leads to the inability to perform activities of daily life independently, known as disability (Fig. 3)(McPhee et al. 2016). These impairments can be defined as dysfunctions and significant structural abnormalities in specific body systems that can lead to functional limitations which are restrictions in performing fundamental physical and mental actions used in daily life (Verbrugge and Jette 1994). This thesis will mainly focus on impairments in the musculoskeletal system and the associations with functional limitations. Although an individuals’ functional performance capacity is multifactorial, researchers and clinicians have been using a multitude of functional tests in order to objectively assess functional performance. In this regard, tests such as standing balance, rising from a chair, timed up and go, usual and fast walk and stair climbing have been validated (Guralnik et al. 1994; Reuben and Siu 1990) and have been shown to reveal age-related declines in functional performance (Bassey et al. 1992; Cuoco et al. 2004; Foldvari et al. 2000).

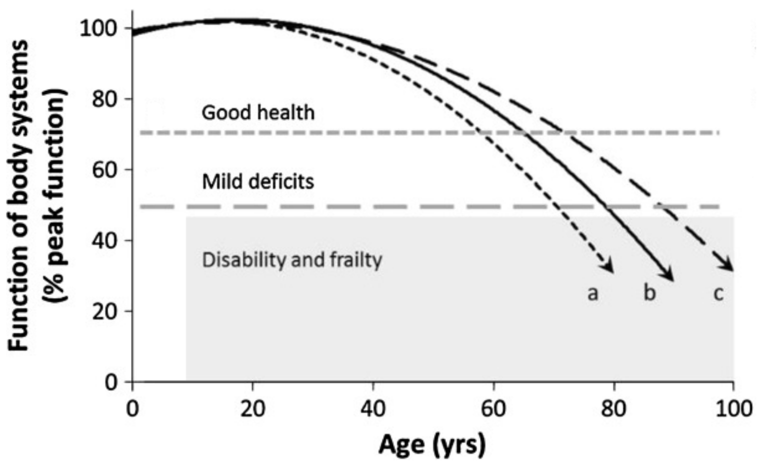

Fig. 3 Schematic representation of aging trajectories. The curved lines represent a) accelerated aging, b) normal aging and c) healthy aging. Adapted from (McPhee et al. 2016).

Aging does not only imply a loss of functionality and independency, but also a higher risk for falling. About 24-40% of community-dwelling people, aged 65 or older, fall at least once a year, whereas this number increases to 50% for residents in care facilities (Milat et al. 2011). The more disabled condition of the latter population is even more pronounced by the finding that almost half of those 50% experience recurrent falls (Kannus et al. 2005). In addition, the number of fall incidents increases with age (World_Health_Organisation 2007) resulting in small (i.e. tissue damage or distortion) or serious injuries (i.e. trauma or fracture)(Gudnadottir et al. 2018; Milat et al. 2011). A fall-related injury in the elderly is the leading cause to be hospitalized (Scuffham et al. 2003). Fall-related fractures, for example hip fractures, may enlarge the dependency and disability of older people, which implies a higher risk to be institutionalized. Moreover, fall-related fractures are one of the most important causes of mortality (Kannus et al. 2005; Sànchez-Riera and Wilson 2017). The National Council for Aging Care declares that every 19 minutes, an older person dies because of a fall (National_Council_for_Aging_Care 2018). Next to the physical consequences, a fall induces also long-term psychosocial consequences, including fear of falling, social isolation and depression, which negatively effects self-confidence and the quality of life (Gillespie and Friedman 2007; Kannus et al. 2005; Roe et al. 2009; Stenhagen et al. 2014; Zijlstra et al. 2007). The problem of falling during aging increases the demand for primary health care and long-term care, requires the creation of more age-friendly environments (World_Health_Organisation 2015) and poses high medical costs caused by a fall incident (Hartholt et al. 2012). In Europe, the cost of a fall corresponds with approximately 1-1.5% of national health care expenditure and increases with age (Hartholt et al. 2012).

Taken together, aging is accompanied by a loss of functional performance capacity and a higher risk of falling, leading to a loss of autonomy. Due to this loss of autonomy, the rising medical costs and the higher need for primary health care, a relevant economic burden for the society exists. This emphasizes the magnitude of this age-related health problem. In an attempt to counteract this problem, a better understanding of the risk factors and underlying mechanisms is warranted. Therefore, many research areas focused on changes that occur during the aging process. A combination of neural, hormonal, immunological, physiological and external factors such as nutrition, physical activity and the environment seem to play a role in the loss of functional performance capacity and the higher risk of falling during aging (Rolland et al. 2008).

2 Aging and muscular function

Although the origin of functional disability with aging may be multifactorial, adequate muscular function is a prerequisite for human movement and locomotion. Muscular function represents the total muscular output driven by numerous neural, physiologic and molecular mechanisms. Over the last half-century, many reports demonstrated that aging is accompanied by declines in muscular function. Moreover, it has been shown that measures of muscular function are strongly related to functional performance in old age. However, as will be described in the following sections, factors such as **response time**, **contraction type**, **movement complexity** and **acceleration rate** may have an influence on muscular function, but need more attention in aging research. A better understanding of age-related changes in muscular function could lead to the improvement of methods to identify risk factors and develop effective treatments to counteract functional decline with aging. In the following chapter, the basic concepts and an overview of the current literature with regard to age-related changes in muscular function are given.

2.1 Muscular function: measures and concepts

A multitude of measures have been used to express muscular function in research and clinical practice. Therefore, the following section describes different measures and concepts of muscular function that are used throughout the thesis. The primary measure that is commonly used in research and clinical practice is maximal muscle strength.

> *Muscle strength* can be defined as the force developed through the contraction of one or multiple muscle groups that is transferred via tendons to the bone to induce joint movement.

Muscle strength is dependent on the **type of contraction**, which can be concentric, isometric or eccentric (Fleck and Kraemer 2004).

> A *concentric* contraction can be defined as a *dynamic* muscle action for which the external load on the muscle is less than the force developed by the muscle fibers, inducing the shortening of the muscle.

An *isometric* contraction can be defined as a *static* muscle action for which the external load on the muscle is equal to the force developed by the muscle fibers.

An *eccentric* contraction can be defined as a *dynamic* muscle action for which the external load on the muscle is larger than the force developed by the muscle fibers, inducing lengthening of the muscle.

Among the abovementioned contraction types, muscle strength can be developed in a static or dynamic way. Static strength or the force that can be applied against an immovable object can be referred to as isometric strength, whereas dynamic strength can be referred to as isotonic or isokinetic strength depending on the contraction type (Fleck and Kraemer 2004).

An *isotonic* contraction can be defined as a dynamic muscle contraction against a constant external load. Explosive isotonic movements are ballistic movements for which maximal velocity is developed against a constant external load.

An *isokinetic* contraction can be defined as a dynamic muscle contraction at a constant speed of movement. Isokinetic movements allow for maximal force production at a fixed velocity.

Muscle strength in dynamic actions is influenced by the velocity of the movement. Isokinetic strength is often expressed as force at a certain velocity, while isotonic strength is mostly expressed as the product of force and velocity, which is referred to as muscle power.

Muscle power describes the muscle's ability to perform work and the amount of energy transferred per unit of time (Macaluso and De Vito 2004). In this dissertation, the term 'muscle power' will refer to a single explosive movement.

In this way, muscle metabolism does not limit the performance of muscle power. This is different from 'sustained power', which refers to the ability to maintain a submaximal level of power output in activities of longer duration such as cycling or running (Macaluso and De Vito 2004). However, the effect of age on muscular function during activities of longer duration, which is referred to as strength endurance or fatigue resistance, is beyond the scope of this thesis. Yet, the duration to reach peak force/power (i.e. **response time**) in a maximal versus an explosive muscle action also differs (Aagaard et al. 2002) and should be accounted for when investigating muscular function. A limited duration to develop force/power explosively may be relevant to short response times (< 75ms) in for example balance recovery after sudden perturbations (Pijnappels et al. 2005a).

> The *rate of force/torque/power development* (RFD/RTD/RPD) reflects the ability to rapidly produce force/torque/power and corresponds to the short response times that are normally available to accelerate the limbs during many functional tasks (Maffiuletti et al. 2016).

RFD/RTD/RPD can be calculated as the magnitude of force/torque/power developed within a certain time period and can thus be identified as a time-dependent parameter.

Parameters of muscular function are often measured using single-joint approaches for standardization. In contrast with simple single-joint actions, multi-joint actions are more complex, because of multiple muscles that work over multiple joints. Therefore, single- and multi-joint actions differ in terms of **movement complexity**.

2.2 Age-related changes in muscular function

2.2.1 Age-related declines in muscle strength

The most standardized way to measure the maximal force generating capacity of the muscles is by using isometric test methodologies. Portable and inexpensive hand grip dynamometers have been used for decades to assess isometric strength in clinical practice (Fisher and Birren 1946). Several reports demonstrated that low hand grip strength can predict disability, hospitalization and mortality (Newman et al. 2006; Rantanen et al. 1999) and may have a role in risk stratification in the elderly (Mitchell et al. 2012). However, age-related loss in muscle strength has been suggested to be region specific with the proximal muscles of the lower extremities being more affected by strength losses compared to those of the upper extremities (Frontera et al. 2000; Lynch et al. 1999). The latter has been ascribed to a reduced use of the lower compared with the upper limb muscles (Frontera et al. 2000; Lynch et al. 1999). For example, individuals with weak knee extensor strength support their knee extensor movements with other muscles, like arm muscles to rise from a chair or alter their behavior to avoid activities such as climbing stairs (Mitchell et al. 2012). Loss of knee extension strength is associated with functional limitations in daily activities (Skelton et al. 1994) and increased fall risk (Pijnappels et al. 2008b). Moreover, knee extension strength is more associated with disability and mortality compared to hand grip strength (Mitchell et al. 2012). Therefore, this dissertation will focus on the knee extensors in order to unravel the mechanisms behind the age-related decline in muscular function.

Generally, the maximum force generating capacity of an individual peaks around the second and third decade, decreases slowly until around the fifth decade and further declines at 12 to 15% per decade with even steeper declines above 65 years of age (**Fig. 4**)(Lindle et al. 1997; Macaluso and De Vito 2004). Cross-sectional studies reported age-related differences of 20-40% in maximal isometric strength of the knee extensors between young (i.e. 20-30 years) and older adults (i.e. 70-80 years), with greater differences between young and older adults in their ninth decade (Doherty 2003). It should be noted that these declines may be an underestimation of the decline in muscular function of the whole population as many older adults might be excluded from investigations because of contra-indications etc. Longitudinal studies reported somewhat greater declines in isometric strength of about 0.3-3.2% per year (Aniansson et al. 1986; Doherty 2003; Greig et al. 1993). Yet, the latter studies were limited to older adults and to relatively short follow-ups (7-8 years) making their results less relevant for young or middle-aged populations. For middle-aged men, Kennis et al. (Kennis et al. 2014) reported a decline of -2.06Nm (± 0.41Nm) of isometric strength per year over a 10-year follow-up.

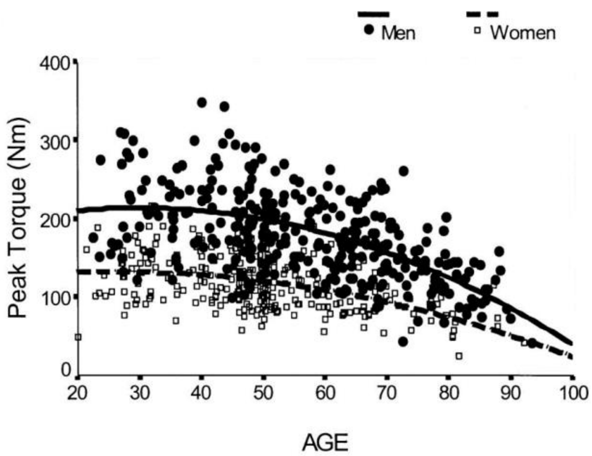

Fig. 4 Age-related decline of knee extensor muscle strength in men and women. Adapted from (Lindle et al. 1997).

As visualized in **Fig. 4**, it is well known that absolute strength is lower in women than in men in all stages of life (Lindle et al. 1997). To note, the relative loss of strength with advancing age is found to be similar for men and women (Macaluso and De Vito 2004). Yet, women may be more susceptible to disability as absolute maximal strength in women at older age can approach the minimum strength needed to perform daily activities (Skelton et al. 1994).

2.2.2 Influence of contraction type on muscular function during aging

Traditional strength assessments like maximal isometric contractions may be less indicative for the functional ability to perform daily activities as they do not include any movement. Most daily movements are developed by the generation of force at a certain velocity. Although isometric strength clearly declines during aging, this decline appears to be even greater for concentric strength (Hortobagyi et al. 1995). Isokinetic testing has shown greater losses of strength of about 30-50% and greater declines at higher velocities (Delmonico et al. 2009; Doherty 2003; Yu et al. 2007). Generally, a shift in the force-velocity relationship at joint level is apparent during aging as visualized in **Fig. 5** (Raj et al. 2010). This force-velocity relationship is characterized by a lower maximal force generating capacity at older age which increases with increasing contraction velocity. In addition, in vivo maximal contraction velocity is shown to be decreased with advancing age (Dalton et al. 2010; Lanza et al. 2003). This maximal contraction velocity has mostly been derived from isotonic testing against minimal loads (i.e. weight of the tested limb and lever arm). Moreover, it has been demonstrated that maximal unloaded velocity may be a key determinant in the onset of functional disability during aging (Pojednic et al. 2012; Van Roie et al. 2011). Taken together, both muscle strength as well as contraction velocity are shown to decline during aging and can give insights into the declines in muscular function.

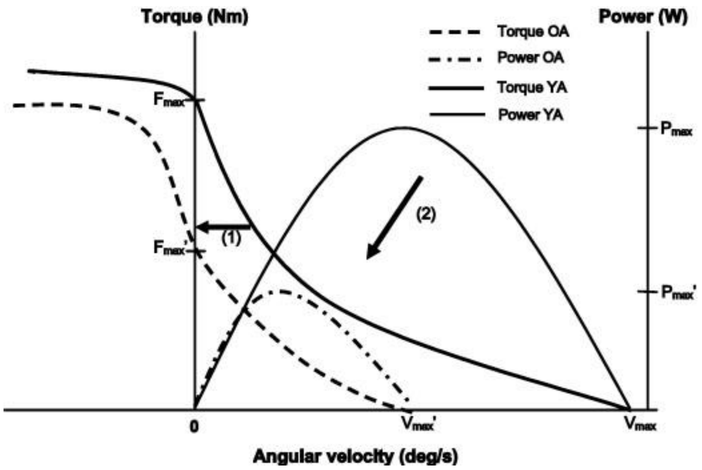

Fig. 5 Summary of the changes to the f-v (1) and p-v (2) relationship with age based on data from studies referenced by Raj et al. OA, old adults; YA, young adults; Pmax’, old adults’ maximal power; Vmax’, old adults’ maximum contraction velocity; Fmax, young adults’ peak isometric torque; Fmax’, old adults’ peak isometric torque. (Raj et al. 2010)

The concomitant age-related declines in muscle strength and contraction velocity suggest that muscle power may be even more vulnerable to the deteriorating effect of aging (Reid and Fielding 2012). **Fig. 5** visualizes the large age-related decline in maximal power production based on data from several studies described by Raj et al. (Raj et al. 2010). As a result of the decline in force and velocity capacities, the power-velocity relationship is clearly shifted due to the effect of aging (**Fig. 5**).

Compared with isometric strength measurements, testing muscle power is more difficult in terms of standardization and equipment. Several methods that differ in **contraction type** and movement complexity have been used to measure muscle power. Compared with isokinetic testing, isotonic testing may better reflect everyday activities as they include load bearing exercises. Average annual declines of 0.7 – 1.8% have been reported for isotonic power, although they were measured in single-joint isotonic tests (Kennis et al. 2014; Lanza et al. 2003). Yet, the majority of research have focused on more functional multi-joint movements, although those are accompanied by a number of limitations due to their **movement complexity**. For example, vertical jump performance on a force platform can be used as a measure of functional muscle power and was found to be reduced with aging (De Vito et al. 1998; Ferretti et al. 1994). However, this method may not be safe for older individuals.

In addition, older adults generally lose force, but keep or gain body weight. Therefore, older individuals need a higher percentage of their maximum strength and have relatively seen more difficulty to lift their body weight compared to younger individuals, which forces their muscles to act in a less favorable portion on the force-velocity curve (Macaluso and De Vito 2004). The latter disadvantage might overestimate age-related declines in power and remains apparent for isotonic test approaches as long as the load is not adapted relative to the subjects' maximal strength (Bassey and Short 1990). To counteract this disadvantage, several isotonic approaches of multi-joint test methods, such as leg-press and squat devices according to the following references, have been created to accurately measure muscle power at relative loads. In this regard maximum explosive power has been shown to be lower in older compared to younger individuals and to be more affected by aging as isometric strength (Izquierdo et al. 1999b; Macaluso and De Vito 2003). Average annual decline rates of about 0.6 – 1.5% have been reported for maximal multi-joint power during aging (Allison et al. 2013; Edwen et al. 2014; Kostka 2005; Yamauchi et al. 2009). Moreover, Skelton et al. (Skelton et al. 1994) showed that after the age of 65 years, muscle power declines at an even higher rate (i.e. 3-4% per year). Taken together, it is generally accepted that the loss in muscle power is greater than the loss in muscle strength (Izquierdo et al. 1999b; Lauretani et al. 2003). This greater loss in muscle power might be explained by the additional loss of contraction velocity over the loss in muscle strength as mentioned above.

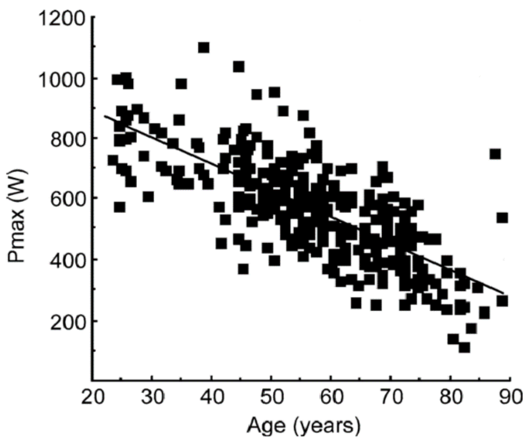

Fig. 6 Age-related decline of maximal quadriceps power in men. Adapted from (Kostka 2005).

The age-related loss of muscle power has a negative impact on functional performance capacity. It is demonstrated that maximal power is strongly related to mobility, functional status and mortality (Fragala et al. 2015). Reduced functional performance in tasks such as stair climbing, raising from a chair and walking is shown to be strongly associated with declines in muscle power, more than muscle strength (Bassey et al. 1992). Furthermore, leg press muscle power was found to be the strongest predictor of functional ability and mobility problems (Foldvari et al. 2000; Lauretani et al. 2003). As a result, dynamic muscle power has greater external validity to functional movements compared to isometric strength.

Altogether, it is well established that isometric and, to a greater extent, concentric muscle strength decrease during aging. As an exception, eccentric strength is shown to be better preserved during aging, probably as a result of increased muscle stiffness due to the accumulation of non-contractile material and changes in the contractile properties of muscle fibers (Mitchell et al. 2012). However, the effect of age on eccentric muscle strength is beyond the scope of this thesis.

2.2.3 Influence of response time on muscular function during aging

The majority of methodologies that evaluated the effect of age on muscular function focused on maximal strength and maximal power characteristics as described above. Since maximal isometric strength sets the reserve limit and maximal power represents maximal strength capacity in dynamic actions, they are of utmost importance to perform many activities of daily life (Lauretani et al. 2003). However, maximal strength requires more than 300ms to be achieved (**Fig. 7**)(Aagaard et al. 2002; Thompson et al. 2018), whereas explosive muscle actions such as balance recovery after sudden perturbations correspond to shorter **response times** (< 200ms)(Maffiuletti et al. 2016). Therefore, the rate of force development might be more relevant in situations that require rapid and powerful muscle actions than maximal strength (Pijnappels et al. 2005a).

Several studies investigated the effect of age on RFD/RTD and reported substantial reductions in old versus young adults (Häkkinen et al. 1998; Klass et al. 2008; Korhonen et al. 2006; Suetta et al. 2009; Thompson et al. 2014b). Moreover, Thompson et al. (Thompson et al. 2013) showed that the age-related decline in RTD was larger than the decline in maximal strength. In addition, the reductions in RFD/RTD at older age are found to be associated with impaired balance recovery during tripping (Izquierdo et al. 1999a; Pijnappels et al. 2005b; Pijnappels et al. 2008a). Even though the majority of studies used single-joint approaches, the effect of age on RFD has also been investigated using multi-joint methods. In this regard, Izquierdo et al. reported a 46% lower peak force and a 64% lower peak RFD for older men (~70 years) compared with young men (~20 years) performing an isometric bilateral squat (Izquierdo et al. 1999a). Moreover, they demonstrated that the age-related reduction in RFD was associated with decreased postural stability. On the other hand, Allison et al. found a 19% lower peak force and a 21% lower peak RFD between young (~24 years) and older (~66 years) men performing an isometric unilateral leg press movement (Allison et al. 2013). Recently, Thompson et al. (Thompson et al. 2018) demonstrated greater reductions of RFD in multi-joint versus single-joint actions during aging. The latter findings underscore the value of multi-joint testing and rapid force characteristics to detect age-related changes in muscular function that are relevant for activities of daily life.

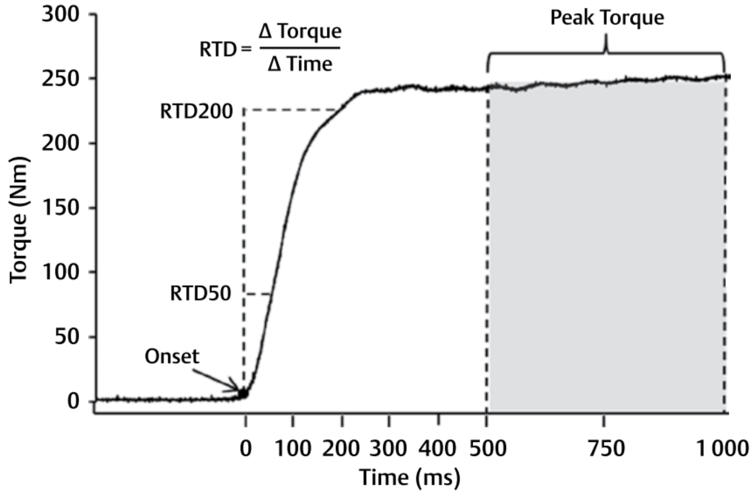

Fig. 7 Representative torque-time curve of a maximal voluntary knee extension contraction. Peak torque is often measured as the highest 500ms epoch, whereas the rate of torque development (RTD) represents the initial ascent of the curve at for example 0-50ms or 0-200ms. Adapted from (Thompson et al. 2018).

Interestingly, Thompson et al. (Thompson et al. 2014a) used a similar approach to look at age-related changes in the rate of velocity development (RVD) or **acceleration rate** and reported a greater difference in RVD compared to maximal unloaded velocity of the knee extensors between young and older men. These findings underline the importance of the time to peak velocity (ttpV) and suggest that RVD can be more discriminatory between age-groups compared to maximal unloaded velocity. Taken together, this chapter emphasizes the importance to focus on time-dependent parameters to identify functionally relevant and substantial declines in muscular function with advancing age.

2.3 Missing factors in current testing

Although a lot of research investigated changes in muscular function that occur with aging as described above, factors that have a clear influence on muscular function such as response time, contraction type, movement complexity and acceleration rate may need further investigation. In terms of **response time** and **contraction type**, no research focused on time-dependent parameters of muscle power, while both time-dependent measures as well as maximal muscle power are shown to be highly discriminative between age-groups and functionally relevant. The effect of age on the rate of power development in isotonic and isokinetic testing and its functional relevance should therefore be investigated. Furthermore, **movement complexity** describes the coordination of agonist, synergist and antagonist muscles that is more complex in multi-joint than in single-joint movements. Therefore, researchers often prefer single-joint testing to better standardize their test set-up. However, single-joint movements such as isolated knee extensions might be less relevant to activities of daily life compared to multi-joint movements such as leg press, squat, vertical jump, etc. For this reason, research should also focus on the influence of multi-joint testing on muscular function. However, no research investigated the effect of age on single- versus multi-joint movements in terms of muscle power characteristics. Finally, it was previously suggested that time-dependent measures of muscular function such as RFD are more relevant to fast actions such as recovery after sudden perturbations than maximal strength. However, no research focused on the effect of age on muscular function in response to sudden perturbations or **accelerations**. Therefore, this thesis will focus on these factors to expand our understanding of the effect of age on muscular function as further explained in chapter 4 'Objectives and general outline of the thesis'.

3 Underlying mechanisms of the age-related decline in muscular function

Aging is accompanied with a variety of quantitative and qualitative physiological changes. Yet, the physiological origin of the age-related declines in muscular function, whether on a muscular, fiber or molecular level, may depend on the specific characteristics of the muscle action. In this regard, it has been suggested that the physiological basis of maximum isometric force production, explosive isometric force production or power production differs. However, the physiological basis of the different characteristics of muscular function are not yet fully understood, neither the underlying mechanisms of its age-related deterioration. The following chapter describes the main physiological changes that occur during aging and that potentially affect muscular function. A better understanding of the mechanisms underlying the declines in muscular function with aging can help to find optimal strategies to counteract this age-related deterioration.

3.1 Mechanism of a muscle contraction

To better understand the mechanisms behind the age-related decline in muscular function, this section describes the main mechanisms of normal muscle contraction. In general, the anatomy of skeletal muscles consists of tightly bundled muscle fibers that are structured in a suspension-bridge cable-like configuration and reinforced by various connective tissues (**Fig. 8**)(Clark and Manini 2008). The **quantity** of this cable-like configuration is referred to as muscle mass, whereas the **quality** of a muscle contraction largely depends on characteristics at the fiber, neural, architectural and tendon level.

Figure 8 visualizes the main physiological mechanisms that regulate muscular function and that are affected by aging as explained in the following sections. The basic element of a muscle contraction are the motor units. Within a motor unit, several muscle fibers are innervated through a single motor neuron by its branches. Slow motor units consist of type I fibers (i.e. slow twitch fibers) and contain a smaller number of fibers compared to fast motor units that consist of type II fibers (i.e. fast twitch fibers)(Silverthorn 2015). Type I fibers have a lower shortening velocity and force generating capacity than type II fibers, whereas the latter are less fatigue-resistant (Bottinelli et al. 1991). The muscle contraction itself consists of three successive phases: excitation, coupling and contraction (Silverthorn 2015). The excitation phase starts when a motor nerve fires off an action potential that moves through the muscle fiber down the sarcoplasmic reticulum and triggers the release of Ca^{2+} (**Fig. 8**). Consequently, myosin heads quickly couple to actin within the sarcomeres, which are the basic units that contract within a muscle fiber, during the coupling phase. During the contraction phase, the myosin heads are constantly cross-bridging, pulling and releasing on actin in order to contract the sarcomere.

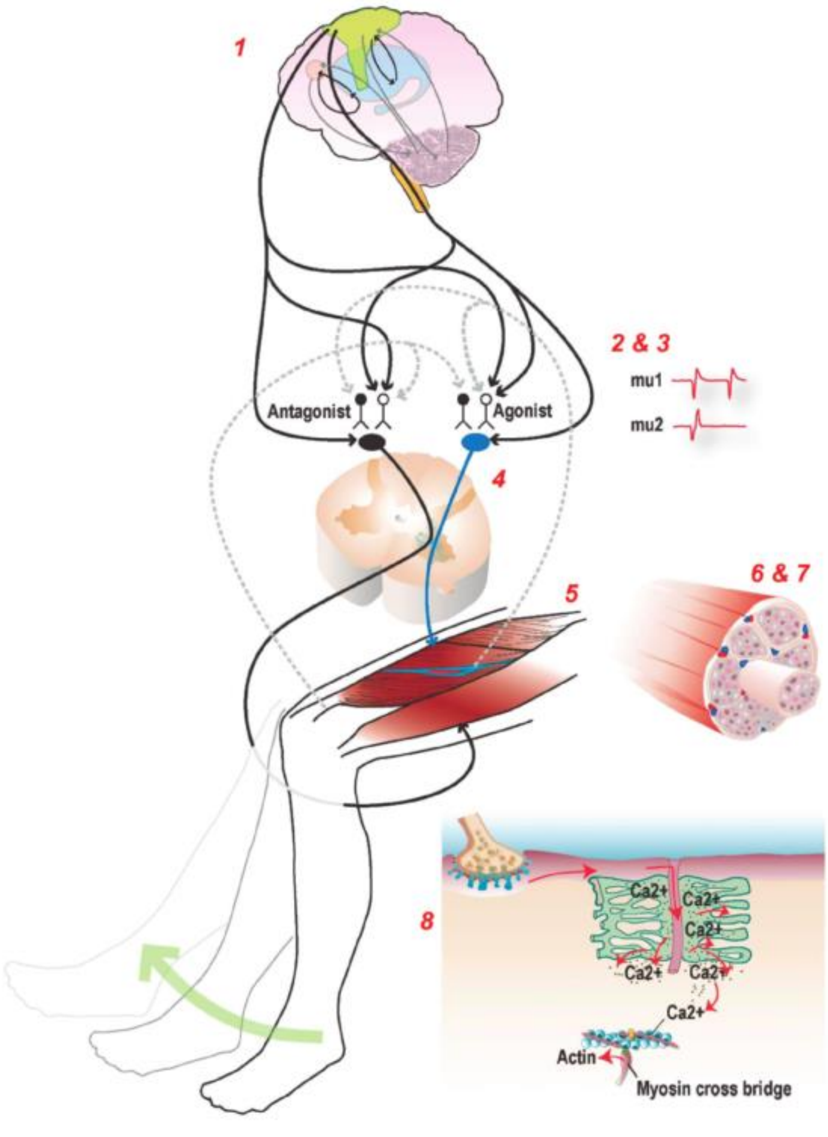

Fig. 8 Potential sites and physiological mechanisms that are affected by age and that regulate muscular function. (1) decreased cortical excitability, (2) decreased spinal excitability, (3) decreased maximal motor unit discharge rate, (4) slowed nerve conduction, (5) alterations in muscle architecture and tendon stiffness, (6) decreased muscle mass, (7) increased myocellular lipid content, (8) excitation-contraction uncoupling. Reproduced from (Clark and Manini 2008).

3.2 Effects of age on muscle morphology and physiology

3.2.1 Age-related loss of muscle mass

The most striking and most studied physiological change with aging is the **quantitative** loss of skeletal muscle mass (Narici and Maffulli 2010). The loss of muscle mass has been referred to as 'sarcopenia', which means 'poverty of flesh' in ancient Greek, as introduced by Rosenberg in 1989 (**Fig. 9**)(Rosenberg 1997). Epidemiological studies demonstrated declines between the ages of 20 to 80 years old in total lean body mass (LBM) of up to 27% (Janssen et al. 2000). These declines were detectable after the age of 45 years. However, from 20 to 40 years, muscle mass remains rather constant, whereas total body mass generally increases. As a result, LBM relative to total body mass was found to decline already from the third decade (Gallagher et al. 1997). In addition, declines in skeletal muscle mass were found to be greater in the lower limbs (-15%) compared to the upper limbs (-10%)(Janssen et al. 2000). The possible reason for this dissimilarity is yet unclear, although this may be likely due to detraining, as physical activity is reduced in aged individuals (McPhee et al. 2016). Specifically for the thigh muscles, regional losses of about 24-27% from the 2nd to the 7th decade have been reported (Janssen et al. 2000).

Generally, the loss in LBM is thought to be mainly the result of increased fat mass relative to total body mass (Narici and Maffulli 2010), increase of intramuscular fat and connective tissue known as 'myosteatosis' (Taaffe et al. 2009) and atrophy of the muscle fibers due to denervation (see following sections). Specifically for the thigh muscles, increments of 59-127% intramuscular fat have been reported for older men compared to younger men, as well as annual increases of 18% in longitudinal designs (Fragala et al. 2015). Despite these increases in fat mass with aging, a decrease in food intake across the life span is observed (Morley 1997). In addition, the intake of high quality proteins has been demonstrated to be less than 1 g/kg/day for more than 50% of older adults aged above 60 years and less than 0.8 g/kg/day, which is recommended for healthy adults, for 30% of a sample of older subjects (Roubenoff and Hughes 2000). Moreover, next to the limited amount of total daily protein intake in older adults, protein intake might be non-equally distributed over different meals, e.g. > 40 g of protein within one meal, but too little during other meals. The existence of a saturable dose-response relationship between muscle protein synthesis and the quantity of protein consumed per meal provides a rationale for promoting a balanced pattern of protein intake during the day (Murphy et al. 2016). Because adequate protein intake, together with physical activity, is necessary to stimulate muscle protein synthesis for maintenance of skeletal muscle mass via amino acid supply, multiple studies suggested that older adults need a higher dietary protein intake compared to younger adults (Deutz et al. 2014; Gray-Donald et al. 2014). However, the existing evidence of enhanced benefits of exercise training when combined with protein supplementation is inconsistent (Denison et al. 2015).

In addition, it is shown that age reduces the efficacy of protein supplementation during resistance training with no additional effect on fat free mass from about the seventh decade onwards (Morton et al. 2018). However, the older adults involved in the latter review consumed on average only 20 g of extra protein per day which could have caused the negative relationship between age and fat free mass. Although more research is necessary, Morton et al. recommended that older adults have an increased need for high quality proteins compared with younger individuals, i.e. up to 1.6 g/kg/day, because older individuals are anabolically resistant (Morton et al. 2018). A protein intake between 1.2 – 1.6 g/kg/day for older adults is currently advised (Bauer and Diekmann 2015; Phillips et al. 2016; Traylor et al. 2018). Even more, the target of 0.4 g/kg/meal of high quality protein may be necessary to apply the per-meal concept into practice (Murphy et al. 2016).

Nowadays, the concept of sarcopenia is not only characterized by a progressive loss in muscle mass, but also incorporates the loss in muscle strength (Roubenoff 2000). Several studies reported that the loss in muscle mass is the primary determinant of the age-related decline in muscle strength (Frontera et al. 1991; Reed et al. 1991; Visser et al. 2005). However, the decline in muscle strength is found to be more severe than the concomitant decline in muscle mass (Delmonico et al. 2009; Frontera et al. 2000; Goodpaster et al. 2006; Metter et al. 1999; Overend et al. 1992). Moreover, muscle strength corrected for muscle mass, which can be referred to as '**muscle quality**', has been shown to be a better predictor of functional performance in older adults compared to muscle strength or muscle mass alone (Barbat-Artigas et al. 2013; Estrada et al. 2007; Misic et al. 2007). The age-related loss of muscle strength independent of the loss of muscle mass has been referred to as 'dynapenia' or 'poverty of strength' (Clark and Manini 2008). The steeper declines in strength relative to mass must originate from other mechanisms than the quantitative loss of muscle. The following sections will describe the possible mechanisms underlying the loss of muscle quality.

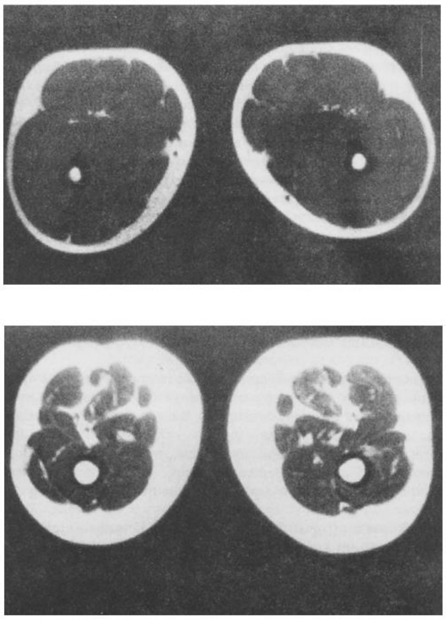

Fig. 9 Proportion of lean-body mass (gray) versus fat (white) in the thighs of a young (upper) versus old woman (lower image). Adapted from (Rosenberg 1997).

3.2.2 Age-related changes at the fiber level

To better understand the mechanisms behind the age-related decline in muscle quantity and quality, this section describes the main age-related changes that occur at the fiber level.

With aging, the loss of **muscle quantity** is attributed to a decrease in muscle fiber size (i.e. atrophy) and a decrease in number (i.e. hypoplasia), particularly in type II fibers (**Fig. 10**)(Larsson et al. 1979; Narici and Maffulli 2010). To note, the effect of aging seems to be different in different muscle groups (Kirkeby and Garbarsch 2000). In particular for the vastus lateralis knee extensor muscle, a difference of 25% fewer muscle fibers between 20 and 70 year old individuals as well as a 42% lower size and total percentage of type II fibers has been reported (Larsson et al. 1978; Lexell et al. 1983). However, other studies found similar age-related declines in the number of type I and II muscle fibers indicating that there is no preferential loss of type I or II fibers (Lexell et al. 1988; Purves-Smith et al. 2014). It has been suggested that both fiber types are lost during aging, but with a different time course (Andersen 2003). Loss of type II fibers mainly occurs from 25 years till the end of the seventh decade, whereas loss of type I fibers is mainly apparent from the eight decade onwards (Narici and Maffulli 2010).

The age-related loss of muscle fiber size and number may be due to motor unit denervation and a preferential loss of fast motor units, although the latter may be argued as mentioned above (Lang et al. 2010). The number of motor units have been found to remain almost constant till the age of 60, but rapidly decline thereafter at a rate of 3% per year (Campbell et al. 1973). In addition, fibers that are de-innervated will either be re-innervated by surviving motor units or will disappear (Mosole et al. 2014). As a result, the size of the remaining motor units increases (Campbell et al. 1973). Yet, several mechanisms that contribute to the loss in fiber size and number take place at a molecular level. In this regard, aging is accompanied with impaired protein synthesis and decreased muscle anabolism, which may be caused by decreased protein intake and physical activity together with decreased expression of hormonal factors that promote protein synthesis (e.g. IGF-1) as well as increased levels of pro-inflammatory cytokines, hormones and oxidative stress that promote protein degradation (e.g. TNF-α, IL-6)(Bautmans et al. 2005). Moreover, aged muscle fibers contain more lysosomes, which increases the potential for protein degradation (Scelsi et al. 1980). Furthermore, satellite cells, which are the major stem cell population responsible for skeletal muscle regeneration during adulthood, are shown to be decreased in number and impaired in function during aging (Chakkalakal and Brack 2012).

Next to the decline in muscle mass, the decline in **muscle quality** may be explained by changes at the fiber level. Changes in the distribution of fiber types may affect muscle quality as fast twitch muscle fibers are known to produce more force compared to slow twitch fibers (Bottinelli et al. 1991). Although a preferential loss of type II fibers may not be true, a transition of fast twitch muscle fibers to take on slow twitch characteristics appears to be apparent during aging and may lead to the reduced force production (**Fig. 10**)(Lang et al. 2010). The most appropriate markers for fiber type delineation are represented by myosin heavy chain (MHC) isoforms (Pette and Staron 2000). Based on this, pure fiber types I or II are characterized by the expression of a single MHC isoform, whereas hybrid fiber types express two or more MHC isoforms (Pette and Staron 2000). In this regard, an increased co-expression of MHC-I and MHC-II at older age has been reported for at least one-third of the fibers that are neither type I nor type II (Andersen 2003; D'Antona et al. 2003). In addition, the loss of specific tension may be due to a reduction in single fiber force per cross-sectional area (D'Antona et al. 2003). The latter has been associated with a decrease in the number of actomyosin cross-bridges, a reduction in excitation-contraction coupling and protein glycation (Narici and Maffulli 2010). The reduction in excitation-contraction coupling may be the result of a decline in the function of dehydropyridine receptors leading to reduced Ca2+ release by the sarcoplasmic reticulum (Delbono 2003). Protein glycation refers to the alteration of the structural and functional properties of contractile myosin (Haus et al. 2007).

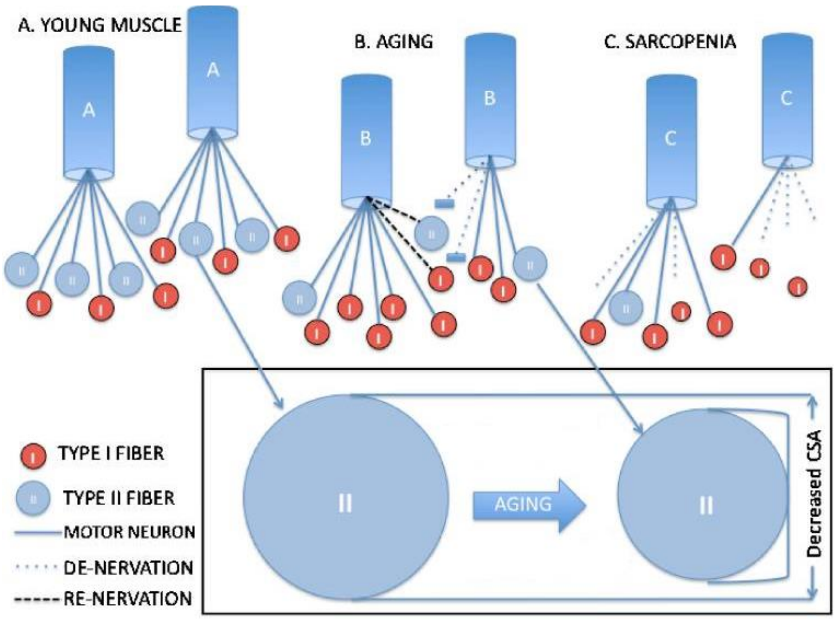

Fig. 10 Effect of age on the motor unit, depicting young, aged and aged sarcopenic fibers. This drawing depicts the decline in fiber size, denervation and renervation of muscle fibers in older subjects, with impairment of renervation in sarcopenic subjects as described in the following section 'Neural drive'. Figure adapted from (Lang et al. 2010).

The loss of power and of force development during fast explosive actions might be explained by an additional decrease in the maximal contraction velocity of the muscle fibers, next to the decreased force potential (Krivickas et al. 2001). For type II fibers, the decrease in shortening velocity might be explained by age-related changes in function and volume of the sarcoplamatic reticulum (Larsson and Salviati 1989). However for type I fibers, this decrease appears to be mainly the result of changes in the properties of the myosin protein (Hook et al. 1999). Because the muscle fibers take on the characteristics of the nerves that innervate them, we can assume that changes in MHC composition result from changes in neural drive (Fragala et al. 2015), which will be described in the following section.

3.2.3 Age-related changes in neural drive

In general, the nervous system is affected by age at multiple levels (**Fig. 9**)(Manini et al. 2013). To start, aging is accompanied by decreased supraspinal drive generated from the cortex (Sale and Semmler 2005). Further, a decline in the number of motor neurons with a preferential loss of alpha motor neurons that supply fast motor units is apparent in the spinal cord together with losses and changes in the properties of peripheral nerves (Lang et al. 2010; Power et al. 2013). Reduced spinal motor neuron excitability and increased pre- and post-synaptic spinal inhibition can lead to a reduction in peripheral nerve conduction speed with aging (Scaglioni et al. 2002). At the neuromuscular junction the number of axon terminals (Ramirez and Ulfhake 1992) and synaptic vesicles are reduced with aging (Kullberg et al. 1998). On the other hand, age-related increases in the number of axon terminals through sprouting and branching and increases in the number of neurotransmitters have been reported (Gordon et al. 2004). The latter may explain the adaptive mechanism of motor units that re-innervate de-innervated muscle fibers (see 3.2.2).

As a result of changes in the nervous system, fine motor control is impaired with aging. The magnitude of neural activation depends on the number of motor units that are activated (i.e. MU recruitment) and the rates at which the motor neurons discharge the action potentials (i.e. MU discharge rate or MU firing frequency)(Duchateau and Baudry 2014). Neural activation is changed in both agonist and antagonist muscles because of aging. Elevated levels of antagonist coactivation have been observed in older adults (Izquierdo et al. 1999a; Macaluso et al. 2002), whereas the neural drive to agonist muscles is shown to be reduced (Harridge et al. 1999; Stevens et al. 2003). To evaluate these neural deficits, previous research have been using electrophysiological techniques by investigating the additional force when delivering a supramaximal electrical stimulus to a nerve or muscle during a maximal voluntary contraction (Clark and Manini 2008). In this way, the reduced neural drive in the older adults was presented by the reduced ability to voluntarily activate their quadriceps muscles compared to younger adults (Harridge et al. 1999; Stevens et al. 2003). In addition, a reduction in MU doublets (Christie and Kamen 2006), which can be described as two consecutive motor unit discharges that occur with short interspike intervals, and maximal MU discharge rate (Kamen 2005) have been shown to be reduced at older age. As an alternative for the electrophysiological techniques, surface electromyography (sEMG), which is a non-invasive method, has been used to monitor changes in overall neural activation. Using sEMG, previous reports found lower absolute sEMG amplitudes in old compared to middle-aged subjects (Hakkinen and Hakkinen 1995; Hakkinen et al. 1998). However, caution is advised when comparing inter-subject differences in sEMG, because sEMG amplitude is not only determined by MU recruitment or firing rate, but is also influenced by factors such as skin, subcutaneous and fat layers, electrode positioning etc.

3.2.4 Age-related changes in muscle architecture

The morphological changes in skeletal muscles that are associated with a reduction in muscular function not only involve the loss of muscle mass, but also a deformation of whole muscle architecture. Muscle architecture refers to the structural arrangement of muscle fibers (Lieber and Friden 2000). The number of sarcomeres in parallel, which reflects the muscle cross-sectional area and pennation angle, has an influence on the force generating capacity of the muscle, whereas the number of sarcomeres in series, which reflects fiber length, influences maximum shortening velocity. In this way, muscle architecture determines the muscle mechanical properties, namely the force-length and force-velocity relationships. Using ultrasound imaging technique, both muscle fiber fascicle length as well as its angle of insertion into the deep aponeurosis (i.e. pennation angle) have been reported to decline with aging (Narici et al. 2003). Consequently, it was suggested that these changes resulted in the loss of muscle shortening velocity and the loss of muscle strength (Thom et al. 2007). However, the effect of age on in vivo fascicle behavior during dynamic actions remains largely unknown, especially for the knee extensor muscles.

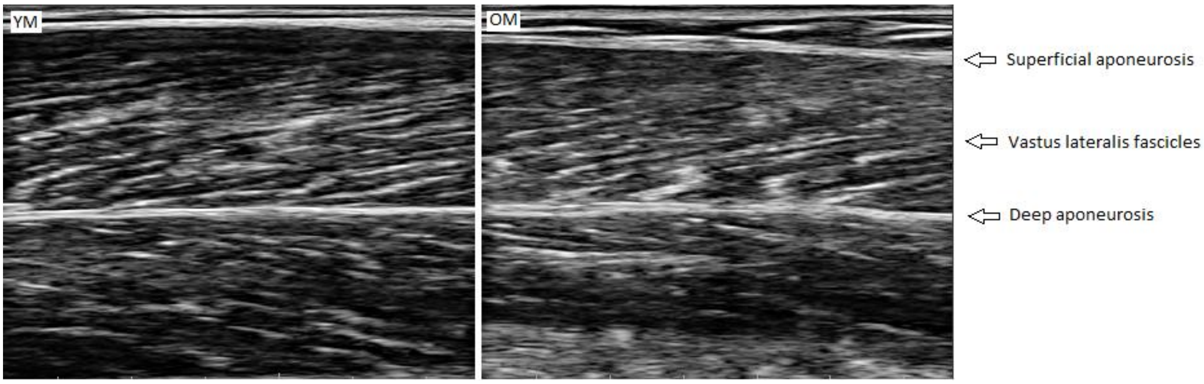

Fig. 11 Example of sagittal plane sonographs in a young (YM) and older (OM) man.

3.2.5 Age-related changes in tendon properties

To get a better idea of the mechanisms underlying age-related declines in performance, the whole muscle-tendon unit (MTU) should be taken into account. Muscle and tendon act as a unit in a way that muscle contractile force is transmitted via the tendon to the bone. Changes in the mechanical properties of the tendon with aging might have important functional consequences. First, a reduction in stiffness would cause the tendon to stretch more during muscle contraction inducing the fascicles to shorten more. As a result, the contraction length of the sarcomeres may be less optimal based on the force-length relationship. This reduction in force production would be additional to the effects of age on muscle mass, fiber composition and neural drive. Second, more compliant tendons require a longer time to be stretched, slowing down the moment of force transmission and increasing the risk for falling after tripping (Narici et al. 2008).

Since the technique of ultrasound imaging allows for the tracking of tendon deformations, studies have used this technique to demonstrate decreased tendon stiffness with advancing age (Karamanidis and Arampatzis 2006; Kubo et al. 2003; Onambele et al. 2006). In addition, stiffness of VL tendon-aponeurosis complex has been shown to significantly correlate with explosive force production (Bojsen-Møller et al. 2005). Moreover, it has recently been shown that reduced tendon stiffness contributes to the reduced rate of torque development in healthy older males (Quinlan et al. 2018). The underlying mechanisms of the age-related reduction in tendon stiffness are not yet fully understood, but might be linked to changes in tendon dimensions, hydration status, glycosamine concentration, elastin content, cross-linking or collagen content (Narici and Maganaris 2007; Quinlan et al. 2018).

4 Objectives and general outline of the thesis

In view of the major clinical and economic burden of sarcopenia, detection of early declines in muscular function during aging and prevention of a reduction in functional performance capacity through the development of effective strategies are of paramount importance. In 2010, the European Working Group on Sarcopenia in Older People developed consensus diagnostic criteria for sarcopenia, based on the presence of both low muscle mass and low muscle function (Cruz-Jentoft et al. 2010). In clinical settings, dual energy X-ray absorptiometry has been the gold standard for estimating muscle mass, while handgrip or knee extension strength tests are advised to measure muscle function (Roubenoff 2000). However, these methodologies are rather limited to capture the complex functioning of muscles during human locomotion and hence the age-related decline in muscular function (see 2.2). Factors such as response time, contraction type, movement complexity and acceleration rate are shown to have a clear influence on muscular function and should be integrated in methodologies (see 2). However, how these factors are affected by aging is not well understood. Therefore, the first objective is to identify early age-related differences in muscular function with the focus on response time, contraction type, movement complexity and acceleration rate. Moreover, a better insight into the underlying mechanisms of age-related differences in muscular function could help to develop effective strategies to counteract age-related deteriorations. Therefore, the second objective is to gain a better insight into the underlying mechanisms of the age-related differences in muscular function. This dissertation will further elaborate on these matters in the following chapters in an attempt to create awareness in clinical practice about underestimated or less known age-related problems and to bring new insights into the field of aging research to help finding solutions.

This doctoral thesis consists of three chapters and covers five scientific articles. **Chapter 1** focusses on factors such as response time and contraction type. More specifically, this chapter investigates the reliability and age-related differences of time-dependent measures of knee extensor function obtained through isotonic testing. **Chapter 2** focusses on movement complexity. It evaluates the effect of age on power production of the leg extensors in single- versus multi-joint movements. **Chapter 3** investigates the effect of aging on power production at different accelerations and aims to gain a better insight in the underlying mechanisms of the age-related decline in muscular function in terms of neural activation and in vivo fascicle behavior. A brief overview of the rationale and the objectives of all articles within the chapters is given in the following paragraphs.

4.1 Chapter 1 – The influence of response time and contraction type on muscular function at older age

Conventional methodologies do not limit the time available to produce force and exclude the factor **response time** by focusing on maximal strength. However, maximal strength requires at least 300ms to be achieved. This makes it less functionally relevant in situations that require quick and powerful responses of muscles, such as balance recovery following sudden perturbations (see 2.2.3). Parameters that reflect the ability to rapidly produce force, such as the rate of force development, correspond to the short response times that are normally available to accelerate the limbs during many functional tasks (< 200ms). Previous research that focused on rapid isometric force production already demonstrated 1) marked differences between young and older adults, between fallers and non-fallers, and 2) its link to functional performance (see 2.2.3). Yet, the research that investigated the effect of age on time-dependent muscle parameters focused on rapid isometric force production, whereas the effect of age on rapid power development remains unknown and may be more relevant to activities of daily life.

When accelerating the limbs during activities of daily life, force is seldom produced isometrically, but at a certain velocity resulting in power production. **Contraction type** is therefore an important factor in the evaluation of muscle function. It is well known that power and its velocity component decline more during aging compared with maximal isometric force production (see 2.2.2). Dynamic contractions are therefore preferred over isometric contractions to address age-related declines.

The gold standard for measuring dynamic muscular function in clinical practice and research settings is isokinetic dynamometry. However, considering that many activities of daily life involve moving a specific object (weight) and include an acceleration component, isotonic contractions could serve as a better indicator for daily life muscular function compared to isokinetic contractions (see 2.2.2). In the isotonic mode, muscle contractions are performed at a predetermined resistance (i.e. % of maximal isometric contraction) and a variable velocity (Power et al. 2011). To date, little is known on the reliability and age-related decline of measures of muscular function obtained through isotonic testing, in particular of parameters that reflect rapid power development. These issues will be addressed in **article 1** and **2** of the first chapter.

4.2 Chapter 2 – The influence of movement complexity on muscular function during aging

The loss of muscle power with aging has been mostly investigated for isolated single-joint actions, excluding **movement complexity**. Most activities of daily life involve lower limb multi-joint muscular work, which stresses the importance to understand the effect of aging on multi-joint actions (Azegami et al. 2007; Pijnappels et al. 2008a). To the authors knowledge, no research focused on the rate of power development during multi-joint actions. In addition, the influence of the velocity component on the loss in muscle power with aging during multi-joint movements remains poorly understood. Therefore, we aim to evaluate the effect of age on power production in single- versus multi-joint movements across different speeds in **article 3** within chapter 2.

4.3 Chapter 3 – The influence of acceleration on muscular function during aging and its underlying mechanisms

An important consequence of sarcopenia is the higher risk of falls. About 24-40% of community-dwelling people aged 65 or older fall at least once a year and frequency of falls increases with age (see 1.2). A better understanding in muscles' behavior in response to unexpected situations could give valuable insights with regard to fall prevention in the aged. During tripping for example, an abrupt change in movement velocity arises. If power can be developed rapidly, the chance that the imposed **acceleration** results in balance recovery increases and the risk of falling decreases. However, within our knowledge, muscle power development in response to different accelerations during multi-joint actions has not yet been investigated. Therefore, we aim to determine the effect of age on the decline in muscle power development at different accelerations in **article 4**.

As explained in chapter 3 of the introduction, several physiological mechanisms contribute to the age-related decline in muscular function. However, the specific mechanisms underlying the loss of maximal muscle strength might differ from those underlying the loss of rapid power development, given the difference in magnitude of the age-related losses (see 2.2). Moreover, the underlying mechanisms of the age-related loss of rapid power development have not yet been the focus of research, neither has the additional effect of acceleration. Therefore, we also aim to evaluate the age-related differences that are accompanied by the loss of rapid power development at different accelerations in terms of neural activity in **article 4**. **Article 5** aims to identify the underlying mechanisms of age-related losses in rapid power development at different accelerations in terms of in vivo vastus lateralis fascicle shortening behavior.

Table 2 gives an overview of the chapters and their focus.

Table 2. Project overview: investigation of factors that could affect muscular function during aging by focusing on different muscle parameters, test modes, test methods and acceleration rates in order to get a better insight into the aging process of muscular function.

		Factors								
		Response time		Contraction type		Movement complexity		Acceleration rate		
Chapter	**Article**	**Focus**	**Muscle parameters**	**Focus**	**Test mode**	**Focus**	**Test method**	**Focus**	**Acceleration**	**Study sample**
1	1	x	pP, RPD	x	Isotonic		Single-joint		n/a	63 older adults (♂ 27, age = 73 ± 4 years; ♀ 36, age = 72 ± 3 years)
	2	x	pP, RPD	x	Isotonic		Single-joint		n/a	36 young (♂ 21, ♀15, age = 22 ± 2 years) versus 56 older adults (♂ 26, ♀ 30, age = 68 ± 5 years)
2	3	x	pP, RPD		Isokinetic	x	Single- versus multi-joint		n/a	96 adults (♂ 49, ♀ 47, age = 20 – 69 years)
3	4	x	RPD		Isokinetic		Multi-joint	x	Imposed at 3200, 5700 and 7200 °/s²	Subgroup of 83 adults (♂ 43, ♀ 40, age = 20 – 69 years)
	5	x	RPD		Isokinetic		Multi-joint	x	Imposed at 3200, 5700 and 7200 °/s²	Subgroup of 39 men (age = 25 – 69 years)

Abbreviations: pP = peak power, RPD = rate of power development

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PART 2

RESEARCH ARTICLES

Chapter 1

The influence of response time and contraction type on muscular function at older age

Article 1

Test-retest reliability of knee extensor rate of velocity and power development in older adults using the isotonic mode on a Biodex System 3 dynamometer.

Van Driessche S, Van Roie E, Vanwanseele B, Delecluse C.

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Abstract

Isotonic testing and measures of rapid power production are emerging as functionally relevant test methods for detection of muscle aging. Our objective was to assess reliability of rapid velocity and power measures in older adults using the isotonic mode of an isokinetic dynamometer. Sixty-three participants (aged 65 to 82 years) underwent a test-retest protocol with one week time interval. Isotonic knee extension tests were performed at four different loads: 0%, 25%, 50% and 75% of maximal isometric strength. Peak velocity (pV) and power (pP) were determined as the highest values of the velocity and power curve. Rate of velocity (RVD) and power development (RPD) were calculated as the linear slopes of the velocity- and power-time curve. Relative and absolute measures of test-retest reliability were analyzed using intraclass correlation coefficients (ICC), standard error of measurement (SEM) and Bland-Altman analyses. Overall, reliability was high for pV, pP, RVD and RPD at 0%, 25% and 50% load (ICC: .85 - .98, SEM: 3% - 10%). A trend for increased reliability at lower loads seemed apparent. The tests at 75% load led to range of motion failure and should be avoided. In addition, results demonstrated that caution is advised when interpreting early phase results (first 50ms). To conclude, our results support the use of the isotonic mode of an isokinetic dynamometer for testing rapid power and velocity characteristics in older adults, which is of high clinical relevance given that these muscle characteristics are emerging as the primary outcomes for preventive and rehabilitative interventions in aging research.

Keywords: Intra-rater; Agreement; Aging; Muscle Function

Introduction

In geriatrics and aging research, measures of muscle function are commonly used to screen for an age-related loss of muscle strength and power and to evaluate the effectiveness of exercise interventions (Abernethy et al. 1995; Keating and Matyas 1996). Hence, measures of muscle function should be consistent and free from error. This is especially relevant for the knee extensor muscles in older adults, as they are crucial in a number of functional and locomotor tasks such as walking, stair climbing, chair rising, balance control and fall prevention (Bento et al. 2010; Hughes et al. 1996; MacRae et al. 1992).

To date, the gold standard for measuring muscle function in clinical practice and research settings is isokinetic dynamometry (Drouin et al. 2004; OSTERNIG 1986). Isokinetic testing allows maximal strength production at a constant predetermined velocity throughout a selected joint's range of motion. It has been shown that maximal strength is an important variable to be tested for monitoring loss of muscle strength in the elderly (Goodpaster et al. 2006). Previous studies have shown highly reliable test results for knee extension strength measurements using the isokinetic mode (Brown et al. 2005; Feiring et al. 1990; Hartmann et al. 2009; Jenkins et al. 2015; Maffiuletti et al. 2007; Sole et al. 2007). In addition to the isokinetic mode, an isokinetic dynamometer can operate in an isometric and an isotonic mode (Keating and Matyas 1996; Power et al. 2011). In the former, maximal strength is produced in a predetermined position without limb movement. In the isotonic mode, muscle contractions are performed at a predetermined resistance and a variable velocity. Considering that most daily activities do not include a constant predetermined velocity or a fixed position as in isokinetic or isometric tests, isotonic tests may better reflect daily activities that involve moving a specific object (weight) and include an acceleration component. The isotonic mode allows for single, explosive movements and can be considered a safe and objective measure of velocity-dependent muscle power (Power et al. 2011). Moreover, isotonic tests can be performed at a certain percentage of the isometric maximum, allowing for power production across the entire power-load relationship. These tests can be considered as relative tests of a subject's ability (i.e. maximal isometric strength) to generate power. In addition, isotonic tests can also be conducted in an unloaded condition. These unloaded tests, interpreted as absolute tests because every subject has to push the same absolute load, are shown to be a key component in the onset of functional difficulties in the elderly (Van Roie et al. 2011). The ability to address relative and absolute power production in one test mode is unique. Although isotonic training and testing has been performed on common weight stack machines for years, little is known about the isotonic mode of an isokinetic dynamometer, which allows for better standardization, accurate continuous measurement of torque and velocity in a predetermined range of motion and reduced muscle soreness (i.e. concentric only) (Stauber et al. 2000). The growing amount of studies investigating muscle function of the ankle plantar- and dorsiflexors support the idea of using the isotonic mode on an isokinetic dynamometer for testing muscle function (Power et al. 2011; Remaud et al. 2010; Stauber et al. 2000). However, little is known about the reliability of isotonic measures of knee extensor function, in particular in older adults.

Irrespective of test mode, current research agrees that muscle power, in particular its velocity component, is a better predictor of functional performance among older adults than maximal strength (Reid and Fielding 2012; Van Roie et al. 2011). In addition, early age-related changes appear to be more pronounced in power and velocity production than in maximal force generating capacities, resulting in an age-related slowing of muscles (Charlier et al. 2016; Kennis et al. 2014). Fundamentally, the majority of these studies investigating muscle function in old age express their results in terms of maximal values of strength, velocity or power. However, recent insights seem to suggest that rapid force production is more functionally relevant (Kirk et al. 2016; Thompson et al. 2013). Parameters that reflect the ability to produce force rapidly correspond to the short response times (i.e., less than ~200ms) that are normally available to accelerate the limbs during many functional tasks (Thompson et al. 2014a). Although it has recently been shown that time-dependent measures of isotonic muscle function decline more during aging than maximal output measures (Van Driessche et al. 2018), there is, to our knowledge, virtually no research that focused on the reliability of these measures.

Therefore, the present study aimed at determining relative and absolute test-retest reliability of knee extensor muscle function using the isotonic test mode on a Biodex System 3 dynamometer in older adults (65-82 years). A particular novelty of this study is the focus on time-dependent measures of muscle function (i.e. RVD and RPD) and their evaluation across loads.

Materials and methods

<u>Participants</u>

According to the recommendations of Hopkins et al. (Hopkins 2000) on sample size for reliability studies, we aimed at recruiting at least 50 participants through advertisements. Participants were community-dwelling older adults aged between 65 and 85 years old. Exclusion criteria were pathologies that prohibit a maximal strength test, such as severe cardiovascular disease, artificial hip or knee, acute hernia, infection or tumor (diagnosed by the subjects' general practitioner). Sixty-three older adults (♂: n = 27, age = 73 ± 4 years, body mass = 83 ± 10 kg; ♀: n = 36, age = 72 ± 3 years, body mass = 69 ± 8 kg) volunteered to participate in the study. All subjects gave written informed consent. The study was approved by the University's Human Ethics Committee ("Commissie Medische Ethiek van de UZ KU Leuven S52221") in accordance with the declaration of Helsinki.

<u>Design</u>

A repeated measures protocol was designed to assess test-retest reliability of the isotonic mode at 0%, 25% and 50% of maximal isometric strength on a Biodex System 3 dynamometer evaluating knee extensor peak velocity (pV), peak power (pP), rate of velocity (RVD) and power (RPD) development (Kottner et al. 2011). The test and retest session were conducted in the same lab on two separate occasions. The time interval between test and retest was 1 week (same time of day and same weekday). All measurements were performed by the same experienced rater.

<u>Procedures</u>

<u>Dynamometry.</u> Measurements of isometric knee extension strength as well as velocity capacities of the knee extensors across different loads were conducted on the Biodex Medical System 3® dynamometer (Biodex Medical Systems, Shirley, New York), in accordance with the procedures of previous studies (Charlier et al. 2016; Kennis et al. 2014; Van Roie et al. 2011). Measurements were performed unilaterally on the right side, unless there was a medical contraindication. Participants were seated on a backward-inclined (5°) chair, which is part of the dynamometer. A strap was applied across the thigh on the test side and the hips and shoulders were stabilized with safety belts to avoid additional movements. The rotational axis of the dynamometer was aligned with the transversal knee-joint axis and connected to the point of force application at the distal end of the tibia (i.e. 5cm above the lateral malleolus) using a length-adjustable rigid lever arm. Range of motion was set from a knee joint angle of 90° to 160°, with a fully extended leg corresponding to a knee angle of 180°. The test protocol included two standardized tests in the following order: isometric and isotonic tests. During each test, the subjects were clearly instructed by the test leader to perform the tests with maximal effort. The protocol was conducted twice per test session.

Isometric test. Isometric strength of the knee extensors was assessed at a knee joint angle of 90°. Subjects were instructed to avoid an explosive contraction, but to extend their leg as hard as possible during 5 seconds, by building up strength gradually until maximal strength was reached. Two maximal isometric knee extensions were performed separated by a 10-second rest interval. Peak torque (pT, Nm) was recorded.

Isotonic tests. The isotonic tests included ballistic knee extensions against constant resistances of consecutively 50%, 25%, 0% and 75% of the maximum isometric strength in a knee joint angle of 90°. Because of practical restrictions, the test at 0% of the isometric maximum was conducted at a fixed resistance of 1Nm, which can be considered as an unloaded test. The subjects were asked to extend their leg as fast and as hard as possible and then passively return the leg to the starting position (90°). Two explosive contractions were performed. Velocity (°/s) and torque (Nm) were recorded.

Signal Processing. Torque and velocity signals were sampled at 100 Hz and processed off-line using a commercial software package (Matlab R2015b, The MathWorks Inc., Natick, Massachusetts, United States). Instantaneous power (Nm/s) was calculated as the product of torque (Nm) and velocity (rad/s). Peak velocity (pV, °/s) and peak power (pP, Nm/s) were determined as the highest values of the velocity curve and power curve respectively. Rate of velocity development (RVD, $°/s^2$) and rate of power development (RPD, Nm/s^2) were calculated as the linear slopes of the velocity- and power-time curve respectively, from the start of the movement until pV or pP was reached (RVD and RPD) as well as at time intervals of 50ms (RVD_{0-50} or RPD_{0-50}, RVD_{50-100} or RPD_{50-100} and $RVD_{100-150}$ or $RPD_{100-150}$). The start of the movement was determined as the point where the acceleration reached a threshold of 150 $°/s^2$ after overcoming the imposed load. The tests with the highest pT for the isometric tests and the highest pV for the isotonic tests were used for further analyses.

Statistical Analyses. All analyses were performed using R software version 3.2.2. Statistical significance was set at $p < 0.05$. All data were screened for normality using the Shapiro Wilk test. To confirm the absence of systematic bias between test and retest, paired t-tests were calculated (Arifin et al. 2014).

Relative reliability, the degree to which the subjects maintain their position in a sample over the repeated measures, was assessed using intraclass correlation coefficients ($ICC_{3,1}$) and their 95% confidence intervals (95% CI). Computation of ICC was based on repeated measures analysis of variance using a single rating, two-way mixed effects model where subject effects are random and rater is a fixed effect (Shrout and Fleiss 1979; van Lummel et al. 2016). As no universally acceptable levels have been adopted for correlation coefficients in describing the amount of reliability, we used previously reported ICC ranges of Youdas et al. (Youdas et al. 1991): >.90 high, .89–.80 good, .79–.70 fair, <.69 poor reliability.

In addition, absolute reliability, the degree to which the repeated measures vary for the subjects, was expressed in terms of standard error of measurement (SEM) and limits of agreement (LoA) (Atkinson and Nevill 1998). SEM was determined as the square root of the residual mean square error from the analysis of variance (Meyer et al. 2013; Webber and Porter 2010). In addition, the reference interval of the difference scores between test and retest data, defined as the limits of agreement (LoA), was calculated as the mean difference ± 1.96 x the standard deviation from the differences between test and retest (Atkinson and Nevill 1998). Both SEM and LoA were expressed as a percentage of the mean to make interpretation and comparison among different measures and across different studies possible. SEM was also expressed in the unit of the measured variable. SEM represents 68% of the error between test and retest for the average individual in the sample, whereas the more strict LoA represent the test-retest differences for 95% of the whole population (Atkinson and Nevill 1998).

Results

There was no drop out. However, 28 % of the subjects were not able to properly overcome the resistance for the isotonic tests at 75% load, resulting in the systematic failure of the test and the retest. Consequently, isotonic testing at 75% can be considered as systematically unreliable and was excluded for further analyses. Therefore, we will focus on the isotonic tests at 0%, 25% and 50% load.

The Shapiro Wilk test allowed us to assume normality for all parameters at a significance level of 0.01. Mean ± standard deviation (SD) of isometric peak Torque (pT) was 144.9 ± 45.9 Nm for the test and 143.6 ± 44.3 Nm for the retest session. Test and retest data of the isotonic tests are represented in table 1. Paired t-tests indicated that no data were significantly different between test and retest ($p > 0.05$).

Table 1. Test and retest data (N = 63 (♂ 27, ♀ 36))

Parameters	0%				25%				50%			
	Test		Retest		Test		Retest		Test		Retest	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
$\boldsymbol{pV}$ $(°/\boldsymbol{s})$	402.3	51.4	401.4	55.2	292.0	44.2	290.4	40.5	169.5	41.7	169.7	38.1
$\boldsymbol{pP}$ $(\boldsymbol{Nm/s})$	244.0	90.0	242.1	91.2	293.3	118.2	298.0	119.5	266.6	118.4	270.7	115.3
$\boldsymbol{RVD}$ $(°/\boldsymbol{s}^2)$	1735.3	495.4	1720.1	512.6	1100.4	296.4	1093.2	270.5	681.4	187.7	688.9	179.0
$\boldsymbol{RVD_{0-50}}$ $(°/\boldsymbol{s}^2)$	1217.5	756.5	1115.2	754.2	870.9	456.7	854.9	384.7	522.7	223.9	521.0	226.2
$\boldsymbol{RVD_{50-100}}$ $(°/\boldsymbol{s}^2)$	2013.0	818.2	1997.3	834.6	1381.1	530.6	1379.8	462.4	924.2	295.3	942.5	295.2
$\boldsymbol{RVD_{100-150}}$ $(°/\boldsymbol{s}^2)$	2048.7	570.9	2096.1	583.4	1493.8	402.2	1518.2	368.3	973.2	287.2	983.9	271.4
$\boldsymbol{RPD}$ $(\boldsymbol{Nm/s}^2)$	1318.1	648.2	1320.4	725.4	1360.9	702.1	1379.0	694.7	1215.9	629.8	1251.9	623.7
$\boldsymbol{RPD_{0-50}}$ $(\boldsymbol{Nm/s}^2)$	885.4	802.7	814.6	745.3	1030.2	765.9	996.8	666.2	931.5	658.1	942.6	617.2
$\boldsymbol{RPD_{50-100}}$ $(\boldsymbol{Nm/s}^2)$	1617.7	958.2	1641.5	1025.3	1767.8	1092.4	1793.1	1083.1	1750.4	1012.7	1806.9	971.9
$\boldsymbol{RPD_{100-150}}$ $(\boldsymbol{Nm/s}^2)$	1340.6	833.9	1448.2	792.1	1704.0	847.5	1817.8	809.2	1601.2	791.6	1642.7	807.5

Mean and standard deviation (SD) of the test and retest session for peak velocity (pV), peak power (pP), rate of velocity development until pV (RVD) and at intervals of 50ms ($\boldsymbol{RVD_{0-50}}$, $\boldsymbol{RVD_{50-100}}$, $\boldsymbol{RVD_{100-150}}$) and rate of power development until pP (RPD) and at intervals of 50ms ($\boldsymbol{RPD_{0-50}}$, $\boldsymbol{RPD_{50-100}}$, $\boldsymbol{RPD_{100-150}}$) measured during the isotonic tests at 0%, 25% and 50% of maximal isometric strength. No test and retest sessions were significantly different from each other at $p < 0.05$.

Table 2. Relative and absolute reliability (N = 63 (♂ 27, ♀ 36))

	0%				25%				50%			
Parameters	**ICC (95% CI)**	**SEM**	**SEM (%)**	**LoA (%)**	**ICC (95% CI)**	**SEM**	**SEM (%)**	**LoA (%)**	**ICC (95% CI)**	**SEM**	**SEM (%)**	**LoA (%)**
$\boldsymbol{pV}$ $(°/\boldsymbol{s})$	.96 (.93-.97)	11.3	3	0 ± 9	.90 (.84-.94)	13.5	5	0 ± 14	.85 (.76-.91)	15.5	9	-2 ± 29
$\boldsymbol{pP}$ $(\boldsymbol{Nm/s})$	.97 (.95-.98)	16.4	7	1 ± 20	.98 (.97-.99)	16.4	6	-2 ± 20	.96 (.94-.98)	23.3	9	-4 ± 37
$\boldsymbol{RVD}$ $(°/\boldsymbol{s}^2)$	.95 (.91-.97)	117.0	7	1 ± 22	.92 (.87-.95)	80.8	7	-1 ± 24	.89 (.82-.93)	61.1	9	-3 ± 30
$\boldsymbol{RVD_{0-50}}$ $(°/\boldsymbol{s}^2)$	.66 (.50-.78)	438.9	38	-12 ± 174	.78 (.66-.86)	198.6	23	-9 ± 90	.62 (.43-.75)	139.6	27	-10 ± 93
$\boldsymbol{RVD_{50-100}}$ $(°/\boldsymbol{s}^2)$	.83 (.74-.90)	336.9	17	-10 ± 118	.83 (.74-.90)	203.5	15	-6 ± 64	.74 (.60-.83)	151.4	16	-7 ± 91
$\boldsymbol{RVD_{100-150}}$ $(°/\boldsymbol{s}^2)$	.86 (.78-.91)	214.4	10	-5 ± 44	.87 (.80-.92)	137.9	9	-4 ± 38	.85 (.77-.91)	106.5	11	-3 ± 37
$\boldsymbol{RPD}$ $(\boldsymbol{Nm/s}^2)$	.97 (.95-.98)	125.9	10	1 ± 34	.97 (.95-.98)	126.2	9	-4 ± 33	.96 (.94-.98)	120.9	10	-6 ± 43
$\boldsymbol{RPD_{0-50}}$ $(\boldsymbol{Nm/s}^2)$	.76 (.63-.85)	381.3	45	-47 ± 354	.88 (.80-.92)	251.8	25	-17 ± 119	.83 (.74-.90)	260.0	28	-11 ± 85
$\boldsymbol{RPD_{50-100}}$ $(\boldsymbol{Nm/s}^2)$	.85 (.77-.91)	379.7	23	-18 ± 159	.94 (.90-.96)	271.8	15	-11 ± 94	.92 (.88-.95)	272.6	15	-9 ± 76
$\boldsymbol{RPD_{100-150}}$ $(\boldsymbol{Nm/s}^2)$	.81 (.71-.88)	350.7	25	-21 ± 183	.92 (.87-.95)	236.1	13	-12 ± 53	.91 (.86-.95)	236.1	15	-7 ± 53

Relative and absolute reliability for peak velocity (pV), peak power (pP), rate of velocity development until pV (RVD) and at intervals of 50ms ($\boldsymbol{RVD_{0-50}}$, $\boldsymbol{RVD_{50-100}}$, $\boldsymbol{RVD_{100-150}}$) and rate of power development until pP (RPD) and at intervals of 50ms ($\boldsymbol{RPD_{0-50}}$, $\boldsymbol{RPD_{50-100}}$, $\boldsymbol{RPD_{100-150}}$) measured during the isotonic knee extension tests at 0%, 25% and 50% of maximal isometric strength: intraclass correlation coëfficients (ICC) with 95% confidence intervals (CI), standard error of measurement (SEM) and limits of agreement (LoA). All ICCs were significant at $p < .001$.

Isometric pT showed very high relative reliability with an ICC of .97. For the isotonic tests, ICCs were good to high for pV, pP, RVD and RPD at all resistances (Table 2). RVD_{0-50} showed poor reliability at 0% and 50% load and fair reliability at 25% load. At time intervals of 50-100ms and 100-150ms, RVD showed fair to good reliability and RPD good to high reliability across all loads.

Absolute reliability for isometric pT was represented by SEM (5.7%) and LoA (-1.1% ± 16.8%). Absolute reliability indices of RVD and RPD (i.e. SEM 7-10%) were good and similar to indices of pV and pP (i.e. SEM 3-9%) across all loads (Table 2). Early phase measures of acceleration capacity (i.e., the first 50 ms) showed poor absolute reliability (i.e. SEM 23-45%). RVD and RPD showed good to fair absolute reliability (i.e. SEM 9-25%) at time intervals of 50-100ms and 100-150ms. LoA of the parameters obtained in the isotonic tests at lower load tended to be smaller compared to the tests at higher load, as visualised using the Bland-Altman plots (Fig. 1). Bland-Altman plots show that LoA were situated symmetrically around the zero line and that variability decreased with higher test scores (Bland and Altman 2010). In other words, no systematic error in the outcome measures was observed and reliability increased with increasing performance capacities.

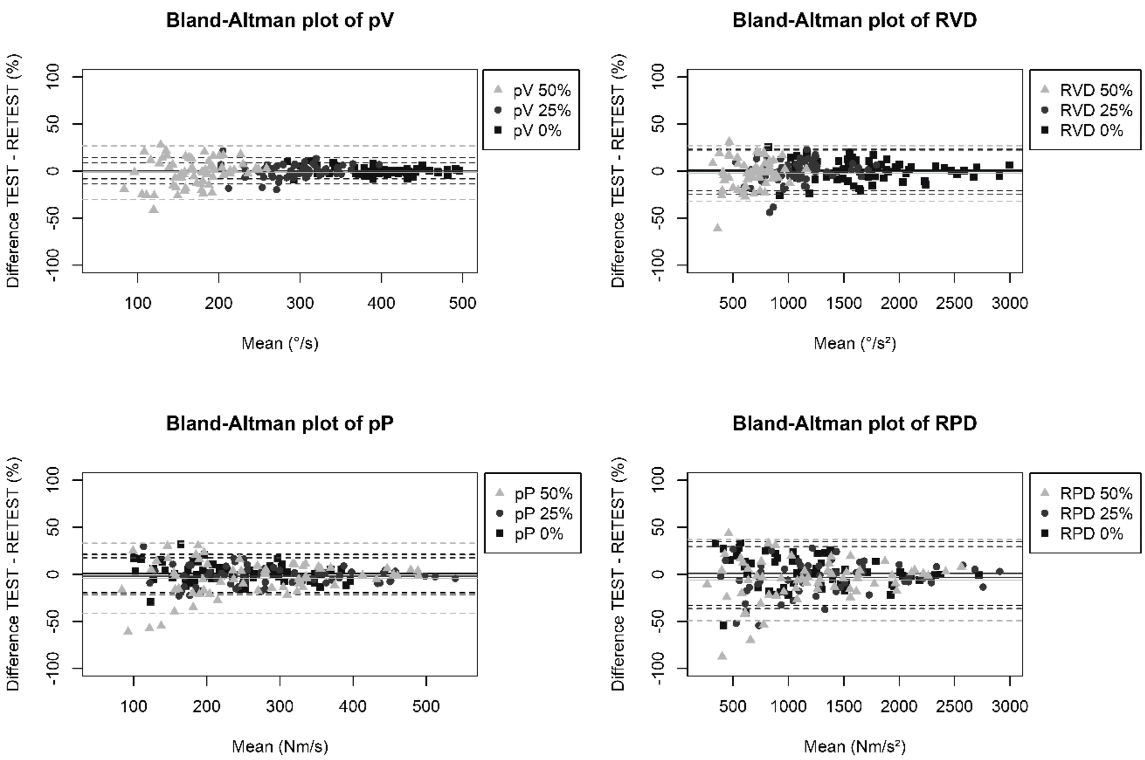

Fig 1. Bland-Altman plots. Bland-Altman plots of peak velocity (pV), rate of velocity development (RVD), peak power (pP) and rate of power development (RPD) illustrate absolute reliability of the isotonic knee extension tests at 0%, 25% and 50% of isometric maximum strength. Individual differences between test and retest values are plotted against their means. For all plots at all loads the mid solid line represents the mean difference, whereas the outer dashed lines represent the limits of agreement (LoA) in percentage.

Discussion

The aim of this study was to evaluate reliability of time-dependent measures of knee extensor muscle function using the isotonic mode on a Biodex System 3 dynamometer. The present results indicate high test-retest reliability for all isotonic measurements at relatively low loads (i.e. 0%, 25% and 50%) in an older population. Similar to frequently reported parameters like pV and pP, RVD and RPD were found to be reliable. Importantly, reliability of muscle function seemed to decrease with increasing load and with decreasing test performance. The acceleration phase of the isotonic leg extension movements (i.e. first 50ms) was highly sensitive to variation and should be interpreted with caution because of poor reliability. Overall, this study demonstrates that several reliable parameters can be identified to provide a basis for a more precise and sensitive use of the isotonic tests in clinical practice.

Loaded isotonic tests were performed relative to maximal strength. Therefore, reliability of these tests was partly based on reliability of the maximum strength tests. The present study showed very high reliability for the isometric test. This finding is in line with former research (ICC: .87-.98), which used isokinetic dynamometry to measure isometric knee extension strength in a knee angle of 90° in elderly using a similar procedure as in the present study (Flansbjer and Lexell 2010; Symons et al. 2005). In addition, the mean difference between test and retest data was about 1% and the SEM was 6%. Given that strength training interventions in older adults have been found to induce gains of approximately 10% to 20% in isometric muscle strength (von Stengel et al. 2012), the present results indicate that the isometric tests on an isokinetic dynamometer are capable of assessing real training-induced changes.

Isotonic pV and pP are regularly reported in the literature. On the one hand, pV gives an indication of a subject's pure velocity capacities independent of the strength capacities. On the other hand, taking into account torque and velocity by calculating power gives a better indication of the subject's overall muscle capacities. This study demonstrated high relative reliability at relatively low loads (i.e. 0%, 25% and 50%) for pV and pP (ICC: .85 - .98). Mean differences between test and retest data for pV ranged from -2% to 0% and for pP from -4% to 1%. Previous research has investigated the reliability of ankle plantar- and/or dorsiflexor tests at low loads (1Nm to 50% load) using the isotonic mode of an isokinetic dynamometer. The ICC's of pV and pP at 20% load reported by Power et al. (Power et al. 2011) in young men and women, i.e. .93 and .98 respectively, are similar to the ICC's for these parameters in our study. Likewise, ICC's reported by Webber et al. (Webber and Porter 2010) were fair to high for pV and pP in older women, ranging from .76 to .96, with mean differences ranging from -2% to 2% for pV and from -6% to -1% for pP.

Across the different loads used in this study, variability between test and retest for all parameters tended to decrease with increasing mean test performance (Fig. 1). In other words, the better the performance of the subject the more reliable the measurement. In addition, absolute reliability of pV and RVD tended to be lower with higher loads compared to lower loads (SEM: 3% - 9%). The same trend of increased variability with increasing loads was illustrated on Bland and Altman plots (LoA: 9% - 30%) (Fig. 1). As opposed to testing at relatively low loads, isotonic testing at high load (i.e. 75%) should be avoided, because of the total failure to perform these tests properly for 28% of the sample subjects. The failure of the isotonic tests at high load might have been related to the greater challenge for the subjects to generate sufficient torque throughout the entire range of motion (OSTERNIG 1986). While maximal dynamic strength testing on weight stack machines at high loads could be used for comparing absolute strength improvements due to training (i.e. 1-RM testing), lower loads should be advised for isotonic testing on an isokinetic dynamometer to be able to reach full range of motion. Power et al. (Power et al. 2011) indicated that a load of 20% of the isometric maximum represents a moderate resistance in which all subjects can perform fast, explosive contractions without range of motion failure. In line with this statement, the results of the current study indicate that relatively low loads (i.e. 25% and 50%) are feasible and highly reliable. In addition, they support the use of isotonic tests at 0% load. Although many daily activities include a minimal load to be moved, it has previously been shown that peak velocity of an unloaded movement (i.e. 0% load) is a key component in the onset of functional difficulties in the elderly (Van Roie et al. 2011).

The main instruction to the subjects when conducting rapid strength tests is 'push as fast and as hard as possible' (Maffiuletti et al. 2016). Consequently, a certain challenge of performing explosive tests is to reach pP as fast as possible. However, pV and pP do not provide information on the development of velocity or power throughout the knee extension movement. RVD and RPD take into account the time needed to develop velocity or power, respectively. Moreover, RVD and RPD are shown to differentiate more between young and older individuals, which emphasizes their potential value in aging research (Thompson et al. 2014a; Van Driessche et al. 2018). Therefore, reliability studies on these parameters are crucial. To our knowledge, this is the first study that evaluated reliability indices of RVD and RPD of the knee extensor muscles obtained through isotonic testing. Previously, Webber et al. (Webber and Porter 2010) calculated the average acceleration obtained from the isotonic tests of the ankle plantar- and dorsiflexors at ~0% and 50% load and reported fair to high reliability. Similarly, our results show that the ICCs of RVD and RPD were high for the isotonic tests at 0%, 25% and 50% load (ICC: .89 - .97). Therefore, RVD and RPD can be used in future research to reliably evaluate age-related changes in muscle function or adaptations after an intervention.

To gain more insight into the development of an explosive knee extension movement, different time phases of the acceleration phase were examined. In line with previous approaches during isometric testing (Aagaard et al. 2002; Thompson et al. 2014b), RVD and RPD were calculated over different time windows of 50ms each. The early phase of explosive contractions (0-50ms), which has been suggested to be predominantly determined by neural activation characteristics (Andersen and Aagaard 2006; Folland et al. 2014), demonstrated poor absolute reliability for the isotonic tests in this study (SEM: 23% - 45%). Next to the starting phase, parameters calculated at time frames of 50-100ms and 100-150ms, which have been suggested to be predominantly determined by muscular characteristics (Andersen and Aagaard 2006; Folland et al. 2014), demonstrated fair to high reliability (ICC: .74 - .94, SEM: 9% - 25%). In agreement with our results, Buckthorpe et al. (Buckthorpe et al. 2012) found that the most reliable rate of force development window, measured during an isometric contraction, lies between 50 and 100ms. They found that the first 50ms, the early phase of rapid force development, demonstrated poor absolute reliability (CV: 16.6 - 18.7%), which was significantly worse than the reliability indices for 0-100ms (CV: 6.4 - 9.8%) and for 0-150ms (CV: 5.1 - 8.4%). Accordingly, Buckthorpe et al. (Buckthorpe et al. 2012) suggested that the variability of the early phase of an explosive contraction is likely due to an inherent variability in neural drive.

An important strength of our study is the use of isotonic tests to evaluate the reliability of RVD and RPD. Although less used, isotonic tests are considered to be more functionally relevant in older adults as compared to isometric or isokinetic tests, because they include dynamic movements at fixed loads with an unconstrained velocity which replicates most daily activities. In addition, isotonic tests include rapid power development suggesting a different physiological basis than maximal muscle strength testing (Stauber et al. 2000). Even more important, the lower incidence of a Valsalva maneuver and consequently the smaller acute elevation in blood pressure (Yamauchi et al. 2008) may have resulted in the participants' experience that the isotonic tests were a lot more comfortable and safer to perform, which is especially relevant in the older population. In addition, there is an increased interest in using fast velocity and power measurements to identify age-related differences in muscle function (Thompson et al. 2014a). However, the following limitations of the study should be taken into account. First, isotonic testing at 75% load led to range of motion failure for 28% of the sample. Therefore, only three loads were analyzed. Second, no conclusions can be made about the level of load that would result in poor reliability outcomes, because no continuum was measured. Third, the 95% LoA presented in this study may be too strict as decision limits for clinical practice and may have been more valuable for practice if tested with a larger sample. The larger the sample, the better the mean and standard deviation of the residuals will approach the real values of the distribution. Nevertheless, in comparison with most reliability studies, our sample size was high. To see a true change in performance for a group of older individuals, the degree of certainty of 95% LoA may be unrealistic and we therefore recommend looking at the SEM for practical applications. The SEM can be interpreted as the limits for change required to indicate a real increase or decrease for a group of individuals following an intervention (Webber and Porter 2010). Though, calculation of the LoA is of practical importance as it provides the minimal change for an individual needed to be considered real (van Lummel et al. 2016; Weir 2005).

In conclusion, this study demonstrated that knee extension velocity and power (i.e. pV and pP) are reproducible at relatively low loads (i.e. 0%, 25% and 50%). At 75% load, isotonic testing was found to be unreliable. The use of loads ≥ 75% of maximal isometric strength in 90° knee angle should be avoided for isolated isotonic knee-extension tests on isokinetic dynamometers, because this load seems too high to allow for an adequate test over the full range of motion. In addition, this study indicated that time-dependent measures of muscle function (i.e. RVD and RPD), which seem to be more sensitive to detect early age-related changes (Van Driessche et al. 2018), are equally reliable compared to maximal measures (i.e. pV and pP). However, caution is advised when interpreting early phase results. Furthermore, a trend for increased reliability with decreasing load and with increasing mean test performance was shown. These results indicate that isotonic testing on an isokinetic dynamometer can be used as a consistent measure of rapid velocity and power capacities for a group of older individuals, in repeated measures designed studies. This is of high clinical relevance, given that muscle power development and movement velocity are emerging as the primary outcomes for preventive and rehabilitative interventions in aging research, due to their predictive value for functional impairments and disability.

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Article 2

Age-related differences in rate of power development exceed differences in peak power

Van Driessche S, Delecluse C, Bautmans I, Vanwanseele B, Van Roie E

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Abstract

Peak power (pP) declines during aging, resulting in reduced functional performance. However, the rate of power development (RPD) takes into account the short response times available during many functional tasks and may therefore add valuable information to functional declines. This study examined the age-related effects on pP and RPD of the knee-extensors across different loads and how these are related to functional performance.

36 young (♂ 21, ♀15, age = 22 ± 2 years) and 56 older adults (♂ 26, ♀ 30, age = 68 ± 5 years) performed four maximal isotonic contractions against three loads (40, 20 and 60% of maximal isometric strength) on a Biodex System 3 dynamometer. pP was calculated as the highest value and RPD as the linear slope of the power-time curve. Functional performance in the older group was tested by 7.5-meter fast walk, timed up-and-go and stair climbing.

pP and RPD were higher in young compared to old and this was more pronounced with lower loads. Age-related differences in RPD (range from 37-44% across loads) were higher than in pP (24-37%). Both pP and RPD showed a positive correlation with functional performance (r: .59-.64).

To conclude, percent differences in RPD exceed differences in pP between young and old. This emphasizes the inability to generate power rapidly at older age and underlines the importance of time-dependent measures to detect age-related changes in muscle function.

Keywords: Rate of Velocity Development; Functional Performance; Aging; Muscle Function; Power-load relationship

Introduction

Human aging has been associated with declines in muscle strength and power (Charlier et al. 2015; Reid and Fielding 2012). These age-related declines lead to a reduction in functionality, a higher risk of falls and a slower general movement pattern, jeopardizing the independency of older adults (Rolland et al. 2008). In order to prevent this loss of independence, a better understanding of aging of muscle function is required.

The majority of methodologies that evaluated muscle function in older adults focused on maximal strength, which is very important in daily tasks since this sets the reserve limit (Lauretani et al. 2003). However, maximal strength requires more than 200-300ms to be achieved (Hakkinen and Hakkinen

1991). This makes it less functionally relevant in situations that require quick and powerful responses of muscles, such as balance recovery following sudden perturbations (Pijnappels et al. 2008). Parameters that reflect the ability to rapidly produce force, such as the rate of force development, correspond to the short response times that are normally available to accelerate the limbs during many functional tasks (i.e., less than ~ 200ms) (Aagaard et al. 2002; Maffiuletti et al. 2016; Thompson et al. 2013). Previous research that focused on rapid isometric force production already demonstrated differences between young and older adults and its link to functional performance (Aagaard et al. 2002; Clark et al. 2013; Izquierdo et al. 1999; Maffiuletti et al. 2016; Thompson et al. 2014b; Thompson et al. 2013).

In comparison to isometric tests, dynamic tests have greater external validity to functional movements. More specific, power, i.e. the product of force and velocity measured during dynamic tests is more strongly related to functional performance than maximal isometric strength (Reid and Fielding 2012). In addition, power and velocity decline more than maximal strength during aging, leading to an age-related slowing of muscles (Macaluso and De Vito 2003; Reid and Fielding 2012). The age-related slowing of muscles suggests that older adults need more time to develop maximal velocity or power. This emphasizes the need to study muscle function in a time-dependent way, which would more closely reflect functional movements in older adults (Tillin et al. 2013). To date, few studies have focused on rapid force characteristics during dynamic actions (i.e. the rate of velocity (RVD) or power (RPD) development) and their relationship to functional capacity in older adults. Interestingly, Thompson et al. observed a greater difference in RVD compared to pV of the leg extensor muscles between young and older men (Thompson et al. 2014a). These findings underline the importance of the time to peak velocity (ttpV) and suggest that RVD can be more discriminatory between age-groups compared to pV.

The scarce research that investigated RVD using dynamometry focused on isokinetic and unloaded testing (Thompson et al. 2014a). However, most activities during daily life are variable in velocity and include loading. More similar to daily tasks, isotonic contractions include an acceleration component and a certain amount of loading (Power et al. 2011). Therefore, isotonic measures of power could serve as a better indicator for functional movements. Accordingly, isotonic testing has been emerging as a more functional though standardized method for the evaluation of muscle function (Dalton et al. 2010; Dalton et al. 2012; McNeil et al. 2007; Valour et al. 2003). This type of testing in the older population seems especially relevant for the knee extensors, given that these muscles are crucial in a number of functional and locomotor tasks (Ploutz-Snyder et al. 2002). To date, research using isotonic tests for knee-extensor muscle function in older adults is limited (Dalton et al. 2012; Macaluso and De Vito

2003; Stauber et al. 2000). Even more, no research has evaluated time-dependent isotonic knee-extensor function and its link to functional movements.

Therefore, the present study aimed at determining age-related differences in pV, pP, RVD and RPD of the knee-extensor muscles using the isotonic mode on a gold standard dynamometer. These differences were evaluated across different loads. Functional performance tests were included to investigate the functional relevance of pV, pP, RVD and RPD. We hypothesized that RVD and RPD would differentiate more between young and older adults compared to pV and pP respectively. In addition, we hypothesized that RPD would be more strongly related to functional performance in older adults than pV, RVD and pP.

Methods

Subjects

Baseline values of the participants of two intervention studies in our lab were used for this study (Van Roie et al. 2013a; Van Roie et al. 2013b). Subjects were community-dwelling and aged between 20-30 or 60-80 years. Exclusion criteria were (i) pathologies that prohibit a maximal strength test, such as severe cardiovascular disease, artificial hip or knee, acute hernia, infection or tumor and (ii) systematic engagement in endurance (i.e. no training with progressive increases in volume and/or intensity) or resistance exercise (i.e. no participation in the prior 12 months). Occasional engagement in physical activity, such as cycling, walking and running was allowed. Thirty-six young (♂ 21, ♀15, age = 22 ± 2 yrs) and fifty-six older adults (♂ 26, ♀ 30, age = 68 ± 5 yrs) volunteered. Young participants were apparently healthy and free of medication use. Based on self-reported health questionnaires, the older participants were classified into health categories following a classification system as described previously (Bautmans et al. 2004; Bautmans et al. 2005; Forti et al. 2014) in order to estimate the risk for complications during physical exercise. Subjects' characteristics are shown in Table1. All subjects gave written informed consent. The study was approved by the University's Human Ethics Committee in accordance with the declaration of Helsinki.

Procedures

Dynamometry. Measurements of static strength as well as power of the knee extensors were conducted on the Biodex Medical System 3® dynamometer (Biodex Medical Systems, Shirley, New York, United States). The tests were performed unilaterally on the right side, unless there was a medical contraindication. This was the case for four older adults, who experienced injuries at the right leg in the past (e.g. knee pain or muscle rupture). None of them reported problems during daily activities, nor during the functional performance tests. Tests were solely performed on the left side for safety reasons. Participants were seated on a backward-inclined (5°) chair. The upper leg on the test side, the hips and shoulders were stabilized with safety belts. The rotational axis of the dynamometer was aligned with the transversal knee-joint axis and was connected to the point of force application at the distal end of the tibia using a length-adjustable rigid lever arm. Range of motion was set from a knee joint angle of 90° to 160°, with a fully extended leg corresponding to a knee angle of 180°. The test protocol, which was used in previous studies in our lab (Van Roie et al. 2013b), was conducted twice and included two standardized tests in the following order: isometric and isotonic tests. Isometric strength was assessed at a knee joint angle of 90°. Subjects were clearly instructed by the test leader to avoid an explosive contraction, but to extend their leg as hard as possible during 5 seconds, by building up strength gradually till maximal strength was reached. Two maximal isometric knee extensions, which were separated by a 20-second rest interval, were performed. Peak torque (pT, Nm) was recorded. The isotonic tests included ballistic knee extensions against constant resistances in the same specific order for every subject (i.e. consecutively 40%, 20% and 60% of maximum isometric strength). The subjects were clearly instructed by the test leader to extend their leg as fast as possible and then passively return the leg to the starting position (90°). Two explosive contractions were performed at each load. The velocity (°/s) and the torque produced (Nm) during the ballistic extension were recorded. The tests with the highest peak value of torque for the isometric tests and the highest peak value of velocity for the isotonic tests were used for further analyses.

Functional performance tests. The following tests, which varied in terms of strength and velocity characteristics, were performed in older adults: 7.5-meter fast walk test (7.5mFWT), timed up-and-go test (TUG) and stair climbing (STC). All tests were timed by hand. To test 7.5mFWT, participants walked a distance of 7.5m as fast as possible without running (Clark et al. 2013). The best result as the shortest total time to walk 7.5m of two performances was used. The TUG was performed by standing up from a standard armchair, walk a distance of 3m, turn, walk back and sit down again as fast as possible without running (Bischoff et al. 2003). Subjects were free to choose left or right turn. The time in seconds was measured and the best result from two trials was used. To measure STC ability, participants were asked to climb a 12-step staircase as fast as possible. The best result in seconds of two performances was used.

Data analyses

Torque and velocity signals from all isotonic tests were sampled at 100 Hz and processed off-line using a commercial software package (Matlab R2015b, The MathWorks Inc., Natick, Massachusetts, United States). Instantaneous power (Nm/s) was calculated as the product of both torque (Nm) and velocity (rad/s). Peak power (pP, Nm/s) and peak velocity (pV, °/s) were determined as the highest values of the power and velocity curve respectively. Time to peak power (ttpP, s) and time to peak velocity (ttpV,

s) were determined as the time from the start of the movement till pP and pV were reached. Rate of power development (RPD, Nm/s²) and rate of velocity development (RVD, °/s²) were calculated as the linear slopes from the start of the movement till pP and pV were reached. The start of the movement was determined as the point where the acceleration reached a threshold of 150 °/s² after overcoming the imposed load. All measures of muscle function reported in this study were found to be reliable in a group of 63 older adults (ICC: .85 - .96, SEM(%): 3.6 – 12.5) with a trend for increased reliability at lower loads (paper under revision). Time-dependent variables (RVD and RPD) showed similar relative (ICC) and absolute (SEM) reliability compared to peak variables (pV and pP).

Statistical Analyses

All statistical analyses were performed using R software, version 1.0.136, R Core Team (2016). Normality was analyzed with Shapiro-Wilk tests. All parameters were normally distributed at α-level 0.01. Two-sample t-tests were used to compare the differences in muscle function between young and older adults for men and women separately. No age-group by sex interaction effect was found using two-way analysis of variance. Therefore, an age-group by load interaction effect was examined for both sexes together with two-way repeated measures analysis of variance with age-group as the between- and load as the within-subjects factor. Post hoc analyses of the difference scores between the age-groups were conducted to determine the age-related difference between the loads. Pearson's correlation coefficients were calculated to examine the relationship of measures of muscle function with the functional performance tests. Fischer z transformation was used to statistically compare correlation coefficients. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Subject characteristics and functional test scores are presented in Table 1.

Table 1. Subject characteristics and functional test scores

Variable	Young Men (n=21)	Old Men (n=26)	Young Women (n=15)	Old Women (n=30)
Age (year)	21.8 ± 2.2	68.3 ± 5.3*	21.8 ± 1.9	67.7 ± 4.9*
Body mass (kg)	74.2 ± 6.4	84.1 ± 10.5*	62.5 ± 13.3	66.4 ± 8.1
Body height (m)	1.82 ± 0.05	1.73 ± 0.05*	1.69 ± 0.07	1.60 ± 0.06*
BMI (kg/m²)	22.4 ± 1.5	28.0 ± 3.3*	21.8 ± 3.9	26.0 ± 3.4*
(Co)morbidity (n)		1.65 ± 1.52		2.30 ± 2.05
Medication use (n)		1.23 ± 0.95		1.93 ± 1.46
†Health Category (n)				
A1		5		3
A2		1		0
B1		8		16
B2		9		11
C		3		0
7.5mFWT (s)	-	3.8 ± 0.6	-	4.5 ± 0.6
TUG (s)	-	5.8 ± 0.9	-	6.3 ± 0.9
STC (s)	-	3.9 ± 0.8	-	4.6 ± 0.9

Data are means ± SD, 7.5mFWT: 7.5-meter fast walk test, TUG: timed up-and-go, STC: stair climbing. *significantly different from young $p < 0.05$. †A1: completely healthy and no medications use; A2: completely healthy, using only preventive medication; B1: Functioning normally; presence of stabilized, non-cardiovascular disease, absence of cardiovascular abnormalities; B2: Functioning normally, using medication with cardiovascular effect, no overt cardiovascular disease other than normalized arterial hypertension; C: (history of) cardio-vascular pathology

Measures of muscle function are listed in Table 2. Young adults performed significantly better compared to older adults for almost all strength-, velocity- and power-related muscle variables in both sexes ($p < 0.05$). While pP was significantly different at every load, difference in pV was only significant when measured at low load (i.e. 20%). Next to pV and pP, the variables ttpV and ttpP were significantly lower in young compared to older adults at every load (table 2). In terms of percent difference, RVD and RPD differentiated more between young and older adults compared to pV and pP respectively. Figure 1 illustrates the difference in mean power development between young and older adults.

Table 2. Muscle function in men and women by age group.

Parameter	Young Men (n=21)	Older Men (n=26)	Percent difference (YM-OM)	Young Women (n=15)	Older Women (n=30)	Percent difference (YW-OW)
Isometric test						
pT (Nm) at 90°	282 ± 48	203 ± 43[a]	28%	169 ± 41	121 ± 27[b]	28%
Isotonic test at 20% load						
pV (°/s)	441 ± 35	389 ± 50[a]	12%	390 ± 40	344 ± 38[b]	12%
ttpV (s)	0.20 ± 0.01	0.22 ± 0.02[a]	11%	0.23 ± 0.03	0.26 ± 0.03[b]	12%
RVD (°/s²)	2252 ± 305	1796 ± 376[a]	20%	1746 ± 366	1353 ± 258[b]	23%
pP (Nm/s)	637 ± 83	430 ± 110[a]	32%	367 ± 67	247 ± 54[b]	33%
ttpP (s)	0.16 ± 0.02	0.18 ± 0.03[a]	10%	0.18 ± 0.04	0.21 ± 0.03[b]	15%
RPD (Nm/s²)	3991 ± 813	2476 ± 799[a]	38%	2219 ± 792	1242 ± 397[b]	44%
Isotonic test at 40% load						
pV (°/s)	289 ± 39	270 ± 39	7%	282 ± 48	250 ± 37[b]	11%
ttpV (s)	0.20 ± 0.02	0.23 ± 0.02[a]	11%	0.23 ± 0.02	0.26 ± 0.03[b]	12%
RVD (°/s²)	1433 ± 246	1201 ± 233[a]	16%	1215 ± 200	963 ± 196[b]	21%
pP (Nm/s)	623 ± 95	435 ± 106[a]	30%	376 ± 71	246 ± 59[b]	35%
ttpP (s)	0.18 ± 0.02	0.20 ± 0.02[a]	12%	0.19 ± 0.02	0.22 ± 0.03[b]	12%
RPD (Nm/s²)	3571 ± 785	2213 ± 689[a]	38%	1957 ± 453	1152 ± 367[b]	41%
Isotonic test at 60% load						
pV (°/s)	176 ± 46	183 ± 40	-4%	201 ± 58	172 ± 38	14%
ttpV (s)	0.18 ± 0.03	0.22 ± 0.05[a]	20%	0.23 ± 0.04	0.26 ± 0.07[b]	14%
RVD (°/s²)	1015 ± 272	854 ± 242[a]	16%	884 ± 209	681 ± 193[b]	23%
pP (Nm/s)	512 ± 116	388 ± 97[a]	24%	344 ± 88	216 ± 60[b]	37%
ttpP (s)	0.16 ± 0.03	0.20 ± 0.05[a]	19%	0.20 ± 0.04	0.24 ± 0.07[b]	14%
RPD (Nm/s²)	3257 ± 1030	2049 ± 759[a]	37%	1721 ± 488	979 ± 366[b]	43%

Data are means ± SD and percent differences of peak Torque (pT), peak Velocity (pV), time to peak Velocity (ttpV), Rate of Velocity Development (RVD), peak Power (pP), time to peak Power (ttpP) and Rate of Power Development (RPD) between young and older men and women. [a]significantly different from young men $p < 0.05$; [b] significantly different from young women $p < 0.05$

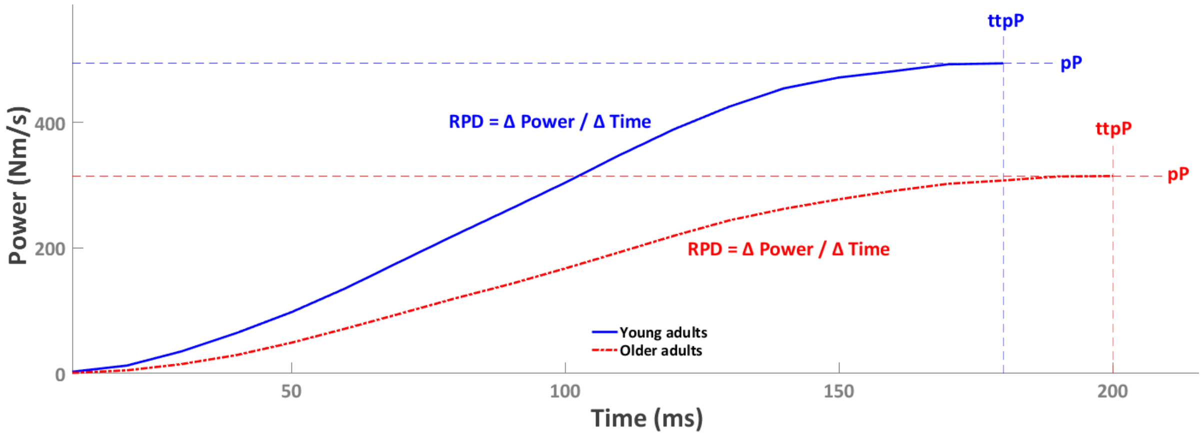

Fig. 1 Age-related differences in power development. Data are expressed as mean power (Nm/s) over time (ms) of young (blue solid line) and older adults (red dashed line) performing an isotonic test at 20% load. Peak power (pP), time to peak power (ttpP) and rate of power development (RPD) as the change of (Δ) power over Δ time are presented.

The data illustrate that absolute maximal power was produced at 20-40% load (Table 2), whereas maximal RPD was clearly produced at 20% load in every age-group. In terms of percent difference, RPD at 20% load showed the greatest difference between young and older adults. Two-way repeated measures analyses of variance showed an age-group by load interaction effect for all measures of muscle function ($p < 0.01$). More specifically for RPD, post hoc analyses showed that the age-related difference at 20% was larger than at 40% and 60% load ($p < 0.05$).

All functional tests were interrelated (r: .63 - .75) and their relation to the muscle parameters was relatively similar (Table 3). Although strength and velocity capacities showed a relatively high correlation with the functional performance tests, the power-related variables seemed to correlate systematically higher, irrespective of the load. However, Fischer z transformation showed that these correlation coefficients were not significantly higher. In addition, there was a trend that isotonic muscle function showed a higher correlation with functional performance with increasing load, although this was not significant. To illustrate, correlation coefficients ranged from .30 to .64 at 40% load and from .11 to .59 at 60% load. All correlation coefficients were significant, except for pV at 60% load. Correlation coefficients for the association of the isometric test and the isotonic test at 20% load with functional performance are presented in Table 3. In addition, Figure 2 gives a representation of the relationship between functional performance and RPD at 20% load.

Table 3. Association between measures of muscle function and functional performance tests in older adults (n=56).

	Isometric	*Isotonic at 20% load*					
	pT	**pV**	**ttpV**	**RVD**	**pP**	**ttpP**	**RPD**
7.5mFWT	-.51	-.55	.60	-.59	-.63	.55	-.64
TUG	-.55	-.52	.58	-.58	-.64	.51	-.64
STC	-.59	-.49	.57	-.55	-.62	.42	-.59

Data are Pearson's correlation coefficients (r-values) for the association of peak Torque/Body Mass(BM) (pT), peak Velocity (pV), time to peak Velocity (ttpV), Rate of Velocity Development (RVD), peak Power/BM (pP), time to peak Power (ttpP) and Rate of Power Development/BM (RPD) with 7.5-meter fast walk test (7.5mFWT), timed up-and-go (TUG) and stair climbing (STC). All correlation coefficients were statistically significant at $p < 0.001$.

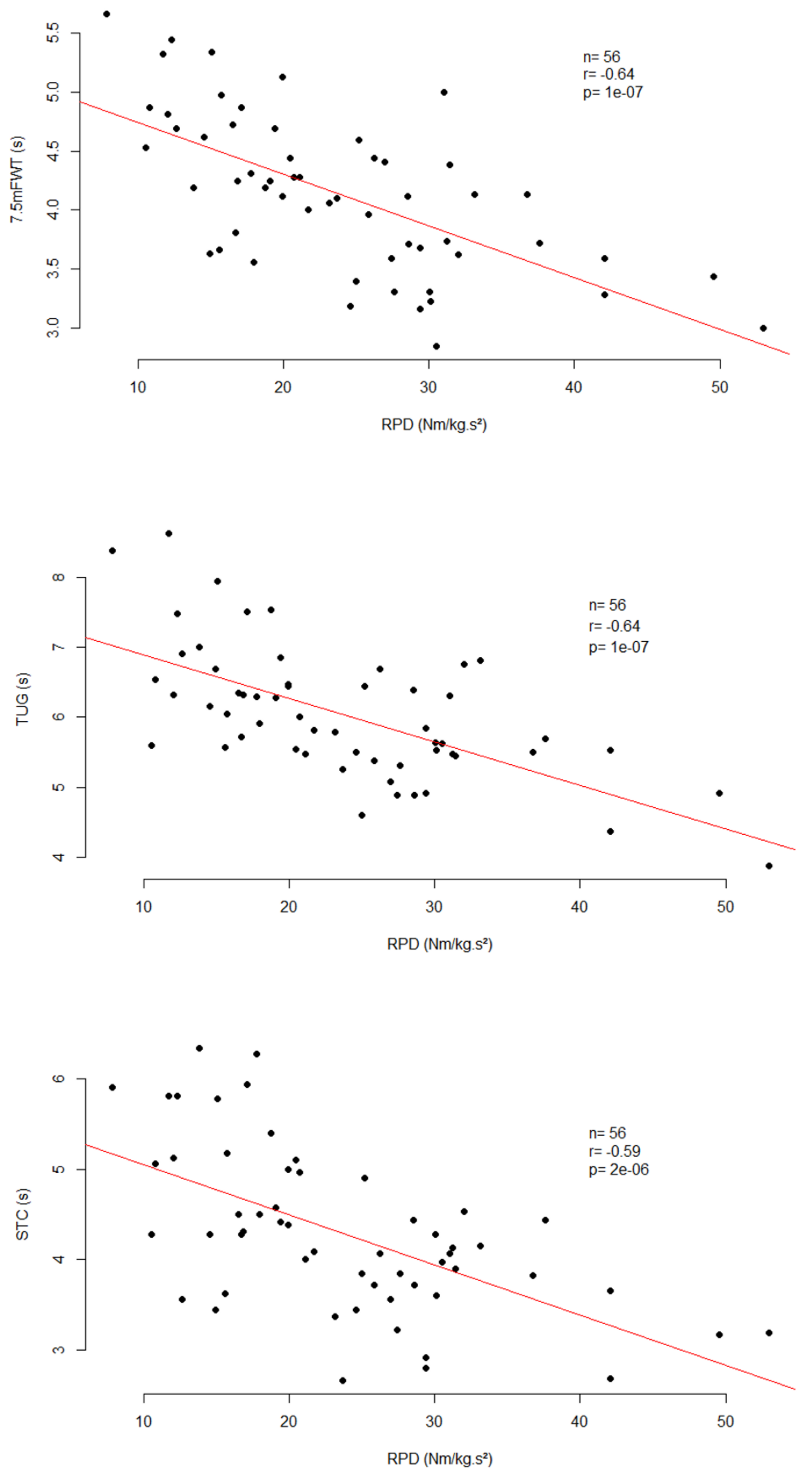

Figure 2. Relationship between functional performance and knee-extension rate of power development. Data represent the association of rate of power development (RPD) measured at a load of 20% of isometric maximal strength with 7.5-meter fast walk test (7.5mFWT), timed up-and-go (TUG) and stair climbing (STC) in 56 older adults. Rate of power development was normalized to body mass (BM). All associations were statistically significant at $p < 0.001$ (see Table 3).

Discussion

The current study investigated age-related differences on time-dependent measures of knee-extensor muscle function during isotonic tests against different loads. The key finding is that RVD and RPD differentiate more between young and older adults in terms of percent difference compared to pV and pP respectively. Furthermore, age-related differences were more pronounced at low load compared to at higher loads. All power-related parameters showed a strong relationship with functional performance in well-functioning community-dwelling older adults. Our results emphasize the inability to generate power rapidly at older age and underlines the importance of time-dependent measures to detect age-related changes in muscle function.

In line with previous research, our findings demonstrate that aging results in significant declines in strength, velocity and power characteristics of the knee extensors. More specifically, the older adults in this study were 28% weaker, 7-14% slower and 24-37% less powerfull than the younger adults, a decline rate of similar magnitude compared to previous reports (Charlier et al. 2015; Dalton et al. 2012; Petrella et al. 2005; Thompson et al. 2013).

A particular novelty of the present study is the use of time-dependent muscle parameters determined from loaded isotonic tests to distinguish young from older adults. More specifically, RVD and RPD take into account the time needed (i.e. ttpV and ttpP) to develop pV and pP respectively. Similar to pV and pP, young performed better than old at every load with regard to ttpV and ttpP. The longer time needed to reach peak power in old age might be influenced by the role of the knee joint angle at which peak power is attained. However, data analyses (not reported here) showed that position at peak power was similar between young and older adults ($p > 0.05$) at all loads.

In terms of percent difference, RVD and RPD differentiated more between young and older adults at every load compared to pV and pP respectively. To illustrate, differences between young and older adults across loads ranged from 24-32% in men and 33-37% in women for pP and from 37-38% in men and 41-44% in women for RPD. To our knowledge, there is no statistical methodology to verify whether these percent differences are significantly different. However, RPD is calculated as the ratio of both pP and ttpP. Increases in RPD are the result of increased pP and/or decreased ttpP. Therefore, we can assume that RPD differs more than pP because of the additional difference between young and old in ttpP. This emphasizes the added value of the time-dependent nature of RVD and RPD to discriminate between age-groups.

In terms of velocity capacities, our results are similar with the reduction in pV and RVD previously reported by Thompson and colleagues (Thompson et al. 2014a). Yet, our older age-group was slightly younger than the oldest age-group of Thompson and colleagues. In addition, Thompson et al.

investigated an unloaded test in men only. Therefore, our study adds to the current literature on RVD in old age by including different loads and both sexes. To illustrate, men were stronger, more powerful and faster than women within each age-group at every load. However, no age-group by sex interaction effect was found, meaning that age-related differences in muscle function were similar between both sexes. Next to RVD, previous research mainly focused on the rate of torque development (RTD), which has been shown to decline during aging and to be more related to falling compared to pT (Bento et al. 2010; Thompson et al. 2013). However, to the authors' knowledge, no previous studies have reported age-related differences in RPD. The effect of aging at a neuromuscular level includes quantitative loss of muscle mass, altered muscle fiber contractile properties, slowing of neuromuscular activation and altered architecture and compliance of muscle and tendon (Reid and Fielding 2012). These changes in muscle quantity and quality have an influence on both strength (Clark and Manini 2008) and velocity capacities (Power et al. 2013). Strength and acceleration (i.e. the change of velocity over time) capacities are combined in RPD, which might explain the greater age-related declines.

The age-group by load interaction effect indicates increasing age-related differences in velocity- and power-related variables with decreasing load. In addition, power at lower loads appeared to be more associated with functional performance than power at higher loads, although this could not be statistically confirmed. Furthermore, RPD was performed maximally at low load (i.e. 20%) in every age group. Therefore, RPD at low load might be considered to detect early age-related declines in muscle function, although more research is necessary to confirm this.

Previous reports showed that both muscle strength and velocity are associated with functional performance (Sayers et al. 2005). Consequently, power, which is more holistic in nature because it incorporates both strength and velocity capacities, has emerged as an important predictor of functional limitations in the elderly (Pojednic et al. 2012; Reid and Fielding 2012). Similarly, although isolated knee-extension movements were used to test muscle function, this study shows that pP during the isotonic contractions was clearly linked with functional performance (Van Roie et al. 2011). Stepwise regression analyses, not reported in this study, showed that pP and RPD were the single best predictors for functional performance, which confirms their holistic nature. In line with previous research on the rate of torque development (Maffiuletti et al. 2010), we hypothesized that time-dependent muscle parameters would more closely reflect daily life functioning in older adults. However, the results did not confirm our hypothesis. This might be caused by the fact that our sample of older adults were still well-functioning (Table 1), which is shown by the high scores on functional performance tests compared to reference values (Bischoff et al. 2003; Bohannon 2006; Morley et al. 2011). In addition, our functional tests might not be a good representation of the short response times needed to accelerate the limbs in many daily activities, such as recovery from perturbations to prevent falling. Next, it should be noted that single-joint isolated tests might not be a good representation of falling as they lack coordination of multiple joints and muscles. Therefore, we should be careful in interpreting these results.

Some limitations of this study have to be recognized. Although the tests were performed using a gold standard dynamometer (Biodex System 3), a sampling frequency of 100Hz could be rather low for time-sensitive measurements. However, previous testings in our lab show good to high reliability for all measures of muscle function reported in this study (Van Driessche et al. 2018). A second limitation of the study is the cross-sectional design. Therefore, reductions in muscle function characteristics should be interpreted as differences between two age groups, rather than longitudinal declines. Further research should focus on differences in RPD across the adult life span with much larger study samples, in order to have a better insight in the early phase of age-related differences.

To conclude, the key finding of this study is that age-related percent differences in RPD exceed differences in pP for the knee-extensor muscles. RPD combines both maximal strength and acceleration capacities of the muscle in one parameter, which might explain the greater age-related declines. Interestingly, the age-related differences in RPD and pP increased as the load decreased. All power-related parameters were related to functional capacity in well-functioning community-dwelling older adults. Future research should investigate whether RPD could be used as a sensitive screening method for future disability.

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Chapter 2

The influence of movement complexity on muscular function during aging

Article 3

Age-related decline in leg-extensor power development in single- versus multi-joint movements

Van Driessche S, Van Roie E, Vanwanseele B, Van Leemputte M, Delecluse C

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Abstract

Rapid muscle characteristics, such as the rate of power development (RPD), are shown to decline more than maximal muscle characteristics during aging in single-joint actions. However, functional disability is mainly the result of multi-joint lower limb failure. The complex activation patterns inherent to multi-joint actions and the deteriorating effect of age on that neural drive suggest a larger effect of age on RPD multi-joint. Yet, this is the first study that compared multi- with single-joint leg extension tests in terms of RPD across the adult life span and assessed its transferability to functional performance.

96 healthy adults (♂ 49, ♀ 47, age = 20 – 69 years) performed dynamic single-joint knee-extension tests on a Biodex System 3 dynamometer and multi-joint leg-extension tests on a custom-made device at low, moderate and high speed. Peak power (pP) was calculated as the highest value of the power-time curve and RPD as the linear slope till isokinetic speed was reached. Functional performance was tested using squat jump height.

RPD showed greater age-related declines in multi-joint (-1.92%/year) versus single-joint (-1.42%/year) actions, which is in contrast with the finding of pP (-0.77% vs. -1.04%/year). Squat jump height was more strongly associated with RPD multi-joint than single-joint (r = .77 – .82 vs. .44 – .61).

These results show greater age-related declines of RPD multi-joint versus single-joint and demonstrate its functional relevance. We believe that this finding may be of high importance for the detection and prevention of functional disability during aging.

Keywords: physical function, rapid strength, sarcopenia, functional performance

Introduction

One of the major problems in our aging and graying society is the age-related loss of independence, resulting in enormous health care costs. This loss of independence, manifested by a decreased physical performance and an increased fall risk, is a consequence of the effects of aging on neuromuscular function (Aagaard et al. 2010; Kennis et al. 2014; Madigan and Lloyd 2005). Therefore, optimized screening and prevention methods for this neuromuscular decline are highly needed.

The majority of screening methods in research and clinical practice focused on maximal muscle strength or maximal muscle power (Goodpaster et al. 2006; Kostka 2005; Macaluso and De Vito 2003; Yamauchi et al. 2009). Maximal power production deteriorates more during aging compared to maximal strength (Lanza et al. 2003; Skelton et al. 1994). Moreover, muscle power is a better determinant of functional capacity compared to muscle strength (Cuoco et al. 2004; Foldvari et al. 2000), which suggest that dynamic tests to evaluate power are preferred over isometric tests for screening of neuromuscular function. However, neither maximal strength nor maximal power take into account the time needed to be developed (i.e. > 300ms). In other words, these variables may not be representative for the initial phase of very quick movements, such as the prevention of a fall after stumbling (Madigan and Lloyd 2005; Pijnappels et al. 2005).

This initial phase of very quick movements is represented by parameters such as the rate of force (RFD) or power development (RPD). RFD, i.e. the ability to produce force rapidly, declines to a greater extent during aging and is more strongly related to functional daily tasks and fall risk than maximal strength (Clark et al. 2013; Häkkinen et al. 1998; Izquierdo et al. 1999; Thompson et al. 2013). In line with these findings, a recent study in our lab demonstrated that the age-related declines in RPD exceeded the declines in maximal power (pP) performed in dynamic contractions (Van Driessche et al. 2018a). Conjointly, we can conclude that older adults have even greater difficulty in developing strength or power rapidly than in reaching high peak values. However, most studies were limited to isolated single-joint movements, which may not be representative for most daily life activities that include multi-joint movements (Azegami et al. 2007).

Multi-joint movements primarily differ from single-joint movements through their complex neural activation and coordination patterns of agonist and antagonist/synergist muscles. This neural activation capacity, which is crucial for rapid force production in older adults (Klass et al. 2008), is detrimentally affected by aging (Billot et al. 2014). Therefore, aging may have a different impact on rapid force production in multi- versus single-joint movements. To date, few studies have focused on rapid force production in multi-joint actions. These studies were either limited to isometric tests or did not compare multi-joint to single-joint tests within the same cohort (Allison et al. 2013; Izquierdo et al. 1999; Thompson et al. 2018).

Therefore, this study investigated the effect of aging on maximal and rapid muscle characteristics in dynamic single- and multi-joint actions across the adult life span. In addition, associations with a functional movement were evaluated. We hypothesized that: 1) RPD declines more than pP in both test methods, 2) RPD declines more in multi-joint compared to single-joint movements and 3) multi-joint RPD is more strongly related to a functional movement than single-joint RPD.

Methods

Subjects

Men and women between 20 and 70 years old (n = 10 ♂ and 10 ♀ per decade) were recruited through advertisements and oral communications. Subjects completed a short medical history and activity questionnaire and were excluded in case of a cardiovascular disease or acute thrombosis, recent surgery, neuromuscular disease, infection or fever, diabetes or pregnancy and systematic strength or endurance training (i.e. progressive increases in volume and/or intensity) in the prior 6 months. Occasional engagement in physical activity, such as cycling, walking and running was allowed. In total, 96 healthy subjects (♂ 49, ♀ 47) aged between 20 and 69 years volunteered and their data were included for all analyses. All subjects provided written informed consent. The study was approved by the University's Human Ethics Committee in accordance with the declaration of Helsinki.

Design

This study had a cross-sectional design to reveal the effect of age, sex, speed and test method on upper leg neuromuscular function. Subjects performed two test sessions separated by a rest day to avoid fatigue. In the first session, familiarization with the multi-joint protocol was performed as a warming-up, followed by the single-joint protocol. The second session was performed at the same time of day as session one and led by the same investigator. Participants performed a warming-up on a bike ergometer at a self-determined submaximal resistance for 10 minutes, before performing the functional performance tests and the multi-joint protocol.

Single-joint testing

Neuromuscular function of the knee extensors was measured using a standardized protocol on a Biodex Medical System 3® dynamometer with a sampling rate of 100Hz (Biodex Medical Systems, Shirley, New York, USA). Measurements were performed unilaterally on the right side, in a seated position on a vertically and horizontally adjustable backward-inclined (5°) chair. Range of motion was set from a knee joint angle of 90° to 160°, with a fully extended leg corresponding to a knee angle of 180°. The upper leg, hips and shoulders were stabilized with safety belts. The rotational axis of the dynamometer was aligned with the transversal knee-joint axis and connected to the distal end of the tibia with a length-adjustable rigid lever arm. After warming-up, subjects performed four isometric knee-extension tests at 90° knee joint angle. They were instructed to push as hard as possible for 5s, separated by a 20-second rest period. Next, after at least 2 minutes of rest, subjects performed a series of three consecutive maximal isokinetic knee extension movements at slow, moderate and high speed (i.e. 60, 180 and 300°/s). During each dynamic test, the subjects were clearly instructed by the test leader to perform the tests as fast and as hard as possible. The rest interval was 30 seconds between the three conditions.

Multi-joint testing

A modified isokinetic version of the Nottingham Power Rig (Bassey and Short 1990) was built to measure neuromuscular function of the leg extensors. The force output was transmitted via a foot plate, lever and chain, which was fixed onto a motor-driven freewheel body and hub (Dura-Ace FH-7700, Shimano® Inc., Osaka, Japan). The technical details of the isokinetic dynamometer have been previously described (Koninckx et al. 2008). Briefly, the rotation speed of the lever arm was synchronized with the servo-controlled rotation of the motor axle (CM71 motor type combined with a Movidrive controller MDS60A, SEW-Eurodrive, Bruchsal, Germany) using a timing belt and two identical pulleys (Synchroforce HTD 925-5M CXP, Contitech, Germany). Torque values were measured by a torque transducer with an overall accuracy of <0.25% (1703 series, Lebow® Products Inc., Troy, United States). A dSpace interface (dSpace-GmBH, Paderborn, Germany) was used for data streaming at 1000Hz, with a real-time control program (Simulink, The Mathworks Inc., Natick, United States). Movement of the lever arm was initiated by surpassing a cut-off torque of 20% of maximal isometric single-joint strength inducing a low-level of pretension (i.e. 20-70Nm) as previously recommended (Tillin et al. 2013). Measurements were performed unilaterally on the right side. Subjects were seated on a backward-inclined (5°) chair, which was vertically and horizontally adjustable. In addition, the lever arm was adjustable to allow standardization of the multi-joint range of motion. Range of motion was set from a knee joint angle of 90° to 160° and from a hip joint angle of 70° to 115°, with a fully extended leg corresponding to a knee and hip angle of 180° (Fig. 1). The hips and shoulders were stabilized with safety belts. The right foot was fully supported and fixed to the foot plate using a solid strap with the lateral malleolus aligned with the point of force application, provoking a heel thrust to minimize the influence of lower leg muscles and ankle movement. Subjects wore the same flat non-cushioning shoes to minimize the cushioning effect during the initial impact of the rapid contractions.

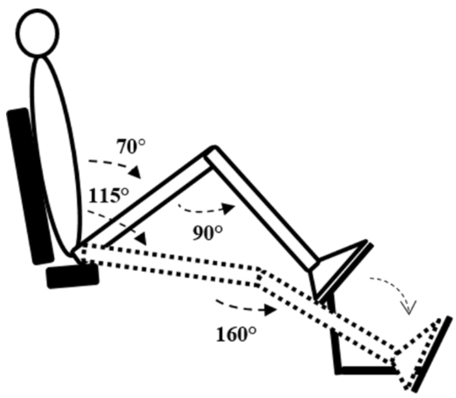

Figure 1. Start and end position of the multi-joint leg press movement

During the tests, subjects were asked to fold their hands across the chest to avoid extraneous movements. They performed maximal leg press movements while lever arm angle speed was held constant at 180°/s, 300°/s and 420°/s. Even though absolute angular velocities of multi- and single-joint tests differ extensively (i.e. read 60, 180 and 300 °/s versus 180°/s, 300°/s and 420°/s), tests were performed at similar knee angular velocities (i.e. 60, 180 and 300 °/s in single-joint versus ~115, 191 and 267°/s in multi-joint tests). Knee angular velocities were calculated as the knee joint's range of motion over the time of the particular tests. Each condition was performed three times with 30 seconds rest periods in between. In between different velocity conditions, participants were allowed to rest for 2 minutes to minimize fatigue. During each test, the subjects were clearly instructed by the test leader to perform the tests as fast and hard as possible.

Functional performance testing

Squat jumps were assessed as a measure of functional performance allowing maximal neuromuscular performance in a similar knee range of motion as the isokinetic test methods, while avoiding the ceiling effects that are often reported in standard functional performance test batteries. The squat jumps were performed on a force platform (OR6-7, Advanced Mechanical Technology Inc., Watertown, United States) at a sampling frequency of 1000Hz. Subjects kept their hands placed on the hips to avoid the effect of arm-swing on jump performance. Subjects were instructed to start in a squat position at 90° knee angle and jump as high as possible without performing any countermovement. All trials that were preceded by a countermovement (i.e. ground reaction force < 0.015*body mass) were excluded. After a first trial, three jumps were performed with 30 seconds rest in between.

Signal processing

All signals were processed off-line using a commercial software package (Matlab R2016b, The MathWorks Inc., Natick, United States). Torque signals of the single- and multi-joint tests were filtered using a fourth-order low-pass Butterworth filter with a 10Hz and 20Hz cut-off frequency, respectively. Instantaneous power (Watt) was calculated as the product of torque (Nm) and velocity (rad/s). It should be noted that due to the isokinetic nature of the present measurements, power production represents the dynamic torque production at standardized movement velocities. Peak power (pP, Watt) was determined as the highest value of the power curve. The rate of power development (RPD, Watt/s) was calculated as the linear slope of the power-time curve from the start of the movement till isokinetic speed was reached. The start of the movement was determined as the point where the acceleration reached a threshold of 150 °/s^2 for the single-joint tests (Van Driessche et al. 2018a) and where the cut-off torque was reached for the multi-joint tests. The tests with the highest pP were used for further analyses. Reliability of maximal and rapid muscle characteristics of the knee extensors using isokinetic dynamometry have been previously reported (ICC: .85 – .96; SEM(%): 3.6 – 12.5)(Brown et al. 2005; Van Driessche et al. 2018b). Reliability of the multi-joint measurements was assessed in 16 older adults, who returned for a third session to repeat the multi-joint tests (ICC: .87 – .97; SEM(%): 4 – 18.7).

Ground reaction force signals of the squat jump tests allowed for the determination of body center of mass (BCM) velocity at take-off and hence the calculation of jump height, according to previous procedures (Edwen et al. 2014). The highest jump performance was used for further analyses.

Statistical analyses

All statistical analyses were performed using R software, version 1.0.153 (R_Core_Team 2017). To study the effects of age and test method on rapid and maximal neuromuscular function, we built linear mixed models for pP and RPD using the function lmer provided by the R-package lme4 (Bates et al. 2015). The response variable in all models was log-transformed to make relative comparison of the age-related declines between speeds and test methods possible (Törnqvist et al. 1985). Age and test method (single- or multi-joint) were entered as fixed effects into the model. The variable age was used as continuous variable. In addition to the fixed-effects terms, the models included subject as a random effect to correct for the repeated measures design. The effect of covariates such as speed, sex, body mass, lever arm length (only for the multi-joint tests) and their possible interactions were analyzed in a series of separate linear mixed effects models using step-up model comparisons. This iterative model fitting procedure started with the basic model of investigating the effect of age and test method on the response variable, then sequentially adding predictor terms. The Akaike information criterion (AIC) and a likelihood ratio test, performing the R-function 'anova', were used to compare models. For all models we tested underlying assumptions (e.g. normality and homogeneity of residuals) by visual inspection of residual plots. We found that no assumption was violated. After fitting the models, model estimates of the log-transformed data were exponentiated for interpretability of the relative slopes (i.e. annual decline rates in percent). P-values were obtained using the R-package lmerTest (Kuznetsova et al. 2016).

Post hoc, to test multi- versus single-joint neuromuscular function at similar speeds, we fitted a new model in which speed was modeled as a categorical variable. As fixed effects, we entered age and speed. Sex and body mass were added as covariates. Subject was included as random effect. The R-function 'relevel' was used in three separate models to compare multi-joint 115°/s with single-joint 60°/s, multi-joint 191°/s with single-joint 180°/s and multi-joint 267°/s with single-joint 300°/s.

Pearson's correlation coefficients were calculated to examine the relationship of multi- versus single-joint power measures with squat jump performance. Fischer z transformation was used to statistically compare correlation coefficients. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Mixed-effects model comparisons revealed significant main effects for age, test method, speed, sex and body mass for both response variables (Table 1). The estimate of the intercept in Table 1 can be interpreted as the reference value (i.e. man of 20 years old that is tested multi-joint at the lowest speed) in log(Watt) for pP and log(Nm/s²) for RPD. In line with this, the estimate of age, test method, speed, sex and body mass can be interpreted as the rate of change in pP and RPD per unit of the independent variable. Lever arm length was first included to test its possible performance enhancing effect during the multi-joint tests in comparison with the single-joint tests, but was removed from the model because it was not significant. A significant interaction effect between age and test method was found for pP and RPD, indicating that pP declines more in the single-joint action whereas RPD declines more in the multi-joint action during aging (Table 2, Fig. 2). No significant interaction effects of age with speed, sex or body mass were found.

Table 1. Results of the linear mixed effects models.

Term	Estimate	SE	p-value
pP			
Intercept	5.618	0.134	< 0.001
Age	-0.008	0.001	< 0.001
Method	-0.667	0.033	< 0.001
Speed	0.004	0.000	< 0.001
Sex	-0.276	0.038	< 0.001
BM	0.010	0.001	< 0.001
Age*Method	-0.003	0.001	< 0.001
RPD			
Intercept	7.091	0.289	< 0.001
Age	-0.019	0.002	< 0.001
Method	-0.483	0.096	< 0.001
Speed	0.004	0.000	< 0.001
Sex	-0.414	0.081	< 0.001
BM	0.015	0.003	< 0.001
Age*Method	0.005	0.002	0.0122

Data represent the effect of age and test method in interaction, speed, sex and body mass (BM) as fixed factors and subject (n = 96) as random factor on maximal power (pP) and rate of power development (RPD). Estimates = change in pP (log(Watt)) and RPD (log(Nm/s²)) per unit of the respective term compared to the intercept, SE = standard error, * refers to an interaction term.

Table 2. Annual decline rates in peak power and rate of power development.

Method	Speed	pP (%)	RPD (%)
Single-joint	**overall**	-1.04	-1.42
	low	-0.93	-1.32
	moderate	-1.06	-1.44
	high	-1.14	-1.51
Multi-joint	**overall**	-0.77*	-1.92*
	low	-0.70*	-1.95*
	moderate	-0.77*	-2.04*
	high	-0.84*	-1.80

Data are exponentiated estimates from mixed model analyses, which express the annual age-related decline rates in percent for maximal power (pP) and rate of power development (RPD) in single-joint tests overall, at 60°/s (low), 180°/s (moderate) and 300°/s (high speed) and multi-joint tests overall, at 115°/s (low), 191°/s (moderate) and 267°/s (high speed). * = significantly different from single-joint ($p < .05$)

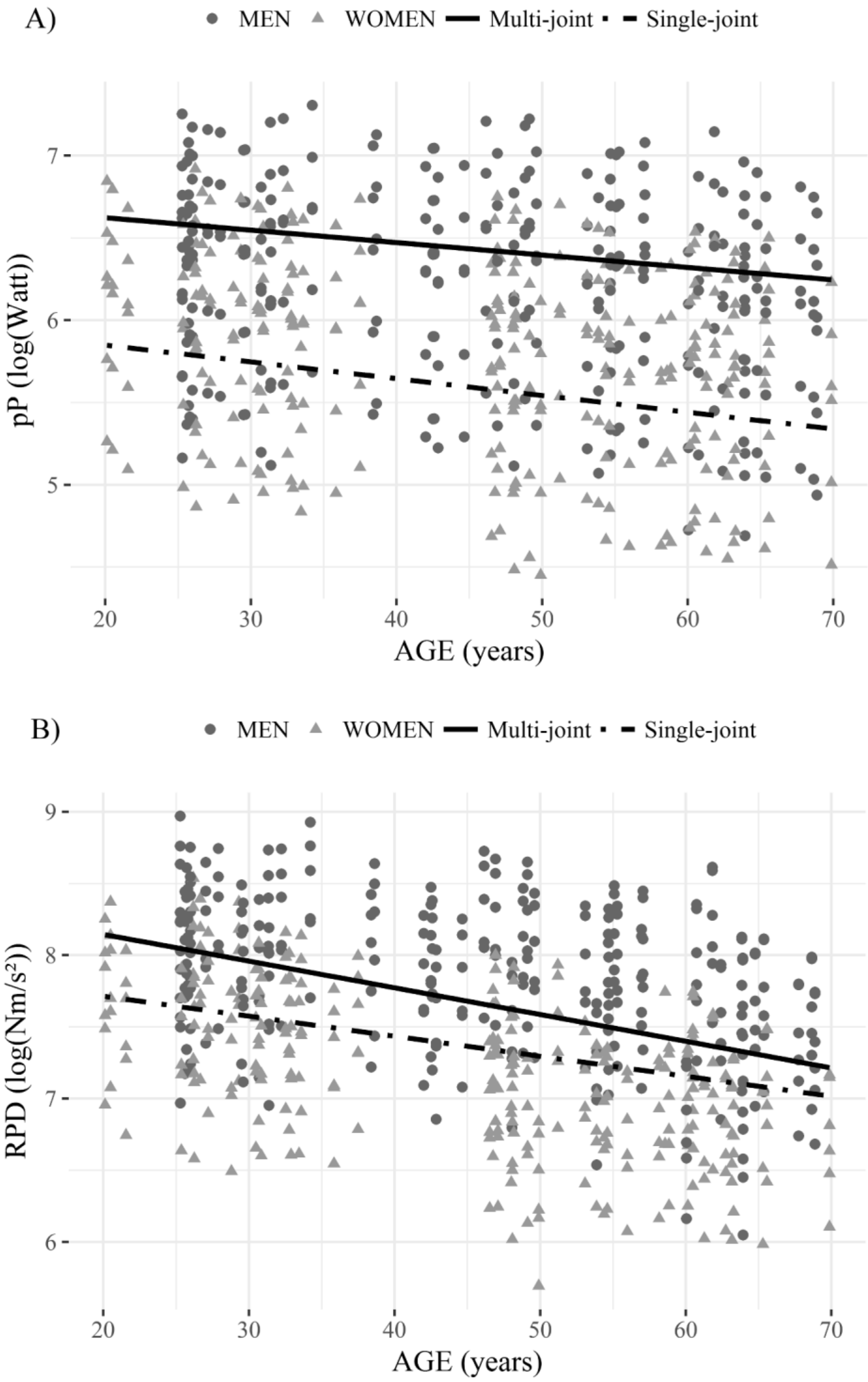

Figure 2. Measures of (A) maximal power (pP) and (B) rate of power development (RPD) in 96 healthy adults (49 men and 47 women), aged between 20 and 70 years, in single- and multi-joint tests at low, moderate and high speed. The overall average age-related decline is represented by a black solid linear fit for the multi-joint tests and a black dotdashed linear fit for the single-joint tests. Data are displayed on a log scale.

The comparison of the age-related decline in multi- and single-joint pP at similar speeds revealed significantly lower declines in multi-joint tests. Interestingly, age-related declines in RPD were higher in multi-joint than single-joint tests at low and moderate speed.

Both single- and multi-joint tests were positively correlated with squat jump performance. Interestingly, the association between squat jump height and RPD multi-joint was significantly higher than the association between squat jump height and RPD single-joint (Table 3). For pP, multi- and single-joint tests were equally related to squat jump performance.

Table 3. Association between squat jump performance and pP or RPD.

Method	Speed	pP/BM	RPD/BM
Single-joint	**low**	.68	.44
	moderate	.74	.50
	high	.77	.61
Multi-joint	**low**	.80	.77*
	moderate	.82	.80*
	high	.85	.82*

Data are Pearson's correlation coefficients (r-values) for the association of maximal power (pP) and rate of power development (RPD) relative to body mass (BM) measured in single-joint tests at 60°/s (low speed), 180°/s (moderate speed) and 300°/s (high speed) and in multi-joint tests at 115 °/s (low speed), 191°/s (moderate speed) and 267°/s (high speed) with jump height measured in squat jump tests in healthy adults (n = 96) aged between 20 – 70 years. All correlation coefficients were statistically significant ($p < .05$). * = significantly more strongly associated with squat jump performance compared to single-joint tests

Discussion

This study investigated the effect of aging on maximal and rapid muscle characteristics in dynamic single- and multi-joint actions across the adult life span. In line with our first hypothesis, leg extension RPD (-1.42 – -1.92%) declines more during aging than pP (-1.04 – -0.77%) for both single- and multi-joint movements. In accordance to our second and third hypotheses, RPD in multi-joint movements declines more during aging and is more strongly related to squat jump performance than RPD in single-joint movements. These observations emphasize the striking age-related decline in rapid muscle characteristics, especially in multi-joint leg extension movements.

Surprisingly, this study showed a greater age-related decline of pP in single- versus multi-joint actions. Across all speeds, pP showed an average decline rate of 0.77% per year in the multi-joint mode, whereas pP in the single-joint mode showed a significantly greater average decline rate of 1.04% per year (Table 1). The magnitude of these annual decline rates are similar as previously described for single-joint (i.e. 0.7 – 1.8%)(Kennis et al. 2014; Lanza et al. 2003) and multi-joint tests (i.e. 0.6 – 1.5%)(Allison et al. 2013; Edwen et al. 2014; Kostka 2005; Macaluso and De Vito 2003; Yamauchi et al. 2009). Although, to our knowledge, no previous research compared the age-related declines in power output between single- and multi-joint test methods, it has previously been suggested that the cooperative work of multiple muscles working over multiple joints could lead to a compensation strategy to prevent for the reduced performance output at older age (Hortobágyi et al. 2003). These findings suggest that the greater age-related decline of pP in single- versus multi-joint actions found in this study may highlight the adaptive mechanical plasticity of the aging neuromuscular system. In this way, multi-joint testing could underestimate the age-related declines in maximal power production, which is in favor of single-joint testing.

However, maximal power may not be representative for the overall decline in neuromuscular function. To illustrate, previous studies have emphasized the importance of the initial phase of rapid single-joint contractions by demonstrating greater age-related declines in RFD and RPD compared to maximal strength and power (Thompson et al. 2013; Van Driessche et al. 2018a). In general, the effect of age on the neuromuscular level refers to a combination of neural and muscular changes. It has been shown that RFD is predominantly influenced by neural characteristics next to type II myofibre content, especially in older adults (Klass et al. 2008). Muscular properties become more relevant in later stages of rapid muscle contractions (> 75 – 150ms) in contrast with the neural input that predetermines the first 75ms (Folland et al. 2014; Maffiuletti et al. 2016). Considering that pP was generally reached after more than 150ms across speeds over the entire adult life span in the current study, compensatory actions of synergist muscles could have been initiated by the neural system in the multi-joint tests and could partly have masked the effect of age on the neuromuscular changes that are reflected in the single-joint tests. Whereas short response times (i.e. < 75ms) may limit the ability to initiate compensatory muscle actions in multi-joint performance, resulting in greater age-related declines. Therefore, we hypothesized that RPD would decline more than pP. The results of the present study confirm that this is true for single-joint contractions, but in particular also for multi-joint leg-extension tests.

The variable RPD is representative for the initial acceleration phase (i.e. first 50 – 75ms). In line with our second hypothesis, the present study showed a greater age-related decline of RPD in multi- (-1.92%) versus single-joint (-1.42%) actions. This greater age-related decline in multi-joint was apparent at slow and moderate speeds, but not at high speed. The latter can be explained by the longer time that was needed to reach the higher isokinetic speeds (i.e. ~ 75ms). The longer the time to develop power, the higher the chance that the complex coordination pattern of agonist and synergist muscles has been well initiated and that compensatory actions of synergist muscles might have led to an underestimation of the age-related deterioration of neuromuscular function in multi-joint movement. Although no previous research focused on rapid power characteristics across the adult life span in single- versus multi-joint movements, recent reports compared rapid strength characteristics between age-groups in multi-joint movements. Izquierdo et al. reported a 46% lower peak force and a 64% lower peak RFD for older men (~70 years) compared with young men (~20 years) performing an isometric bilateral squat (Izquierdo et al. 1999). Allison et al. only found a 19% lower peak force and a 21% lower peak RFD between young (~24 years) and older (~66 years) men performing an isometric unilateral leg press movement (Allison et al. 2013). Surprisingly, the latter did not find an effect of age on the rapid force production during the initial phase (i.e. first 100ms) of a multi-joint isometric contraction, suggesting that older men and young men have a similar ability to activate the involved muscles during rapid efforts. However, the more extended position and initial pretension in their measurements (~150N) might explain their different results. Furthermore, both aforementioned studies did not perform single- and multi-joint tests within the same cohort, making comparison between methods difficult. Only recently, Thompson et al. demonstrated greater age-related reductions of RFD in multi-joint versus single-joint actions within the same cohort (Thompson et al. 2018). They suggested that single-joint static strength tests may underestimate age-related rapid strength impairments, which is in line with our findings of rapid power (RPD) characteristics in dynamic tests.

At this point, we can only speculate on the relative contribution of neural and muscular determinants of RPD. However, our results suggest that the effect of age on the neural drive of muscle action has a detrimental role on power development during very fast actions, especially in multi-joint movements compared to single-joint movements. This is especially relevant at older age, considering that most daily activities include multi-joint movements and failure to perform fast actions can lead to falling and fractures. In the current study, squat jump height was highly related to pP in single- and multi-joint movements. According to our third hypothesis, jump height was more strongly related to RPD in multi-joint compared to single-joint movements, indicating the functional relevance of the multi-joint test methodology.

A potential methodological limitation of the present study was the isokinetic test approach. Isokinetic tests can be considered as less functional compared to isotonic tests because of their speed controlling nature. This speed control could have led to an underestimation of power compared to non-isokinetic approaches (Aagaard et al. 1994). Furthermore, differences in machine control between clinical/commercial (i.e. Biodex) and custom made equipment could have influenced our results. Though, the use of this approach enabled the comparison of single- and multi-joint movements at similar predetermined speeds. Next, the cross-sectional design of this study may be confounded by inter individual differences and age-related declines may be different in a longitudinal design. Furthermore, the oldest subject was 69 years old. Although we found large age-related declines in neuromuscular function in our sample of adults between 20 and 69 years of age, we are not able to extrapolate our results to ages over 70 years. To note, an accelerated deterioration of power output after the age of 65 was previously reported with decline rates of 3-4% per year, which emphasizes the age-related deterioration of neuromuscular function at older age (Skelton et al. 1994). However, we believe that it is important to explore the early age-related declines in neuromuscular function to allow for appropriate screening and prevention methods before daily life functioning becomes limited.

To conclude, for the first time multi-joint leg extension tests were compared to single-joint tests in terms of rapid power characteristics across the adult life span. The key finding is that RPD declines more in multi-joint than in single-joint actions during aging. Although the majority of research and clinical practice is focused on single-joint testing and maximal output parameters like Ppeak, this study indicated that aging has an even more detrimental effect on the initial phase of rapid power development (RPD) especially in multi-joint tests. Moreover, multi-joint RPD was shown to be strongly associated with functional performance. Given that many daily life activities include fast multi-joint movements, multi-joint RPD can be considered relevant for daily life functional performance. Therefore, these findings may be of high importance for the detection of functional disability at older age. Whether training interventions targeting gains in multi-joint RPD can lead to prevention of functional disability should be further investigated. Finally, the mechanisms behind the age-related decline in RPD in multi-joint actions should be investigated in future research.

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Chapter 3

The influence of acceleration on muscular function during aging and its underlying mechanisms

Article 4

Effect of acceleration on the rate of power development and neural activity of the leg extensors across the adult life span

Van Driessche S, Van Roie E, Vanwanseele B, Delecluse C

Under review in European Journal of Applied Physiology.

Abstract

The rate of power development (RPD) represents the capacity to rapidly generate power during a dynamic muscle contraction. As RPD is highly susceptible to aging, its decline can have important functional consequences. However, the effect of age on RPD in response to rapid changes in movement velocity (cfr. fall incidence) is not yet clear. Therefore, the present study aimed to examine the effect of age on RPD and neural drive in response to different accelerations.

Three maximal isokinetic leg-extensor tests at 540°/s with different initial acceleration phases at 3200, 5700 and 7200°/s² were performed. RPD, which is the slope of the power-time curve during the acceleration phase, was calculated for eighty-three subjects aged between 20-69 years. Mean electromyography (EMG) signal amplitude was determined for rectus femoris (RF), vastus lateralis (VL) and biceps femoris (BF) muscles.

The average annual age-related decline rate of RPD at highest acceleration was -2.93% and was higher compared to lower acceleration rates. This deficit can probably be explained by an age-related impairment in neural drive during the first 75ms of the acceleration phase, as evidenced by a reduced neuromuscular activity of RF and VL.

These findings highlight the inability of aged individuals to quickly respond to abrupt changes in movement velocity, which requires more focus in training and prevention programs.

Keywords: Sarcopenia, Aging, Fall prevention, Explosive power

Introduction

Aging is associated with a decrease in functional capacity leading to a reduced quality of life (Rolland et al. 2008). More specifically, an important consequence of the aging process is the higher risk of falls. About 24-40% of community-dwelling people aged 65 or older fall at least once a year and frequency of falls increases with age (Milat et al. 2011). A better understanding of age-related changes in neuromuscular function in response to abrupt perturbations could give valuable insights with regard to fall prevention in the aged.

The majority of research investigating age-related changes in dynamic neuromuscular function have been focused on changes in maximal muscle power (Lanza et al. 2003; Skelton et al. 1994). However, maximal power measures are limited to represent daily life functional capacity, because they do not take into account the time needed to reach peak power. Recently, we have shown that the age-related decline in the rate of power development (RPD) exceeds the decline in peak power because of the additional decline in the time needed to reach peak power (Van Driessche et al. 2018a; Van Roie et al. 2018). This age-related decline is even more pronounced in multi-joint actions, as shown by our previous work (Van Driessche et al. 2018b). The latter reports indicate that aging has a detrimental effect on the initial acceleration phase of a contraction.

Many daily life activities such as fast walking, stair climbing, chair rising and balance recovery after tripping involve fast dynamic actions. These actions include a velocity component that is characterized by an acceleration phase, which requires a fast response of muscle action. Next to fiber type content, neural activation has been shown to have a predominant influence on neuromuscular function during fast actions (Folland et al. 2014; Maffiuletti et al. 2016). In addition, it has been shown that aging has a detrimental effect on neural activation of skeletal muscles in terms of electromyographic (EMG) activity and motor unit firing rates (Clark et al. 2010; Klass et al. 2008). In this regard, age-related impairment in neural activation may even be enlarged in fast accelerative actions. Although a link between the age-related decline in neuromuscular function and neural activity in fast actions has been suggested in the literature, the effect of age on neural activity and neuromuscular function in response to different accelerations remains unclear.

Therefore, this cross-sectional study investigated the effect of different preprogrammed accelerations on power production and neural drive in multi-joint leg extensor tests across the adult life span. We hypothesized that age-related changes in RPD are greater at higher accelerations compared to lower accelerations. In addition, we hypothesized that this age-related change in neuromuscular function can be attributed to changes in neural activity.

Methods

Subjects

Ninety-six healthy subjects (♂ 49, ♀ 47) aged between 20 and 69 years volunteered after recruitment through advertisements and oral communications. Subjects completed a short medical history and physical activity questionnaire and were excluded in case of a cardiovascular disease or acute thrombosis, recent surgery, neuromuscular disease, infection or fever, diabetes or pregnancy and systematic participation in strength or endurance training (i.e. progressive increases in volume and/or intensity) in the prior 6 months. Occasional engagement in physical activity, such as cycling, walking and running was allowed. After thorough examination of all EMG signals and exclusion of incomplete test samples because of measurement failure of one or more tests, complete data of 83 healthy subjects (♂ 43, ♀ 40) were used for further analyses. All subjects provided written informed consent.

The study was approved by the University’s Human Ethics Committee in accordance with the declaration of Helsinki.

Power measurements

Power measurements and signal analysis procedures have been previously described (Van Driessche et al. 2018b). Briefly, a multi-joint isokinetic machine was developed to measure multi-joint neuromuscular function of the leg extensors at a sampling frequency of 1000Hz. The seat and lever arm were adjustable to allow for standard range of motion (i.e. knee joint angle of 90° to 160° and hip joint angle of 70° to 115°)(Fig. 1).

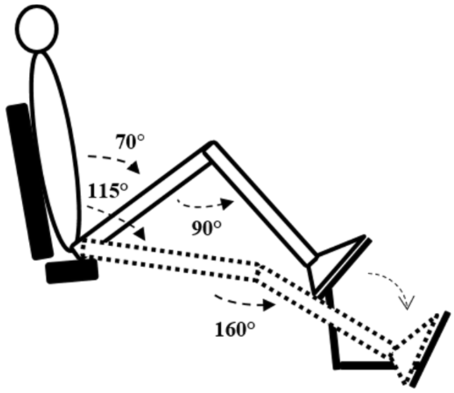

Fig. 1 Start and end position of the multi-joint leg press movement (Van Driessche et al. 2018b).

Measurements were performed unilaterally on the right side. The right foot was fully supported and fixed to the foot plate using a solid strap with the lateral malleolus aligned with the point of force application, provoking a heel thrust to minimize the influence of lower leg muscles and ankle movement. Movement of the lever arm was initiated by surpassing a cut-off torque of 20% of maximal isometric single-joint strength inducing a low-level of pretension (i.e. 20-70Nm) as previously recommended (Tillin et al. 2013).

Subjects performed two test sessions separated by a rest day to avoid fatigue. In the first session, familiarization with the protocol was performed as well as isometric and isokinetic knee-extension tests (data not included). The second session was performed at the same time of day as session one and led by the same investigator. Participants started with a warming-up on a bike ergometer at a self-determined submaximal resistance for 10 minutes. For the leg extensor tests, lever arm angular acceleration was preprogrammed using a real-time control program (Simulink, The Mathworks Inc., Natick, United States) at 5700°/s² (medium), 3200°/s² (low) and 7200°/s² (high acceleration) respectively until a fixed isokinetic velocity of 540°/s was reached. The terms medium, low and high acceleration are chosen for readability, although it should be noted that all accelerations used in the present study are high to extremely high. These lever arm angular accelerations correspond to knee angular accelerations of ~3627°/s², 2036°/s² and 4582°/s² respectively (calculated based on the knee joint's range of motion and the time of the particular tests). Each condition was performed three times with 30 seconds rest periods in between. During each test, the subjects were clearly instructed by the test leader to push as fast and as hard as possible.

Electromyography measurements

The EMG activity of rectus femoris (RF), vastus lateralis (VL) and biceps femoris (BF) were collected during the multi-joint leg extensor tests. Surface electrodes were positioned following the European Recommendations for Surface Electromyography (SENIAM) after careful preparation of the skin (i.e. shaving and cleaning with alcohol) to keep skin impedance low. EMG signals were recorded using wireless EMG electrodes (KINE®, KINE Ltd., Hafnarfjördur, Iceland) with an input impedance of 10GΩ, a common mode rejection ratio of 110dB, a signal-to-noise ratio of 60dB, a differential detection mode and a built in A/D converter of 10bit with a range of 4mV, resulting in a sensitivity of 4µV (Martens et al. 2015). EMG signals were sampled at 1600Hz. An extra electrode unit was used to catch a trigger pulse from the real-time control program at the start of each leg extensor test to enable synchronization of the EMG signals and the power output.

Signal processing

All signals were processed off-line using a commercial software package (Matlab R2016b, The MathWorks Inc., Natick, United States). Torque signals were filtered using a fourth-order low-pass Butterworth filter with a 20Hz cut-off frequency. Instantaneous power (watt) was calculated as the product of torque (Nm) and velocity (rad/s). As acceleration is defined as a change in velocity over time, we examined the ability to produce power in the acceleration phase of our three test conditions in two different manners: either at a fixed time interval (i.e. 75ms) till different velocities between the three tests, or till a fixed velocity (i.e. 540°/s) at different time intervals. This approach allows us to examine the impact of both time and velocity in the effect of acceleration on power production during aging. In this way, the rate of power development (RPD, watt/s) was calculated as the linear slope of the power-time curve from the start of the movement till 75ms (RPD_{0-75ms}) and till isokinetic speed ($RPD_{0-540°/s}$) was reached. The start of the movement was determined as the point where the cut-off torque was reached.

Raw EMG signals were band-pass filtered (20-500Hz), full-wave rectified and smoothed using a fourth order low-pass Butterworth filter with a cut-off frequency of 6Hz. Mean EMG amplitude was determined from the onset of activation (i.e. > 3 SD of baseline signal) till the start of the movement (electromechanical delay + pretension), till 75ms and till the end of the acceleration phase (Fig. 2).

EMG signals were normalized to the test at lowest acceleration to enable comparison of age-related changes between acceleration rates.

For both RPD and EMG, the mean of the three trials was used for further analyses. Reliability of the multi-joint measurements was assessed in 16 older adults, who returned for a third session to repeat the multi-joint tests (ICC: .95 - .98; SEM(%): 7.3 – 24.5).

Statistical analyses

All statistical analyses were performed using R software, version 1.0.153 (R_Core_Team 2017). To study the effect of acceleration on RPD and muscle activation across the adult life span, we built linear mixed models for RPD and parameters of muscle activation using the function lmer provided by the R-package lme4 (Bates et al. 2015). The response variables were log-transformed to make relative comparison of the age-related declines between accelerations possible in all models (Törnqvist et al. 1985). Age, acceleration, sex and body mass were entered as fixed effects into the model. The variable age was used as continuous variable. In addition to the fixed-effects terms, the models included subject as a random effect to correct for the repeated measures design. An iterative model fitting procedure was conducted to analyze the effects of all factors (Van Driessche et al. 2018b). P-values were obtained using the R-package lmerTest (Kuznetsova et al. 2016). The R-function 'relevel' was used for comparison between acceleration phases. Statistical significance was set at $p < 0.05$ for all analyses.

Pearson's correlation coefficients were calculated to examine the association between muscle activity and the age-related decline in power output at high versus low acceleration rate, for which power data was also set relative to the test at lowest acceleration.

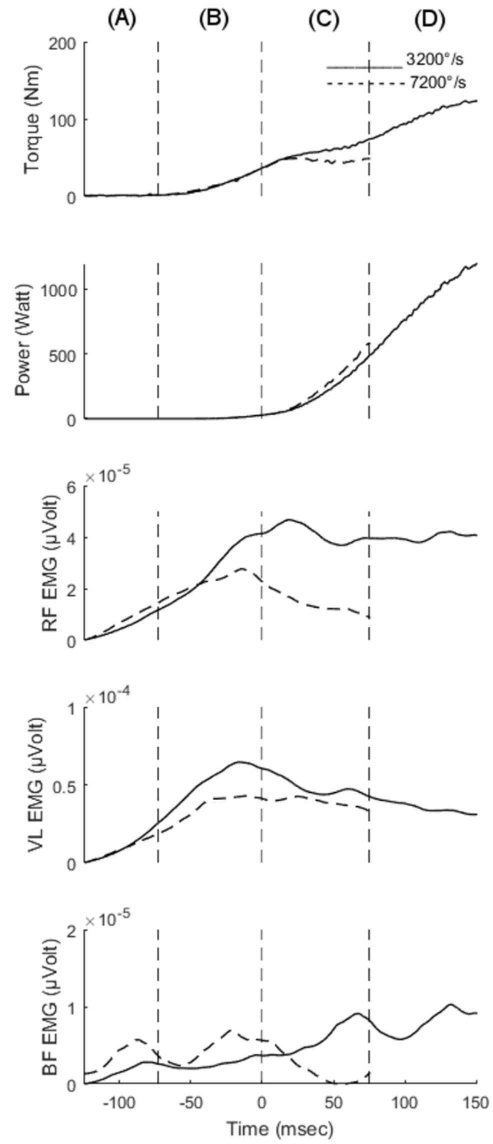

Fig. 2 Representation of torque, power and muscle activity signals at lower (3200°/s², solid line) and higher (7200°/s², dashed line) acceleration rate of a young male subject. Tests can be divided in three phases: (A) a phase of electromechanical delay, (B) a phase of pretension till 20% of maximal isometric knee extension strength is reached and (C) the acceleration phase which can be calculated over a fixed time period (75ms) or (D) until a fixed velocity (540°/s).

Results

All participants succeeded in performing the high accelerative knee extensor tests. Across participants, absolute mean (±SD) RPD scores were as follows: low till 75ms – 3069 (1450) Nm/s²; low till 540°/s – 4253 (1617) Nm/s²; medium till 75ms – 3375 (1819) Nm/s²; medium till 540°/s – 4204 (1919) Nm/s²; high – 3071 (2121) Nm/s². The mixed effects model for RPD demonstrated a main age effect and an age*acceleration interaction effect. The average annual decline rate of $RPD_{0-540°/s}$ across the study sample was -1.11% at low, -1.43% at medium and -2.93% at high acceleration with the decline rate at high acceleration significantly steeper than at low and medium acceleration (p < 0.01)(Fig. 3). Similar results were found for RPD_{0-75ms} with -1.37% at low, -1.85% at medium and -2.85% at high acceleration. No age*sex or age*body mass interaction effect was found. Therefore, these factors were excluded from the model.

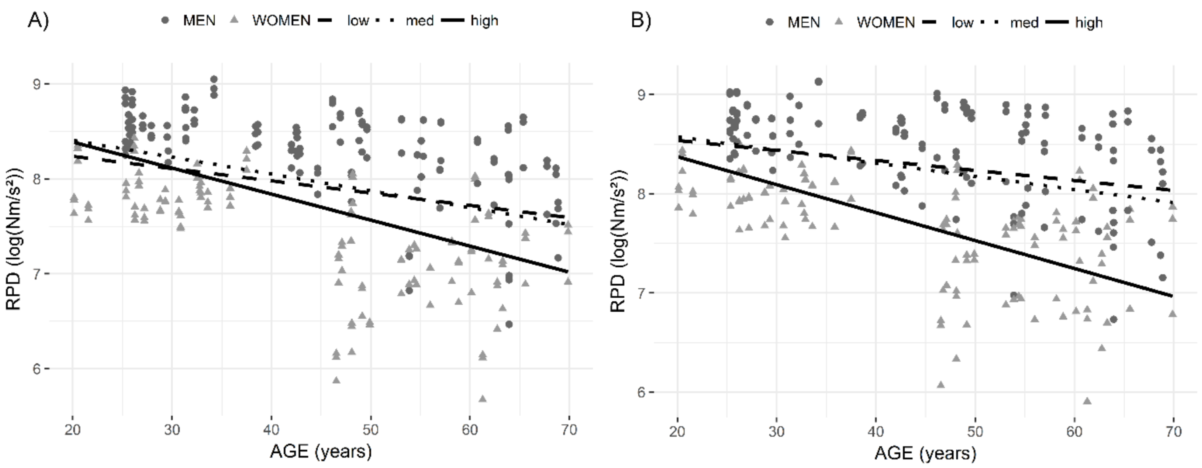

Fig. 3 Age-related decline of leg-extensor rate of power development (RPD) across 83 subjects (♂ 43, ♀ 40, aged 20 to 69 years) at low (3200°/s², dashed line), medium (5700°/s², dotted line) and high (7200°/s², solid line) acceleration till fixed time point of 75ms (A) and till fixed velocity of 540°/s (B).

To visualize the impact of both time and velocity on the age-related decline in RPD, we interpolated the results of the age-related decline rates of RPD at every time point across the three acceleration tests and plotted them against both time and velocity (Fig. 4).

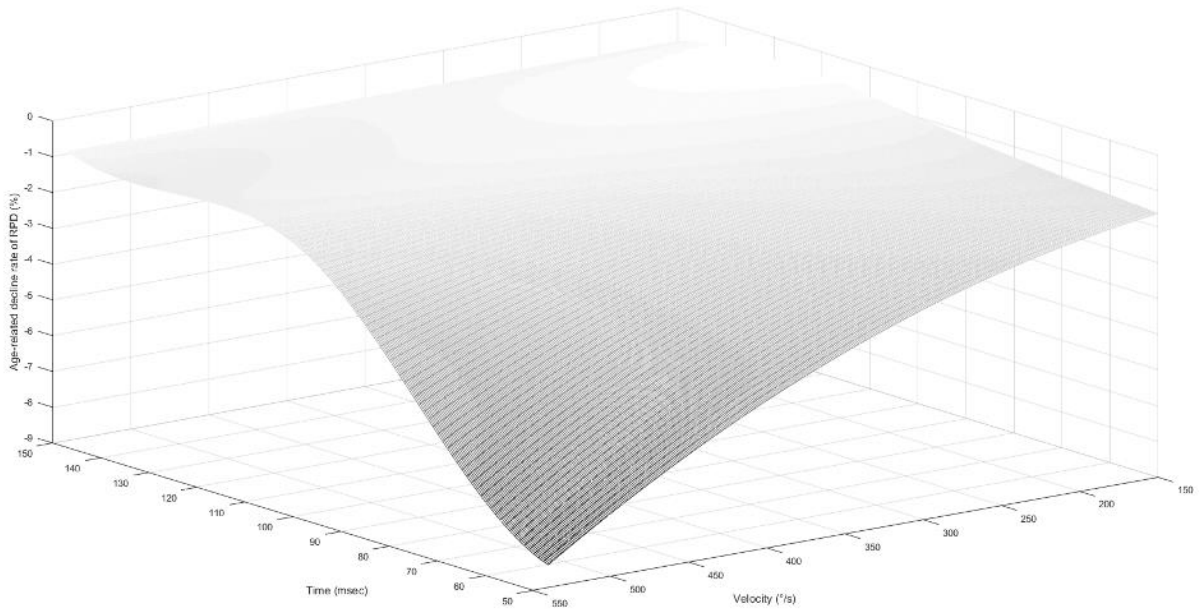

Fig. 4 Age-related decline of leg-extensor rate of power development (RPD). Data across 83 subjects (♂ 43, ♀ 40, aged 20 to 69 years) at low (3200°/s²), medium (5700°/s²) and high (7200°/s²) acceleration were interpolated and visualized in terms of time and velocity.

All EMG parameters from the onset of muscle activation till the start of the movement (i.e. electromechanical delay and small pretension phase) were the same across acceleration rates. Therefore, potential differences between the tests can only be attributed to differences in the acceleration phase and EMG parameters further on in the manuscript will represent neuromuscular activation from the onset of muscle activation till the end of the acceleration phase.

In line with the results of $RPD_{0-540°/s}$, neuromuscular activation of RF and VL declined more at high compared to low acceleration with advancing age (Table 1, Fig. 5). No interaction effect with age was found for BF neuromuscular activation. For high acceleration relative to low acceleration, the age-related changes in RF and VL activation were associated with the age-related decline in RPD across the sample, except for the association between RPD_{0-75ms} and RF activation. No association was found between BF neuromuscular activation and age-related changes in RPD.

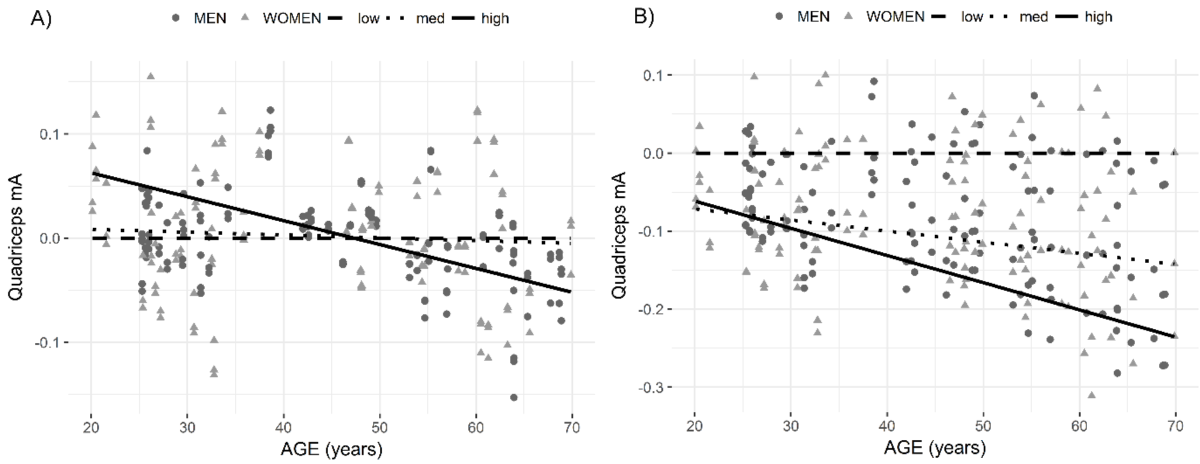

Fig. 5 Age-related decline of quadriceps muscle activity across 83 subjects (♂ 43, ♀ 40, aged 20 to 69 years) during leg extensor tests at low (3200°/s², dashed line), medium (5700°/s², dotted line) and high (7200°/s², solid line) acceleration till fixed time point of 75ms (A) and till fixed velocity of 540°/s (B). Quadriceps mean EMG amplitude (mA) was calculated as the sum of rectus femoris (RF) and vastus lateralis (VL) mA for visualization.

Table 1. Relative annual decline rates and associations with RPD

Test target	Parameter	Decline rate medium vs. low (%)	Decline rate high vs. medium (%)	Decline rate high vs. low (%)	Association with RPD high relative to low (r-value)
540°/s	**RPD**	-0.32	-1.52***	-1.82***	1
	RF mA	-0.17	-0.12	-0.30*	0.26*
	VL mA	-0.15	-0.22	-0.36**	0.30**
75ms	**RPD**	-0.48	-1.01**	-1.49***	1
	RF mA	-0.08	-0.10	-0.19	0.19
	VL mA	0.01	-0.21	-0.20	0.24*

Data represent differences in average annual age-related decline rates and associations of the rate of power development (RPD), rectus femoris (RF) and vastus lateralis (VL) mean EMG amplitude (mA) between low (i.e. 3200°/s²), medium (i.e. 5700°/s²) and high (i.e. 7200°/s²) acceleration (n = 83). *p < .05, **p<.01, ***p<.001.

Discussion

This study demonstrates that the rate of power development is more affected by aging at high compared to lower acceleration rate and that this phenomenon is associated with impaired quadriceps neuromuscular activation. These results indicate that reduced neural activity during healthy aging likely limits the capacity to rapidly develop power in very fast dynamic actions.

The primary finding of the current study is the highly impaired leg extensor RPD (-2.93% per year) at advancing age in response to a high acceleration rate. This average annual decline rate is much higher than the decline rates of -0.6 to -1.9%, reported for peak power and RPD in isokinetic and isotonic single- and multi-joint leg extension tests (Allison et al. 2013; Edwen et al. 2014; Kostka 2005; Macaluso and De Vito 2003; Van Driessche et al. 2018a; Van Driessche et al. 2018b; Yamauchi et al. 2009) and reported in the current study for low and medium acceleration. To note, comparison between the previous studies is difficult because of differences in distinct age-groups and statistical analyses, yet the large age-related decline of RPD at high acceleration presented in this study is remarkable. Although this age-related decline was significantly greater at high compared to low and medium acceleration, we found no difference between low and medium acceleration. This finding suggests that rapid power production becomes increasingly difficult at advancing age at acceleration rates of more than 5700°/s² lever arm displacement, which corresponds to knee angular accelerations of about 3627°/s².

It should be noted that the combination of little time and high velocity, together expressed as high acceleration, leads to the largest age-related declines. To visualize this phenomenon, we interpolated the results of the age-related decline rates of RPD at every time point across the three acceleration tests and plotted them against both time and velocity (Fig. 4). On the one hand, this figure shows that a test at for example high velocity (> 450°/s lever arm angular velocity) reached within longer time periods (> 150ms) or a test at low velocity (< 150°/s lever arm angular velocity) reached within short time periods (< 75ms) both result in age-related decline rates of RPD that are similar to previous reports (i.e. -0.9 to -1.1%). On the other hand, short time periods and high velocities, together expressed as high acceleration, seem to result in large decline rates of RPD. According to Thompson et al. (Thompson et al. 2014a), these findings suggest that not high velocity as such, but acceleration might be highly susceptible to aging, taking into account the time needed to reach those velocities.

The present results indicate that muscle action in response to extremely high accelerations (e.g. abrupt perturbations) is extremely vulnerable to the effect of aging. This may explain the lower probability to recover successfully after a trip at advancing age (Pijnappels et al. 2008). Although, the direct link with falling could not be made, the present findings are in accordance with previous reports about rapid torque development that has been shown to be more relevant for the performance in fast actions, like to prevent for a fall after stumbling (Maffiuletti et al. 2016; Pijnappels et al. 2005). Although the age-related decline in RPD was the largest for the highest acceleration, it should be noted that the low, medium and high accelerations used in this study were all high and that all participants succeeded to perform the tests and to produce additional torque. This suggests that muscular action in response to high accelerations could be trained in the way we tested it. Although, it should be further investigated whether training can improve RPD at high acceleration rates and whether this could lead to a reduced risk of falling.

Interpretation of absolute age-related declines of surface EMG activity across the adult life span may be misleading because of differences in subcutaneous tissue thickness and in distribution and characteristics of motor units between young and older adults (Masakado et al. 1994). Therefore, surface EMG signals were normalized to the test at lowest acceleration. In line with our hypotheses, the higher age-related decline in mean EMG amplitude of RF and VL at high versus low acceleration demonstrates the inability of older adults to increase neuromuscular activation in response to high accelerations. This decline in neuromuscular activation at high versus low acceleration was associated with the age-related decline in RPD. Remarkably, Fig. 5 demonstrates that younger adults activated their quadriceps muscles more at high compared to low acceleration within the first 75ms, whereas the older adults' quadriceps activation was less at high compared to low acceleration. The latter indicates that within the first 75ms, higher movement velocity requires higher neural activation, in which the older adults fail. Although the age-related declines in neural activation between accelerations till 75ms were not significantly different, these trends and the significantly higher age-related declines in neural activity at high acceleration (i.e. till 540°/s in 75ms) compared to low acceleration (i.e. till 540°/s in 169ms) suggest that older adults particularly have difficulties in fast activation of muscles in short time periods (≤ 75ms), whereas longer time periods (i.e. > 75ms) may allow to compensate for the early phase deficits in neural activation. This is in line with previous reports, which suggested that neural input predetermines the first 75ms (Folland et al. 2014; Maffiuletti et al. 2016). In addition, it has been shown via intramuscular EMG that the age-related decline in rapid torque development is predominantly influenced by neural characteristics, next to type II myofibre content (Klass et al. 2008). However, previous studies that investigated rapid muscle activation in fast single-joint isometric tests using surface EMG in healthy well-functioning adults failed to find any age-related decline in neural activation (Clark et al. 2010; Clark et al. 2011; Thompson et al. 2014b). Next to differences in test procedures, the tests in the latter studies might not have been challenging enough to reveal age-related changes in neural activation compared to the challenging high acceleration test used in the current study. Moreover, a significant decline in neural activity and a high association (r = .73) between power output and neural activity were previously reported when subjects with mobility limitations were included, for which the tests are expected to be even more challenging compared to for healthy and well-functioning subjects (Clark et al. 2011).

The results of the current study suggest that impairments in neuromuscular activation during aging may be a major physiologic mechanism contributing to the age-related deficit in rapid power development, especially within the first 75ms of a fast movement. However, the significant but relatively small associations found between reduced neuromuscular activity and RPD at high versus low acceleration suggest that the increased age-related decline rate of RPD can only be partly explained by impaired quadriceps neuromuscular activation. These findings suggest that other factors may have an influence on the age-related impairment of RPD at high accelerations. Although no age-related differences were found between acceleration rates in biceps femoris neuromuscular activity in the present study, the coordination and activation of other synergist and antagonist muscles could have influenced neuromuscular function as it has been shown that the level of coactivation is increased with aging (Izquierdo et al. 1999; Macaluso et al. 2002). However, in line with the current findings, it has been shown for the ankle dorsiflexors that age-related changes in coactivation were absent during fast contractions (Klass et al. 2008). In addition, other potential mechanisms like shortening velocity of the fascicles, musculotendinous stiffness and fibre type composition may have an influence on neuromuscular function during fast contractions (Maffiuletti et al. 2016).

Some limitations have to be considered. Surface EMG was only recorded in RF, VL and BF, whereas other muscles contribute to a leg extensor movement. Next, this study was limited to a cross-sectional design which does not allow for longitudinal interpretations of aging effects. Furthermore, only healthy well-functioning participants were measured in this study, making it difficult to find an association with mobility limitations or fall risk. However, excluding the latter allows us to refer the current findings predominantly to the effect of aging as such. The challenging test conditions of the present study revealed significant age-related declines in neuromuscular function that are relevant to a healthy and well-functioning population between 20 and 70 years of age. Yet, this may emphasize the problem for older and mobility limited people that are highly susceptible to falling. Moreover, the present findings underscore the importance of early detection of the age-related deterioration of neuromuscular function for prevention purposes.

To conclude, this study emphasizes the magnitude of the age-related decline in rapid leg extensor power development in response to abrupt changes in movement velocity across the adult life span and demonstrates that impairment in neuromuscular activity is associated with this age-related deficit. Future research should examine how these findings relate to fall risk at old age. In addition, training interventions in older adults should focus on the ability to accelerate the lower limb in short time periods.

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Article 5

Vastus lateralis fascicle behavior during fast accelerative movements across the adult life span

Van Driessche S, Vanwanseele B, Van Roie E, Delecluse C

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Abstract

Knee extensor rate of power development (RPD) decreases during aging, which may result in increased fall risk. Investigations on contractile changes underlying the age-related decline in knee extensor function have been limited to in vitro and whole muscle approaches. This study aimed to identify the underlying mechanism of age-related declines in RPD during fast accelerations in terms of in vivo vastus lateralis (VL) fascicle shortening behavior.

Thirty-nine men aged between 25-69 years performed three maximal isokinetic leg extensor tests with an initial acceleration of 3200, 5700 and 7200°/s² until 540°/s lever arm angular velocity. RPD, VL activity and ultrasound images were recorded to assess fascicle shortening and maximum shortening velocity for the phases of electromechanical delay, pretension and acceleration within the tests.

Our findings provide experimental evidence that in vivo VL fascicle shortening and shortening velocity during fast actions increase with aging (~1.2% per year on average) and are associated with RPD (r = .19), mainly due to more shortening in the phase of electromechanical delay. Yet, no change in fascicle shortening behavior was found between accelerations.

These results indicate that VL fascicle behavior changes with aging, which is likely the result of previously reported increases in compliance of the series elastic element (SEE). Higher fascicle shortening might result in less optimal fiber lengths, which may partly explain the age-related decline in RPD. These findings suggest that a certain SEE stiffness and specific fiber force are required to perform fast muscle actions and should therefore be trained at older age.

Keywords: explosive strength, force-velocity relationship, fascicle shortening velocity, knee extensors, rate of power development

Introduction

Impaired maximal knee extensor strength is an important delimiter of functional capacity at older age, which can lead to increased fall incidence (Pijnappels et al. 2008). Yet, to prevent falling, muscle strength should also be developed extremely fast (< 200ms) (Pijnappels et al. 2005) and at a certain movement velocity, resulting in power production. Fast dynamic muscle actions can be represented by the rate of power development (RPD). Recently, we showed that RPD of the knee extensors is decreased during aging (Van Driessche et al. 2018a; Van Driessche et al. 2018b; Van Roie et al. 2018) and significantly more at high accelerations compared to lower accelerations (paper under review). In order to counteract these age-related deteriorations in muscle function and the concomitant increase in fall risk, a better understanding of the physiological mechanisms behind the age-related decline in RPD at fast accelerations is warranted.

Muscle force generation is influenced by many factors. In particular, rapid force production is influenced by motor unit recruitment and discharge rate, next to muscle fiber type composition (Maffiuletti et al. 2016). In addition, the larger decline in leg extensor RPD with aging at higher compared to lower accelerations is accompanied by a reduction in neural drive (paper under review). Yet at fiber level, it is well known that the length and shortening velocity of muscle fibers have a predominant influence on the magnitude of maximal force production (Hill 1938). For in vitro muscle fibers, the force-velocity relationship shows that the higher the shortening velocities the lower the maximal force output (Bottinelli et al. 1999). A leftward shift in the force-velocity relationship, for example due to a reduction in maximal shortening velocity, results in lower force production at a certain shortening velocity. In this way, the age-related reduction in maximal shortening velocity of in vitro muscle fibers has been suggested to explain age-related impairments in muscle function (D'Antona et al. 2003; Krivickas et al. 2001). However, to the authors' knowledge, the effect of aging on in vivo fiber shortening velocity of the knee extensors has not yet been investigated.

As an alternative, whole muscle force-velocity characteristics have been the focus of many studies in aging research (Raj et al. 2010). Similar to the in vitro fiber level, knee extensor muscle strength and maximal contraction velocity have been reported to be reduced during maximal dynamic contractions, inducing a shift in the force-velocity relationship during aging (Petrella et al. 2005). Moreover, whole muscle maximal contraction velocity has been shown to decline significantly during aging (Dalton et al. 2010; Lanza et al. 2003) and was suggested to be a key component in the onset of functional difficulties in the elderly (Pojednic et al. 2012; Van Roie et al. 2011). However, these findings may not be representative for in vivo human muscle fibers (Chino et al. 2008; Kawakami and Fukunaga 2006). In vivo human muscle fiber shortening velocity depends on fiber geometry, muscle force and compliance of the series elastic components (Cronin and Lichtwark 2013). Regarding the leg extensors, previous findings may represent whole vastus lateralis (VL) muscle-tendon unit (MTU) shortening velocity, which is linearly related to knee joint angular velocity (Hawkins and Hull 1990). In particular, the shortening velocity of the MTU has been shown to respond differently to changes in joint angular velocity compared to the fascicles (Fontana Hde et al. 2014; Ichinose et al. 2000). Yet, the effect of aging on in vivo VL fascicle shortening velocity during fast actions remains elusive.

Therefore, this cross-sectional study investigated the effect of age on in vivo VL fascicle shortening behavior and its relation with RPD in multi-joint leg extensor tests across the adult life span. We hypothesized that fascicle shortening velocity during fast actions decreases with aging and is related to the decline in RPD. Furthermore, we hypothesized that this effect would be emphasized at higher accelerations compared to lower.

Methods

Subjects

Forty-nine men aged between 20 and 70 years (~ ten per decade) were recruited through advertisements and oral communications (Van Driessche et al. 2018b). Subjects completed a short medical history and physical activity questionnaire and were excluded in case of a cardiovascular disease or acute thrombosis, recent surgery, neuromuscular disease, infection or fever, diabetes or pregnancy and systematic participation in strength or endurance training (i.e. progressive increases in volume and/or intensity) in the prior 6 months. Occasional engagement in physical activity, such as cycling, walking and running was allowed. After thorough examination of power output, electromyography (EMG) signals and ultrasound images and after exclusion of incomplete test samples because of measurement failure of one or more tests, complete data of thirthy-nine healthy subjects aged between 25 and 69 years were used for further analyses. All subjects provided written informed consent. The study was approved by the University’s Human Ethics Committee in accordance with the declaration of Helsinki.

Power measurements

Power measurements and signal analysis procedures have been previously described (Van Driessche et al. 2018b). Briefly, a multi-joint isokinetic machine was developed to measure multi-joint neuromuscular function of the leg extensors at a sampling frequency of 1000Hz. The seat and lever arm were adjustable to allow for standardized range of motion (i.e. knee joint angle of 90° to 160° and hip joint angle of 70° to 115°). Measurements were performed unilaterally on the right side. The right foot was fully supported and fixed to the foot plate using a solid strap with the lateral malleolus aligned with the point of force application, provoking a heel thrust to minimize the influence of lower leg muscles and ankle movement. Movement of the lever arm was initiated by surpassing a cut-off torque of 20% of maximal isometric single-joint strength inducing a low-level of pretension (i.e. 20-70Nm) as previously recommended (Tillin et al. 2013).

Subjects performed two test sessions separated by a rest day to avoid fatigue. In the first session, familiarization with the protocol was performed as well as isometric and isokinetic knee-extension tests (data not included). The second session was performed at the same time of day as session one and led by the same investigator. Participants started with a warming-up on a bike ergometer at a self-determined submaximal resistance for 10 minutes. For the leg extensor tests, lever arm angular acceleration was preprogrammed using a real-time control program (Simulink, The Mathworks Inc., Natick, United States) at 5700°/s² (medium), 3200°/s² (low) and 7200°/s² (high acceleration) respectively until an isokinetic velocity of 540°/s was reached. The terms medium, low and high acceleration are chosen for readability, although it should be noted that all accelerations used in the present study are high to extremely high. These lever arm angular accelerations correspond to knee angular accelerations of ~3627°/s², 2036°/s² and 4582°/s² respectively (calculated based on the knee joint's range of motion and the time of the particular tests). Each condition was performed three times with 30 seconds rest periods in between. During each test, the subjects were clearly instructed by the test leader to push as fast and as hard as possible.

Electromyographic activity

EMG activity of vastus lateralis (VL) was collected during the multi-joint leg extensor tests. Surface electrodes were positioned following the European Recommendations for Surface Electromyography (SENIAM) after careful preparation of the skin (i.e. shaving and cleaning with alcohol) to keep skin impedance low. EMG signals were recorded using wireless EMG electrodes (KINE®, KINE Ltd., Hafnarfjördur, Iceland) with an input impedance of 10GΩ, a common mode rejection ratio of 110dB, a signal-to-noise ratio of 60dB, a differential detection mode and a built in A/D converter of 10bit with a range of 4mV, resulting in a sensitivity of 4µV. EMG signals were sampled at 1600Hz. An extra electrode unit was used to catch a trigger pulse from the real-time control program at the start of each leg extensor test to enable synchronization of the EMG signals and the power output. Onset of activation was determined as > 3 SD of the baseline signal (Fig. 1).

Ultrasound measurements

B-mode ultrasound images of VL muscle were obtained at 60Hz using a Telemed Echoblaster 128 CEXT system (UAB Telemed, Vilnius, Lithuania). A 128-element linear transducer (LV 7.5/60/128Z-2, UAB Telemed, Vilnius, Lithuania) with a 60mm field of view was used at 8MHz. The ultrasound probe was securely fixed to the skin on the lateral mid-thigh of the right leg using a semi-flexible holder, elastic bandage and wrapping tape. The probe was oriented in a way to get the best image quality and as parallel as possible to the deep aponeurosis. The start of the ultrasound recordings was used as a trigger pulse and sent to the real-time control program to allow synchronization with EMG and power output.

Signal processing

All signals were processed off-line using a commercial software package (Matlab R2016b, The MathWorks Inc., Natick, United States). Torque signals were filtered using a fourth-order low-pass Butterworth filter with a 20Hz cut-off frequency. Instantaneous power (watt) was calculated as the product of torque (Nm) and velocity (rad/s). The rate of power development (RPD, watt/s) was calculated as the linear slope of the power-time curve during the acceleration phase. Reliability of the multi-joint power measurements was previously described (ICC: .95 - .98; SEM(%): 7.3 - 24.5)(paper under review).

Fascicle pennation angle and the distance between superficial and deep aponeuroses were determined using a semi-automated algorithm (Farris and Lichtwark 2016) to allow calculation of fascicle lengths (Aeles et al. 2018). All data were anonymized to avoid bias within and between individuals. The ultrasound data was filtered using a 4^{th} order low-pass Butterworth filter with a cut-off frequency of 10Hz. Fascicle shortening was calculated as the change in fascicle length (1) from the onset of VL activation till the start of torque production (i.e. phase of electromechanical delay – P1), (2) from the start of torque production till the moment the cutoff torque was reached (i.e. phase of pretension – P2), (3) from the moment the cutoff torque was reached till the end of the acceleration phase (i.e. acceleration phase – P3) and (4) from the onset of VL activation till the end of the acceleration phase (i.e. complete test)(Fig. 1). Fascicle shortening velocity was determined as the change in fascicle shortening over time. Maximum shortening velocity was calculated as the peak of the fascicle shortening velocity – time curve. Intra-rater reliability of the ultrasound processing was tested by non-consecutively tracking the same images twice for six older subjects (ICC: .96 - .98; SEM(%): 4.9 - 7.9). For all data, the mean of the three trials was used for further analyses.

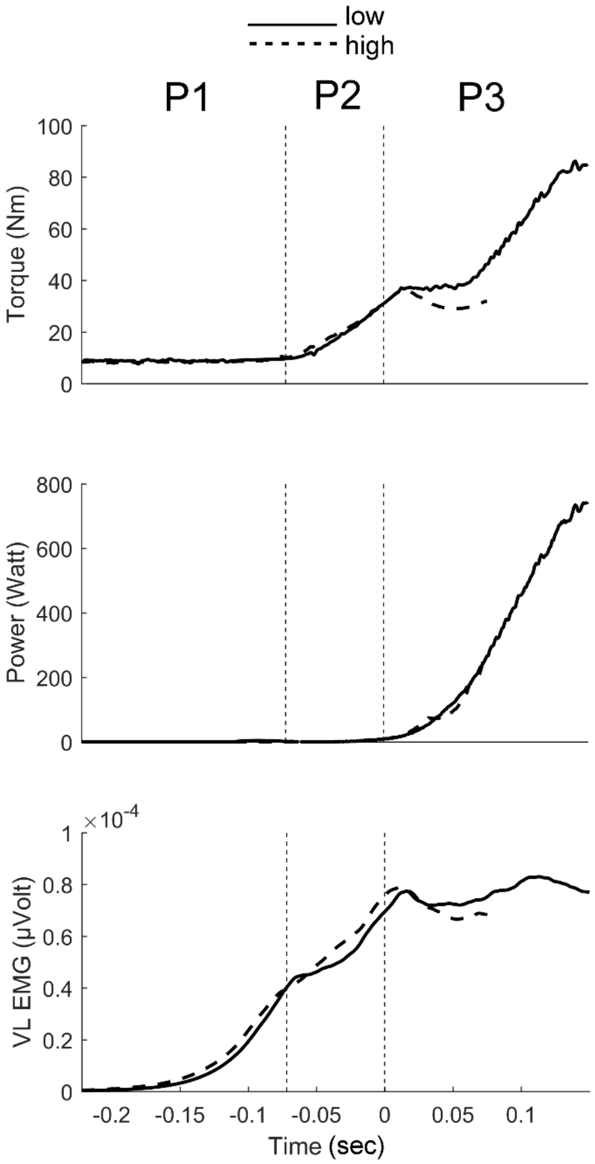

Fig. 1 Representation of torque, power and vastus lateralis (VL) electromyographic activity (EMG) at low (3200°/s², solid line) and high (7200°/s², dashed line) acceleration rate of a random subject. Tests can be subdivided in three successive phases: (P1) phase of electromechanical delay, (P2) phase of pretension and (P3) the acceleration phase.

Statistical analyses

All statistical analyses were performed using R software, version 1.0.153 (R_Core_Team 2017). To study the effect of age and age*acceleration on fascicle shortening and maximum shortening velocity across the adult life span, we built linear mixed models using the function lmer provided by the R-package lme4 (Bates et al. 2015). The response variables were log-transformed to make relative comparison of the age-related declines between accelerations possible in all models (Törnqvist et al. 1985). Age and acceleration were entered as fixed effects into the model. The variable age was used as continuous variable. In addition to the fixed-effects terms, the models included subject as a random effect to correct for the repeated measures design. An iterative model fitting procedure was conducted to analyze the effects of all factors (Van Driessche et al. 2018b). P-values were obtained using the R-package lmerTest (Kuznetsova et al. 2016). Statistical significance was set at $p < 0.05$ for all analyses.

Pearson's correlation coefficients were calculated to examine the association of fascicle shortening and maximum shortening velocity with RPD normalized to body mass.

Results

For the complete tests from the onset of VL activation till the end of the acceleration phase, VL fascicle shortening increased significantly with aging, but no age*acceleration interaction effect was found (Fig. 2). The average annual increase of fascicle shortening across our sample was -1.2%, which is comparable with an average increase of about 0.6mm per year. Similarly, maximum shortening velocity increased significantly with aging, with no difference in the effect of age between accelerations (Fig. 2). The average annual increase in maximum shortening velocity was -1.15%, which is comparable with an average increase of about 0.00486m/s per year.

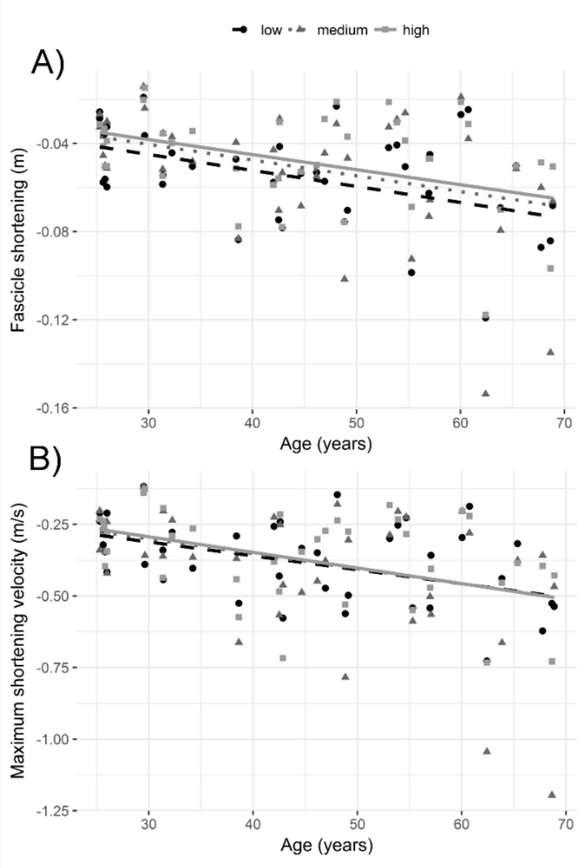

Fig. 2 Age-related increase in vastus lateralis fascicle shortening (A) **and maximum shortening velocity** (B) across 39 subjects (aged 25 to 69 years) at low (3200°/s², dashed line), medium (5700°/s², dotted line) and high (7200°/s², solid line) acceleration.

Subdivision of the complete test in successive phases of electromechanical delay (P1), pretension (P2) and acceleration (P3) revealed that fascicle shortening increased with on average 2.04% (p = 0.016), 0.72% (p = 0.297) and 0.64% (p = 0.242) per year in P1, P2 and P3, respectively, which is comparable with an average increase of about 0.3mm, 0.1mm and 0.1mm per year (Fig. 3). To note, only in P1 fascicle shortening increased significantly. Although less pronounced, maximum shortening velocity demonstrated similar trends of increases with 1.86% (p = 0.068), 1.19% (p = 0.076) and 0.51% (p = 0.318) per year on average in P1, P2 and P3, respectively.

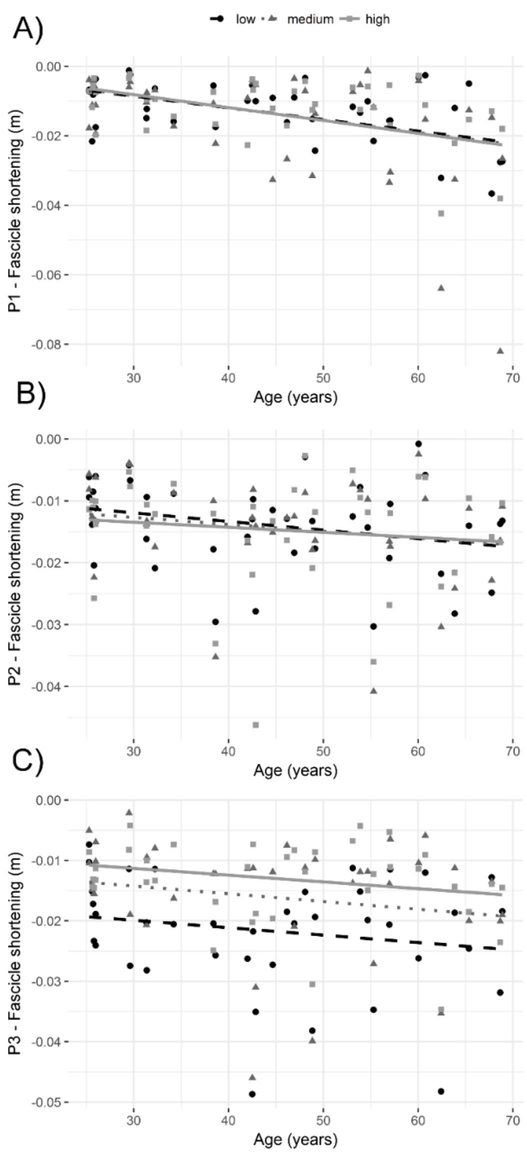

Fig. 3 Age-related increase in vastus lateralis fascicle shortening across 39 subjects (aged 25 to 69 years) at low (3200°/s², dashed line), medium (5700°/s², dotted line) and high (7200°/s², solid line) acceleration during the A) phase of electromechanical delay (P1), B) the phase of pretension (P2) and C) the acceleration phase (P3).

In relation to RPD normalized to body mass, VL fascicle shortening as well as maximum shortening velocity during the complete tests showed significant correlations across all tests (r = .19 and .22, respectively)(Fig. 4).

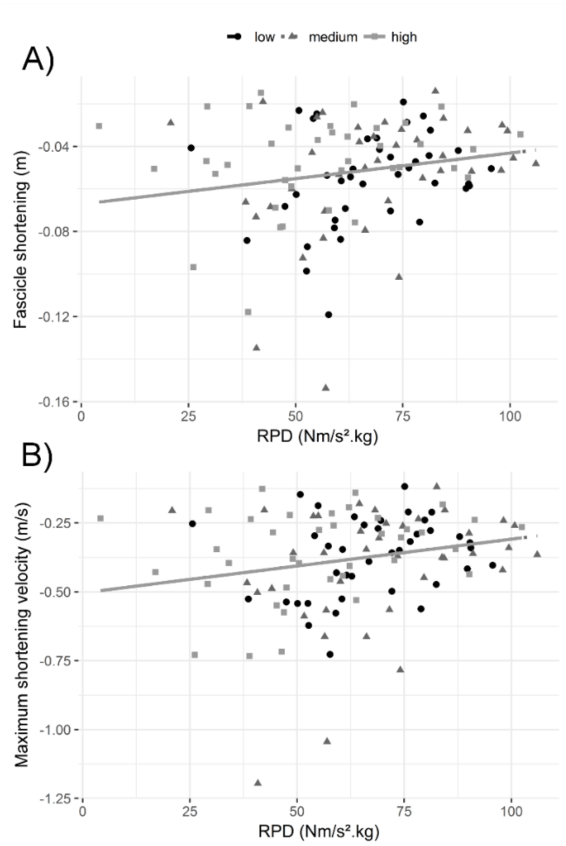

Fig. 4 Association between the rate of power development (RPD) **and vastus lateralis fascicle shortening** (A) **and maximum shortening velocity** (B) across 39 subjects (aged 25 to 69 years) at low (3200°/s², dashed line), medium (5700°/s², dotted line) and high (7200°/s², solid line) acceleration. RPD was normalized to body mass.

Discussion

This study aimed to identify the underlying mechanisms of age-related declines in leg extensor rate of power development in response to fast accelerative actions in terms of vastus lateralis muscle fascicle changes. Our findings provide experimental evidence that in vivo fascicle shortening and shortening velocity during very fast actions increase with aging, mainly due to more shortening in the phase of electromechanical delay. Moreover, fascicle shortening and shortening velocity were found to be associated with the rate of power development across accelerations. Yet, no age-related changes in fascicle shortening or shortening velocity were found between different accelerations.

The results of this study demonstrate that, when performing very fast actions, in vivo fascicle shortening velocity increases with aging, which is in contrast with our first hypothesis. Multiple studies that focused on in vitro fiber level or whole muscle level suggested an age-related decline in maximal contraction velocity as an explanation for the impairments in muscle function with aging (Krivickas et al. 2001; Pojednic et al. 2012; Van Roie et al. 2011). However, this study demonstrates that in vivo fascicle shortening velocity in fast actions is not declined. On the contrary, in vivo fascicle shortening velocity was found to increase with aging. A different behavior of the VL fascicles in response to fast actions compared to the MTU is in accordance with the findings of Fontana et al. (Fontana Hde et al. 2014). Taken together, these results indicate that in vivo fascicle shortening velocity is not a limiting factor during aging. Consequently, the age-related decline in rapid power development must originate from other than the shortening velocity capacities of the fascicles.

VL fascicle changes were further investigated in the successive phases of the leg extensor tests, namely the phase of electromechanical delay, the phase of pretension and the acceleration phase. Fascicle shortening was found to be significantly increased with aging only in the phase of electromechanical delay. The similar amount of fascicle shortening during P2 and P3 suggests that the fascicles of older adults can act similarly to those of younger adults as soon as the electromechanical preparation phase is finished. The higher fascicle shortening at older age during P1 coincides with an increase in the duration of the phase of electromechanical delay. In this regard, it was previously suggested that the phase of electromechanical delay is accompanied by an increase in compliance of the patellar tendon (Reeves et al. 2003). Multiple reports already demonstrated decreases in tendon stiffness with advancing age (Karamanidis and Arampatzis 2006; Kubo et al. 2003; Onambele et al. 2006). In addition, stiffness of VL tendon-aponeurosis complex has been shown to significantly correlate with explosive force production (Bojsen-Møller et al. 2005) and it has recently been shown that reduced tendon stiffness contributes to the reduced rate of torque development in healthy older males (Quinlan et al. 2018). The underlying mechanisms of the age-related reduction in tendon stiffness are not yet fully understood, but might be linked to changes in tendon dimensions, hydration status, glycosamine concentration, elastin content, cross-linking or collagen content contribute (Narici and Maganaris 2007; Quinlan et al. 2018). Taken together, higher compliance of the series elastic element (SEE) at older age could have forced the fascicles to shorten more in order to transmit the muscle force to the segment. Moreover, fascicle shortening was associated with RPD in a way that higher shortening led to a lower RPD. More fascicle shortening at old age could have resulted in fascicle lengths that are less optimal for force production based on the force-length relationship of skeletal muscles (Ichinose et al.

1997), whereas less shortening at young age may have allowed the fascicles to act more at their optimal lengths.

Next to changes in the SEE properties and the consequently less optimal contraction lengths of the muscle fibers, changes in fiber properties have been proposed to be key determinants in the decline of fast force production with advancing age (Maffiuletti et al. 2016). In addition, aging is accompanied by a reduction in fast twitch muscle fiber size (Lexell et al. 1988) and an increase in the co-expression of myosin heavy chain isoforms, which affects the contractile characteristics (Andersen et al. 1999). Although it has been suggested that in vitro fiber shortening velocity may largely influence fast force production (Krivickas et al. 2001; Wilkie 1949), our findings indicate that in vivo fascicle shortening velocity is not limited during aging while performing very fast actions. This suggests that the force of fibers per unit of cross-sectional area (i.e. specific fiber force), which is shown to be reduced with age in slow and fast twitch muscle fibers (D'Antona et al. 2003), might have a larger influence on fast force production compared to their capacity to shorten fast. This loss of tension has been proposed to be mainly the result of reduced myosin concentrations (D'Antona et al. 2003).

In contrast with our second hypothesis, the effect of age on fascicle shortening velocity was found to be similar at different acceleration rates. Moreover, fascicle shortening only changed significantly with aging during the phase of electromechanical delay and not in subsequent phases where torque was produced or acceleration initiated. While tendon stiffness might be an important factor to perform fast actions and to allow the fascicles to act at their optimal length, it seems to have no influence on power production at high compared to lower accelerations. As soon as the contractile and series elastic element are tensioned during fast actions, neuromuscular activation might have bigger influence on RPD, as demonstrated by a reduced neural activation with advancing age at higher acceleration rates (paper under revision). These findings may indicate that a certain SEE stiffness is required to tension the MTU complex in preparation of force transmission to the bone and to allow the muscle to act at optimal length. However, after the initial phase of tension development, neural drive, next to specific fiber force characteristics, seems to determine the magnitude and rapidness of force production during fast actions.

The following limitations should be kept in mind when interpreting our findings. First, age-related changes were based on cross-sectional findings, which may be confounded by inter individual differences and may be divergent from longitudinal findings. Next, only VL fascicle shortening was analyzed, whereas other muscles contribute to leg extensor movements. Furthermore, although some muscle deformation may only be visible in 3D, fascicle measurements were based on two-dimensional ultrasound images. For the analysis, it was assumed that fascicles are represented by straight lines, although it has been shown that this may result in an underestimation of absolute lengths of 2-7% (Finni et al. 2003; Ishikawa et al. 2003). However, these possible systematic errors do not have affected our result, given that we used the same protocol across individuals.

In conclusion, this study demonstrates that the age-related decline of RPD in fast actions is accompanied by an increase in fascicle shortening and shortening velocity. Therefore, the in vivo shortening velocity of the fascicles may not be a limiter for muscular function at advancing age. This suggests that specific fiber force may have a bigger influence on rapid power production than maximal fiber shortening velocity. The changes in VL fascicle shortening might result in less optimal fiber lengths and lower force production at advancing age during fast actions. The increase in VL fascicle shortening might be associated with the previously reported age-related change in patellar tendon stiffness. Yet, the greater age-related decline of RPD at high compared to lower acceleration rates was not explained by changes in fascicle behavior. To conclude, a certain tendon stiffness might be a prerequisite to perform fast muscle actions at older age, followed by adequate specific force of the muscle fibers.

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PART 3

SUMMARY AND GENERAL DISCUSSION

The purpose of this doctoral thesis was twofold. The first purpose was to identify early age-related differences in muscular function and to get more insight into the functional outcomes of the aging process by investigating the effect of aging on muscular function with the focus on factors such as response time, contraction type, movement complexity and acceleration rate. These factors are shown to have a clear influence on muscular function, but how these factors are affected by aging is not well understood. **Chapter 1** focused on factors such as response time and contraction type. Within chapter 1, **article 1** first looked at the reliability of time-dependent parameters of muscular function obtained through isotonic testing and **article 2** evaluated the effect of age on these parameters and their functional relevance. **Chapter 2** focused on movement complexity by investigating the difference in age-related decline rate of muscular function across the sample between single- and multi-joint movements in **article 3**. **Chapter 3, article 4** evaluated the effect of age on muscular function at different acceleration rates. The second purpose of this thesis was to gain a better insight into the underlying mechanisms of the age-related differences in muscular function. In this regard, **Chapter 3** evaluated neural activity and in vivo fascicle shortening behavior that are accompanied by the age-related decline in rapid power development in **article 4** and in **article 5**.

In the following paragraphs, the main findings of the five research articles will be summarized. Furthermore, a general discussion, including methodological considerations, practical implications and suggestions for future research will follow after this summary.

1 Summary of the main findings

1.1 Chapter 1 – The influence of response time and contraction type on muscular function at older age

Article 1 aimed at determining the reliability of knee extensor muscular function using the isotonic mode on a Biodex System 3 dynamometer in older adults. Sixty-three older adults (♂: n = 27, age = 73 ± 4 years; ♀: n = 36, age = 72 ± 3 years) underwent a test-retest protocol performing isotonic knee extension tests at relative loads of 0%, 25%, 50% and 75% of maximal isometric strength.

Parameters such as peak velocity (pV), peak power (pP), rate of velocity development until pV (RVD) and rate of power development until pP (RPD) showed good to high relative (ICC: .85 - .98) and absolute reliability (SEM: 3 – 10%) at 0%, 25% and 50% load. The initial phase of the isotonic contractions represented by time-dependent parameters such as RVD and RPD at intervals of 0-50ms were found to be poorly reliable (ICC: .62 - .88, SEM: 23 – 45%). Measures with time intervals that last longer than the first 50ms were found to be fairly to highly reliable (ICC: .74 - .94, SEM: 9 – 25%). Remarkably, reliability seemed to decrease with increasing load and with decreasing test performance.

In addition, the isotonic tests at the highest load used in this study (i.e. 75%) resulted in the systematic failure of the test and the retest for almost one third of the subjects, because they were not able to overcome the high resistance over the full range of motion.

Conclusions article 1

- Maximal knee extension velocity and power (i.e. pV and pP) are reproducible at relatively low loads (i.e. 0%, 25% and 50%).
- The use of loads ≥ 75% of maximal isometric strength in 90° knee angle should be avoided for isolated isotonic knee extension testing on isokinetic dynamometry.
- Caution is advised when interpreting early phase results (< 50ms).
- Time-dependent measures such as RVD and RPD are equally reliable compared with maximal measures such as pV and pP and can be used as consistent measures of muscular function in older adults.

The purpose of **article 2** was to determine age-related differences in pV, pP, RVD and RPD of the knee extensors using isotonic testing at different loads and to evaluate their functional relevance. Thirty-six young (♂ 21, ♀15, age = 22 ± 2 yrs) and fifty-six older adults (♂ 26, ♀ 30, age = 68 ± 5 yrs) performed isotonic knee extension tests against 20%, 40% and 60% of maximal isometric strength, 7.5-meter fast walk, timed-up-and-go and stair climbing.

Maximal measures of muscular function such as peak isometric torque (pT), peak velocity (pV) and peak power (pP) were significantly different between the young and older subjects across the loads. pT was 28% lower in the old, pV 11 – 12% lower and pP 24 – 37% lower. Time-dependent parameters such as RVD and RPD were respectively 16 – 23% and 37 – 44% lower in the older than in the young subjects. This larger age-related difference in the time-dependent parameters is due to an additional age-related increase in the time to pV and pP of 11 – 20%. In addition, an age-group by load interaction effect was found, which indicates that the lower the load the higher the age-related difference. Furthermore, RVD (r = .55 - .59) and RPD (r = .59 - .64) were similarly associated with the functional performance tests as pV (r = .49 – 55) and pP (r = .62 – 64).

Conclusions article 2

- RVD and RPD differentiated more between young and older adults compared with pV and pP.
- Age-related differences in RPD and pP increased as the load decreased.
- All power-related parameters showed a strong relationship with functional performance in well-functioning community-dwelling older adults.

- These results underline the importance of time-dependent measures to detect age-related changes in muscular function. These measures emphasize the inability to generate power rapidly at older age.

1.2 Chapter 2 – The influence of movement complexity on muscular function during aging

Article 3 investigated the effect of age on maximal and rapid power characteristics in single- versus multi-joint actions across the adult life span and their association with functional performance. Ninety-six healthy subjects (♂ 49, ♀ 47) aged between 20 and 69 years performed isokinetic single-joint knee-extension tests, multi-joint leg-extension tests and a squat jump.

In both single- and multi-joint tests, RPD declined more across the life span (-1.42 – -1.92% on average per year) compared to pP (-0.77 – -1.04% on average per year). A significant interaction effect between age and test method demonstrated that pP declined more with aging in the single-joint compared to the multi-joint test (-1.04% vs. -0.77% on average per year), whereas RPD declined more in the multi-joint compared to the single-joint test (-1.92% vs. -1.42% on average per year). This phenomenon was apparent at different velocities. In addition, pP and RPD in the multi-joint tests were positively associated with squat jump performance, with RPD multi-joint being more associated with squat jump height compared to RPD single-joint.

Conclusions article 3

- RPD declines more in multi-joint compared to single-joint actions during aging.
- RPD was strongly associated with functional performance in terms of squat jump height.
- The initial phase of rapid power development and multi-joint testing deserve more attention in aging research. Whether RPD multi-joint can be used for the detection of functional disability during aging in clinical practice needs further investigation.

1.3 Chapter 3 – The influence of acceleration on muscular function during aging and its underlying mechanisms

The aim of **article 4** was to investigate the effect of age on RPD and neural drive during different accelerations across the adult life span. Eighty-three healthy subjects (♂ 43, ♀ 40) aged between 20 and 69 years performed multi-joint leg extensions at relatively low, medium and high accelerations.

RPD declined on average -1.11% to -2.93% per year with the steepest decline at the highest acceleration. Neuromuscular activation in terms of mean EMG amplitude from the onset of muscle activation till the end of the acceleration phase declined more at higher compared to lower acceleration for rectus femoris (RF) and vastus lateralis (VL) muscles. No age-related change between accelerations was found for biceps femoris (BF) neuromuscular activation. The age-related changes at high relative to lower acceleration in RF and VL activity were associated with the age-related decline in RPD across the sample.

Conclusions article 4

- These findings emphasize the magnitude of the age-related decline in rapid leg extensor power development in response to abrupt changes in movement velocity across the adult life span.
- These findings suggest that not high velocity, but acceleration as such is highly susceptible to aging, taking into account the time needed to reach high velocities.
- This age-related deficit seems to be associated with impairments in neuromuscular activity.

Article 5 aimed to investigate the effect of age on in vivo fascicle shortening behavior and its relation with RPD in multi-joint leg extensor tests at different accelerations across the adult life span. Thirty-nine healthy men aged between 25 and 69 years performed multi-joint leg extensions at relatively low, medium and high accelerations.

VL fascicle shortening and shortening velocity from the onset of VL activation till the end of the acceleration phase increased significantly with aging (~ 1.2% per year on average) with no difference between accelerations. This age-related change was mainly due to a higher shortening during the phase of electromechanical delay of about 2.04% per year on average. In addition, VL fascicle shortening and shortening velocity were positively associated with RPD ($r = .19 - .22$).

Conclusions article 5

- These findings demonstrate that the age-related decline in RPD in fast actions is accompanied by an increase in fascicle shortening and shortening velocity.
- While in vivo fiber shortening velocity seems to be no limiter, specific fiber force may have a bigger influence on rapid power development at advancing age.
- Increased VL fascicle shortening might result in less optimal fiber lengths.
- Increased VL fascicle shortening may be the result of decreased stiffness of the series elastic element.
- The greater age-related decline of RPD at high compared to lower acceleration rates could not be explained by changes in fascicle behavior.

2 General discussion

2.1 Discussion of the main findings

For years, researchers and clinicians are searching for an applicable definition of sarcopenia (Rolland et al. 2008). While this definition was mainly focused on the loss of muscle mass, the decline in muscular function gained more and more attention over the past decade (see introduction). However, aging is a degenerative process making it problematic to be encountered by just one definition. A general definition of sarcopenia could identify individuals that are already at risk, but could not be used to properly identify early age-related changes in muscular function. Next to a general definition of sarcopenia, tools should be sought in an attempt to identify early age-related changes in muscular function. The challenging tests performed in our studies show that they have a great potential to encounter a broader aspect of muscle aging compared to traditional measurements. Given the large age-related declines we found, our tests seem to better fit as possible identifiers for the aging process. This thesis focused on rapid power measures as tools to identify early declines in muscular function with aging. This focus was chosen because previous research emphasized the usefulness of time-dependent measures of muscular function and dynamic testing to test muscular function in a way that is relevant to many functional tasks (Aagaard et al. 2002; Dalton et al. 2010; Dalton et al. 2012; Maffiuletti et al. 2016; McNeil et al. 2007; Thompson et al. 2013; Valour et al. 2003).

2.1.1 Reliability of muscular function

First, reliability of isotonic testing, in particular the time-dependent measures, was evaluated in **article 1**. In agreement with previous research that investigated the ankle plantar- and dorsiflexors, we showed that single-joint pP and RPD of the knee extensors could be reliably measured using isotonic testing (Power et al. 2011; Webber and Porter 2010). Relative and absolute reliability ranged from ICC's of .85 to .98 and SEM's of 3 to 10% across the different loads. While studies that evaluated reliability of isotonic measures of the ankle plantar- and dorsiflexors only investigated loads of 0% to 50% of maximal isometric strength, our results show that a load of 75% is too high to allow for an adequate test over the full range of motion and should be avoided. In addition, it could be expected that next to high load, high velocity tests would be less reliable. However, our results show that there was a trend for increased reliability at lower load, which allows for higher velocity development. This may be due to the increased mean test performance and total power output, which was higher at 25% compared to 50% load. To note, maximal dynamic strength testing on weight stack machines at high loads could still be used for comparing absolute strength improvements due to training (i.e. 1-RM testing), as long as the load allows for full range of motion. However, relatively low loads should be advised for maximal power measurements using isotonic testing on an isokinetic dynamometer.

Moreover, many daily activities include low loads to be moved which makes them more functionally relevant. These findings led to the choice of lower load testing (i.e. 20%, 40% and 60%) in **article 2**.

In **article 3** and **4** a custom-build isokinetic machine was used to measure muscular function during multi-joint leg extensor actions. Again, reliability was checked for pP and RPD and found to be in a similar range as reported in **article 1** (ICC: .87 - .97; SEM: 4 – 18.7%). The slightly higher SEM's in **article 3** and **4** may be explained by the shorter acceleration phases (i.e. ~ 75ms) for which RPD was calculated during the single- and multi-joint isokinetic tests compared to the calculation of isotonic RPD (≥ 150ms) in **article 1** and **2**. **Article 1** already demonstrated that caution is advised when interpreting early phase results (≤ 50ms). However, the measures of RPD used in **article 3** and **4** can be better compared to RPD from 50 to 100ms in **article 1**, which demonstrated a similar fair to high reliability. In accordance with the findings in **article 1**, a great inter-individual variability in neural activity during the early phases of rapid contractions (< 50ms) has been reported (de Ruiter et al. 2004; Folland et al. 2014; Klass et al. 2008). This may indicate that the neural system largely contributes to the inter-individual variability that is reflected in the initial rate of power and velocity development. The underlying mechanisms in the central and peripheral nervous system mediating this high variability are multifactorial (see introduction).

Generally, to evaluate muscular function during aging or after an intervention, the aim is to observe changes that are not associated with measurement error. To illustrate, the difference between two tests ± SEM as reported in **article 1** for a particular variable represents a possible range within which the "real" value can be situated. A priori, in 68% of the cases, this range will contain the "real" value. To find a significant change at a 5% significance level after an intervention or due to aging, zero should be situated outside the following interval: difference between pre-post ± 1.96*SEM. Based on the results of **article 1,** a real change for example for RPD at 25% load should be under or above 18% of the baseline value to be significant**.** These prescriptions may be of great value in clinical practice.

To conclude, time-dependent parameters such as RPD, whether measured using an isotonic or isokinetic approach, whether measured in single- or in multi-joint tests, can be considered as consistent measures of muscular function. Caution is advised when interpreting early phase results (≤ 50ms) and isotonic testing using high loads (≥ 75% of maximal isometric strength) should be avoided.

2.1.2 Age-related declines in muscular function

A main objective of this thesis is to find appropriate tools to identify deficits in muscular function with aging. These tools should be consistent as mentioned in the previous section, but should also be able to detect the largest deficits as early as possible. **Article 2** used the isotonic test mode to measure single-joint pP and RPD in young and older adults to investigate age-related differences in muscular function in a well standardized, but more functional way than isometric testing. Previous studies showed that pP is declined during aging (Dalton et al. 2012; Petrella et al. 2005) as well as isometric RFD (Aagaard et al. 2002; Izquierdo et al. 1999; Thompson et al. 2014; Thompson et al. 2013). However the effect of age on RPD during isotonic actions was not investigated in previous research. Our results show that RPD differed more between the young and older adults compared to pP. In line with the findings of RFD versus peak force (Bento et al. 2010; Thompson et al. 2013), these results show that time-dependent measures of muscular function are able to uncover age-related deficits that are additional to the deficits acknowledged by only maximal measures of muscular function such as pT, pV and pP. Moreover, the large age-related difference in RPD (~ 40%) during dynamic isotonic actions compared with previously reported differences in pT (~25%), pP (~30%) or RTD (~35%) between similar age-groups emphasize the importance to focus on the decline of RPD in aging research and clinical practice. In addition, the age-related difference in RPD and pP increased with lower loads. This indicates that the use of low loads (i.e. 20% of maximal isometric strength) is advised when using isotonic testing to identify age-related deficits.

The large age-related deficit in RPD measured during the isotonic tests may incorporate several factors that are influenced by age. On the one hand, the larger difference of RPD compared to pP can be explained by the factor **response time**. The time to reach pP was shown to be about 10% to 19% shorter in the young compared to the older adults. The older the individual, the more time it takes to develop pP. On the other hand, the higher magnitude of the age-related difference in pP and RPD compared to previously reported declines in pT and RTD may be explained by the difference in **contraction type**. Research investigating rapid force characteristics such as RFD during dynamic contractions is scarce given the complexity of torque, angle and velocity relations that may confound its evaluation. However, the evaluation of RFD during dynamic contractions is much more relevant to functional tasks compared to the assessment of isometric contractions. In this way, the dynamic isotonic tests allow for a more functional representation of pT and RTD in terms of pP and RPD. One of the few articles that investigated the influence of contraction type on RFD demonstrated that RFD normalized to maximal isometric torque was 60% greater in concentric compared to isometric conditions and was achieved in less than half the time (≤ 125ms vs. > 300 ms)(Tillin et al. 2012). These differences in RFD between contraction types may partly explain the large age-related declines of RPD in the isotonic tests.

It is clear that the factors ‘response time’ in terms of ttpP and ‘contraction type’ in terms of dynamic versus isometric testing have an influence on muscular function during aging. However, another limitation in most strength measurements in research and clinical practice is the use of single-joint testing, which lacks '**movement complexity**'. This methodology allows the isolation of just one joint to easily answer research questions specific to that joint, but might be less relevant to test total muscular function for clinical practice. Therefore, **article 3** included multi-joint testing, which is more representative for most daily life activities that include multi-joint movements (Azegami et al. 2007). For the first time, rapid power characteristics during dynamic multi-joint tests were evaluated across age. In line with **article 1** and **2**, RPD declined more during aging compared to pP in the single-joint, but also in the multi-joint tests. Moreover, our results show that the age-related decline of RPD in the multi-joint tests was significantly greater (-1.92%) than the decline in the single-joint tests (-1.42%). Accordingly, higher differences between young and older individuals have been previously reported for RTD/RFD compared to pT/peak force (pF) in single- and multi-joint testings (Allison et al. 2013; Izquierdo et al. 1999; Thompson et al. 2018). However, the latter studies were limited to isometric testing or did not compare multi- with single-joint tests within the same cohort. Our results indicate that aging has a detrimental effect on the initial phase of rapid contractions especially in multi-joint tests, which emphasizes the importance to include movement complexity to detect a more holistic deterioration of muscular function with aging.

Another factor that should be taken into account when investigating changes in muscular function is the influence of changes in movement velocity (i.e. '**acceleration**') on muscular function. It is known that joint angle, velocity and acceleration influence force production when moving (King et al. 2006). In terms of RFD, it is previously shown that the higher the acceleration during explosive concentric contractions the higher the ability to utilize a large proportion of maximal voluntary strength and thus the higher RFD (Tillin et al. 2013b). However, the effect of age on RPD at different accelerations was not investigated previously. The results of **article 4** show that RPD is more affected by aging at high compared to lower acceleration. A remarkable finding of this study is the magnitude of the age-related decline of about -2.93% on average per year at the highest acceleration measured, which matches with a knee joint angular acceleration of 4582°/s². This finding highlights the additional difficulty of a high acceleration to develop power quickly in multi-joint dynamic actions at older age. In this way, the factors 'response time', 'contraction type', 'movement complexity' and 'acceleration rate' improved our understanding of age-related declines in muscular function and can help to create appropriate tools to better identify age-related deficits.

It should however be noted that the setting to measure RPD multi-joint as used in our studies is not directly employable, cheap or practical to work with in clinical practice. Furthermore, although we were able to capture large age-related declines, we were not able to show that RPD declines earlier during life compared to other measures of muscular function. Taking that into account, RPD multi-joint may be a potential identifier for aging of muscular function, but needs further investigation before it could be implemented in clinical practice. As for sarcopenia, certain absolute cutoff points could be created to use as identification thresholds (e.g. 2SD of a norm population)(Lauretani et al. 2003). However, an alternative approach with regular monitoring across the life span to detect changes within individuals might be more appropriate. In this regard, real changes that exceed measurement error may serve as an alarm signal.

In conclusion, the findings within this thesis provide evidence that the age-related decline in muscular function is especially reflected when response time is short, during explosive dynamic contractions, during complex movements, at high accelerations and even more if these factors are combined. RPD measured using explosive dynamic multi-joint actions should be considered as a potential tool to identify declines in muscular function with aging.

2.1.3 Functional relevance of muscular function

Any tool to identify muscular aging should be relevant to activities of daily life. Time-dependent measures such as RTD have previously been shown to be functionally relevant and more related to falling compared to pT (Bento et al. 2010; Clark et al. 2013; Izquierdo et al. 1999; Thompson et al. 2013). pP, which is more holistic in nature because it incorporates both strength and velocity capacities, has emerged as a more important predictor of functional limitations in the elderly compared with pT (Pojednic et al. 2012; Reid and Fielding 2012). Accordingly, the results in **article 2** and **3** demonstrated high associations with the functional performance tests for pP and RPD. However, we were not able to find a higher association between functional performance and RPD compared to pP. This might be explained by our study samples and the type of functional performance tests. On the one hand, our samples of older adults were healthy and still well-functioning, which is shown by the high scores on the functional performance tests compared to reference values (Bischoff et al. 2003; Morley et al. 2011). On the other hand, the functional tests used in the studies might not be a good representation of the short response times available to accelerate the limbs during many daily activities. To illustrate, recovery from perturbations requires a fast and powerful reaction of the limbs to prevent falling. However, the latter is much more difficult to measure, particularly in a safe and standardized manner.

The high associations between functional performance and the power related parameters in **article 2** might be explained by the isotonic nature of the tests. Isotonic testing allows to test muscular function in a more functional way compared to isometric and isokinetic testing (see introduction). In line with previous research, our results showed that the power-related variables were the single best predictors for functional performance (Pojednic et al. 2012; Van Roie et al. 2011). This was especially true for the tests at lower loads (~ 20% of maximal isometric strength), which demonstrated higher age-related differences. Moreover, RPD was found to be maximal when tested against a load of 20% compared to 40% and 60%. It has previously been suggested that a load of 20% of the isometric maximum represents a moderate resistance that can be handled by most individuals and is relevant to many activities in daily life (Power et al. 2011). Therefore, low load isotonic testing can be recommended as a safe and relevant tool to test muscular function in the elderly.

However, the isolated single-joint tests used in **article 2** might not be the best representation of functional performance, because they lack the coordination of multiple joints and muscles that are used in most daily movements. We tried to tackle the latter issue in **article 3** for which we measured both single- and multi-joint tests and evaluated their relevance to functional performance. Our results showed that RPD measured multi-joint was more related to squat jump performance compared to RPD single-joint. These findings indicate the functional relevance of the multi-joint test methodology.

In **article 4** we tried to mimic sudden perturbations to investigate muscular function in response to fast accelerations across the life span. Although a direct link with fall risk could not be made, the magnitude of the age-related decline in RPD at fast accelerations emphasizes the difficulty at older age to appropriately react to sudden perturbations. This may explain the lower probability to recover successfully after a trip at advancing age (Pijnappels et al. 2008).

To conclude, the factors ‘response time’, ‘contraction type’, ‘movement complexity’ and ‘acceleration rate’ likely play a role to recover from sudden perturbations. Fall incidence might be the result of the simultaneous failure of various factors for which the likelihood increases at older age. Therefore, our findings support the use of time-dependent power measures such as RPD in dynamic multi-joint actions at fast accelerations to identify declines in muscular function with age. Such measures can be considered as safe, accurate and functionally relevant, which makes them appropriate to use in clinical practice.

2.1.4 Underlying mechanisms

The underlying mechanisms of the age-related declines in muscular function likely depend on the specific characteristics of the muscle action. Primarily, the concept of sarcopenia was mainly focused on the decline in muscle mass (Janssen et al. 2000). However, steeper declines in isometric strength relative to mass indicated that other mechanisms than the quantitative loss of muscle mass are affected by aging and have an influence on muscular function (Clark and Manini 2008). These qualitative changes are generally considered as a combination of neural and contractile changes, which may be stressed even more in fast actions.

The importance of neural factors to determine the performance in rapid contractions is demonstrated by several studies that compared maximal voluntary contraction with electrical stimulation (de Ruiter et al. 2004; Klass et al. 2008). Rapid voluntary knee extension force (i.e. RFD) was found to be significantly lower than that produced by an electrically induced tetanic contraction, which suggests that RFD is highly dependent on the neural drive. In addition, the neural determinants of fast or slow maximal force production differ. Following 'the 'size principle', low threshold motor units are recruited before higher ones with a similar order in slow and rapid contractions (Duchateau and Enoka 2011). However, a progressive augmentation of motor unit recruitment till the upper limit of MU recruitment and maximal force production characterizes slow contractions, whereas lower recruitment thresholds allow motor units to be recruited at lower forces in rapid contractions (Maffiuletti et al. 2016). Consequently, as most motor units are recruited at a submaximal force in rapid contractions, a further increase of force produced beyond the upper limit of MU recruitment must be due to other factors, like an increase in discharge rate (Maffiuletti et al. 2016). Moreover, slow contractions are characterized by progressive increases in discharge rate, whereas a high initial discharge rate at the onset of activation that declines progressively with successive discharges is specific to rapid contractions (Klass et al. 2008; Maffiuletti et al. 2016). These findings emphasize that there is a difference in motor unit activation pattern at different contraction speeds. Moreover, an association has been demonstrated between discharge rate and RFD, being both reduced during aging (Klass et al. 2008). It seems that the ability to rapidly develop force at the onset of a contraction is largely mediated by maximal discharge rate, which might be an important factor to be trained during aging. Therefore, these findings suggest that RFD largely depends on the muscles neural activation. Together with other studies that investigated early and late phases of force development, the literature indicates that neural factors play an important role at the onset (< 75ms) of rapid contraction, whereas the contractile properties more strongly determine the later phases of contraction (> 75ms)(Aagaard et al. 2002; Andersen and Aagaard 2006; Folland et al. 2014). In line with these findings, **article 4** demonstrates that younger adults activated their quadriceps muscles more at high compared to low acceleration within the first 75ms, whereas the older adults' quadriceps activation was less at high compared to low acceleration. The latter indicates that within the first 75ms, higher movement velocity requires higher neural activation, in which the older adults fail. These trends and the significantly higher age-related declines in neural activity at high acceleration (i.e. till 540°/s in 75ms) compared to low acceleration (i.e. till 540°/s in 169ms) suggest that older adults particularly have difficulties in fast activation of muscles in short time periods (≤ 75ms).

Dynamic actions demonstrate larger declines in concentric power compared to isometric strength, which emphasizes the additional effect of age on the muscle's velocity characteristics (Reid and Fielding 2012). Whole muscle maximal contraction velocity is shown to decline with aging (Dalton et al. 2010; Lanza et al. 2003). However, **Article 3** was not able to find any age-related differences in RPD between different velocities. Yet, the accelerations between the different velocities in **article 3** were the same, whereas previous studies did not take into account the influence of the initial acceleration phase. Accordingly, **article 4** shows that a test at high velocity reached within longer time periods (> 150ms) or a test at low velocity reached within short time periods (< 75ms) can both result in similar age-related decline rates of RPD that are also similar to previous reports (i.e. -0.9 to -1.1% on average per year). Yet, short time periods and high velocities, together expressed as high acceleration, seem to result in larger decline rates of RPD (> 1.4% on average per year). These findings suggest that not high velocity as such, but acceleration might be highly susceptible to aging. In this regard, previous research suggested that the age-related reduction in maximal shortening velocity of in vitro muscle fibers could explain the age-related impairments in muscular function (D'Antona et al. 2003; Krivickas et al. 2001). Although, this could be questioned as shown in **article 5**. On the other hand, differences between isometric and concentric contraction types have been attributed to differences in neural drive as the higher RFD in the concentric condition was accompanied by a greater EMG amplitude (Tillin et al. 2012). In addition, previous research demonstrated that RFD is influenced by contractile acceleration in a way that fast concentric contractions elicit higher RFD through higher neural activation in young adults (Hahn et al. 2017; Tillin et al. 2013b). In line with these findings, **article 4** shows that the larger decline in RPD at high compared to lower acceleration was accompanied by a reduced neural activity of the agonists during aging. These findings support the idea that the decline in RPD is partly determined by changes in neural drive.

In addition, increased co-activation reported during aging may also be an explanation for the decline in force production (Izquierdo et al. 1999; Macaluso et al. 2002). Co-activation or co-contraction may serve as a protective mechanism to stabilize the knee joint during force production (Baratta et al. 1988). No change in co-activation with aging was found for biceps femoris between acceleration rates in **article 4.** To note, during the leg extensor tests, biceps femoris may have acted as an agonist of the movement as it induces hip extension.

The reduction in neural drive may also explain the difficulty at older age to rapidly develop power in multi-joint actions as suggested in **article 3**. The short response times during the initial acceleration phases (< 75ms) may have limited the neural system to properly initiate compensatory muscle actions in the multi-joint tests at older age resulting in larger age-related declines of RPD, whereas the longer duration to reach pP (> 150ms) may have allowed the neural system to initiate compensatory actions of synergist muscles masking the effect of age on power production. The effect of age on neural drive might thus have a detrimental effect on the performance of fast actions, especially in multi-joint movements. Although this should be confirmed by future research.

While neural activity seems to be a critical determinant of rapid force production especially in dynamic multi-joint actions, contractile factors still play a role. A major factor that could have an influence on RFD/RPD is the rate of tension development of specific muscle fibers, which is shown to be faster in type II compared to type I fibers (Harridge et al. 1996). The faster cross-bridge cycling rates in type II fibers are related to greater Ca^{2+} release and faster myosin heavy chain isoforms (Bottinelli et al. 1999). Accordingly, previous studies on in vitro fibers demonstrated impaired specific fiber tension (D'Antona et al. 2003) and impaired maximal contraction velocities with aging (Krivickas et al. 2001). The results in **article 5** show that fiber contraction velocities in vivo during fast actions are not impaired. This suggests that specific fiber force might have a larger influence on fast force production compared to the fiber's capacity to shorten fast. Nonetheless, next to neural drive, specific fiber properties only could explain a portion of the variance in rapid force production (Hvid et al. 2010).

Another interesting finding in **article 5** was the increased fascicle shortening in the phase of electromechanical delay together with an increase in the duration of this phase. It is previously suggested that a longer duration of electromechanical delay is accompanied by an increase in compliance of the patellar tendon (Reeves and Narici 2003). In addition, tendon stiffness is shown to decrease with aging (Karamanidis and Arampatzis 2006; Kubo et al. 2003) and to contribute to reduced RTD in healthy older males (Quinlan et al. 2018). This means that the higher compliance of the SEE at older age could have forced the fascicles to shorten more in order to transmit the muscle force to the segment. **Article 5** showed that fascicle shortening was associated with RPD in a way that higher shortening led to a lower RPD. More fascicle shortening at old age could have resulted in fascicle lengths that are less optimal for force production based on the force-length relationship of skeletal muscles (Ichinose et al. 1997).

In conclusion, previous reports together with the findings of our research articles highlight the importance of quantitative, neural, contractile and tendon properties to rapidly develop power during fast dynamic multi-joint movements. RPD seems to incorporate a multitude of factors that are affected by age and may therefore be considered as an appropriate measure to detect muscular aging given its holistic nature.

2.1.5 Training to counteract age-related declines in muscular function

Despite the deteriorating effect of aging, muscle tissue retains its plasticity into very old age and thus appropriate training could reverse the age-related decline in muscular function (Power et al. 2013). To reverse sarcopenia, no pharmacological or behavioral intervention has proven to be as effective as traditional resistance training (Rolland et al. 2008), even for the frail elderly (Fiatarone et al. 1990). In addition, adequate nutrition including 1.2 – 1.6 g/kg/day of high quality protein intake in adults older than 65 years is currently recommended to stimulate muscle anabolism (Bauer and Diekmann 2015; Phillips et al. 2016; Traylor et al. 2018). A protein intake of only 0.45 g/kg/day was shown to lead to rapid loss of skeletal muscle mass and function in older women (Castaneda et al. 1995). Additional dietary supplementation of 0.25 g/kg/day of protein via oral amino acids was shown to increase muscle mass in sarcopenic patients (Solerte et al. 2008). Moreover, in combination with resistance training, the optimal post-exercise dose to stimulate an increase in fat free mass seems to be about 40 g for older adults (Churchward-Venne et al. 2016). However, several studies demonstrated that protein supplementation in absence of malnutrition appears to have no improving effect on the muscle composition responses to resistance exercise compared with resistance exercise alone (Campbell et al. 1995; Fiatarone et al. 1994; Iglay et al. 2009; Welle and Thornton 1998). Due to these inconsistencies, future research should focus on using higher protein doses, larger sample sizes and longer interventions in aging populations (Morton et al. 2018). In addition, Morton et al. strongly suggested that resistance training is a far more potent stimulus to increase muscle strength than the addition of dietary protein supplementation (Morton et al. 2018).

A multitude of reports support the efficacy of resistive exercise (Liu and Latham 2009). Regular strength training can be considered as a safe method to be used also in people with coronary artery disease, arthritis, renal failure and heart failure, which often occur at older age (Beniamini et al. 1997; Rall et al. 1996). High-resistance training has been shown to induce morphological changes such as preferential hypertrophy of type II fibers and neural changes such as improved recruitment and firing frequency, which could be beneficial to improve rapid power characteristics (Folland and Williams 2007). However, traditional resistance training programs are usually performed at relatively slow velocities, lacking the specificity of training to induce improvements in rapid power characteristics.

Compared with traditional resistance training, explosive resistance or high-velocity power training in older adults is shown to be able to increase strength, power and RFD (Caserotti et al. 2008; Henwood et al. 2008). High-velocity power training involves the lifting of weights as quickly as possible during the concentric phase of an exercise. Moreover, power training seems to be more effective to improve functional capacity in older adults (Bottaro et al. 2007; Fielding et al. 2002; Pereira et al. 2012). Studies that conducted high-velocity power training demonstrated that it is feasible, well tolerated and effective even for the frail elderly (Caserotti et al. 2008; Fielding et al. 2002; Marsh et al. 2009; Reid et al. 2008). However, the effectiveness of high-velocity power training to improve RPD remains to be investigated in future research.

As mentioned in the previous sections and in **article 4,** initial rapid force production is primarily determined by neural drive, which should be a main focus of training during aging. Accordingly, moderate to strong positive associations have been reported between training-induced changes in EMG amplitude and RFD for the quadriceps muscles (Blazevich et al. 2008; de Ruiter et al. 2012). Yet, to delay the typical age-related loss of MU's during healthy aging, it is required to chronically activate the motor neuron pool specific to rapid muscle actions (Power et al. 2012). Fortunately, the capacity to produce coordinated actions rapidly with an optimal efferent drive to the agonist and antagonist muscles can be trained quickly through learning (Jensen et al. 2005). Although neural plasticity and learning are shown to be diminished in older adults (Hinder et al. 2011; Rogasch et al. 2009), gains in RFD after explosive contraction training (i.e. with maximal intentional RFD) were accompanied by increases in neural activation and substantially larger gains in RFD compared with traditional resistance training in young (Tillin and Folland 2014), but also in older adults (Caserotti et al. 2008; Suetta et al. 2004). On the other hand, it should be noted that non-explosive albeit heavy training loads (≥ 75% of 1RM) also seem effective in eliciting improvements in RFD within 8 weeks (Aagaard et al. 2002). However, prolonged heavy-resistance training (i.e. more than 8-12 weeks) is shown to reduce the content of myosin heavy chain IIX isoforms and increase the content of myosin heavy chain IIA isoforms, leading to reduced RFD (Andersen et al. 2010). This means that neural changes that occur during the first two months of heavy resistance training might have a positive influence on RFD without substantial transformations in fiber types or hypertrophy, whereas prolonged heavy resistance training and its concomitant reductions in type IIX myosin heavy chains may result in an adverse effect. These findings highlight the importance of a proper periodization.

Article 5 emphasizes that a certain stiffness of the series elastic element is required to transmit muscle force to the segment. This is especially relevant for fast movements as tendon and aponeurosis stiffness have been demonstrated to be positively associated with RFD (Bojsen-Møller et al. 2005). Prolonged strength training has been beneficial to increase patellar tendon stiffness in both young and older adults (Kongsgaard et al. 2007; Reeves et al. 2003). Whether an increase in tendon stiffness through training leads to an improvement in RFD or even RPD remains to be investigated.

Regardless of the training method, it is difficult to translate these findings into a large scale public health intervention. A main reason for this difficulty may be that prevention programs of exercise training are not reimbursed, whereas physical therapy is covered by insurance. Training should be promoted via low-tech, relatively low-cost equipment at home or at specific settings such as senior settings or gyms (Roubenoff and Hughes 2000). In addition, many practitioners are still reluctant to prescribe high intensity or high-velocity exercise for elderly patients, because of safety concerns. However, high-velocity power training has been proven to be safe and well tolerated by the elderly (Caserotti et al. 2008; Fielding et al. 2002; Marsh et al. 2009; Reid et al. 2008). In line with the test movements used in **article 3, 4** and **5**, a high-speed cycling intervention on a recline bike was recently shown to be effective in improving RFD and functional performance in older adults (Bellumori et al. 2017). Based on the current findings, we suggest to improve qualitative muscle characteristics through explosive training with the intention to develop the highest speed in combination with more traditional resistance training to target quantitative muscle loss. However, in the light of prevention, promotion of muscle training activities in the younger years may be of great value to delay sarcopenia in later life. Life-long improvements in physical activity and diet are probably the most effective public health interventions (Roubenoff and Hughes 2000).

2.2 Methodological considerations

2.2.1 Study design

One of the limitations of **article 2, 3, 4** and **5** is the cross-sectional design. Cross-sectional data should be interpreted with caution, because the effect of age may be confounded by differences in genetic and phenotypic characteristics. When compared in similar populations (45 – 80 years of age), strength loss was about 60% greater in longitudinal designs compared to cross-sectional designs over a 10-year life span (Hughes et al. 2001). These findings highlight the importance of longitudinal designs in aging research. In this way, the age-related declines reported in this thesis might be an underestimation of real age-related declines within individuals. To note, follow-up testing in longitudinal designs often include the very best of a sample population, which may also lead to a misrepresentation of changes within the whole population.

2.2.2 Study population

2.2.2.1 Sample representativeness

An important objective within our research is that the captured data are highly accurate and reliable. Reliability could especially be an issue when testing older adults as their test results often demonstrate a larger variability compared to young adults (Sosnoff and Newell 2006). In addition, **article 1** demonstrated higher variability when the test performance was weaker, which is true for older adults as demonstrated throughout this thesis. If good reliability can be demonstrated for older adults, it can be expected that it would be even better for young adults. Therefore, reliability was checked using an older sample of subjects in **article 1, 3, 4** and **5.**

Physical activity level or muscle disuse can have a confounding influence on muscular function additional to the effect of aging (McPhee et al. 2016). Therefore, the whole sample of young to older adults in **article 3, 4** and **5** had to fill in a physical activity questionnaire to control for its confounding effects. All participants that were included did not participate in systematic strength or endurance training (i.e. progressive increases in volume and/or intensity) in the prior 6 months. Occasional engagement in physical activity, such as cycling, walking and running was allowed. Therefore, our study sample may be representative for a large portion of the relatively active population. To note, we found similar results for maximal strength measures in our sample compared to a large scale study at our lab (n = 1387 Flemish Caucasions), which is expected to be more representative to the whole population (Van Roie et al. 2018). However, a large portion of the population is not that active and is often underrepresented in studies based on voluntarism (McPhee et al. 2016). Consequently, our results may be an underestimation of the age-related declines of the whole population as it was previously shown that physical activity can reverse the deteriorating effect of aging (McPhee et al. 2016). Furthermore, our results may be confounded by differences in genetic and phenotypic characteristics (Carmelli and Reed 2000). Another factor that can have a confounding influence on muscular function is adequate nutrition (Deutz et al. 2014). No dietary habits or the amount of daily protein intake were recorded. Consequently, nutritional differences could have had an influence on the variability in the muscle function variables between subjects.In addition, we only implemented healthy community-dwelling older adults in all our studies to highlight that the deteriorating effect of aging is already measureable before mobility gets limited. Optimization of identification tools may result in early detection and consequently allows for prevention programs to postpone functional disability. In other words, it is better to predict and prevent than to test and treat.

2.2.2.2 A limitation that is inevitable in research with human participants is voluntarism. The participants in all of our studies were willing to participate, probably driven by their interest to know their current level of performance. This may have resulted in a relatively motivated study sample, which makes our data less generalizable to less motivated people. Sample size

In comparison with most reliability studies, the sample size in **article 1** (n = 63) was high. However, the 95% limits of agreement (LoA) may have been more relevant for clinical practice if tested with an even larger sample. LoA provide the minimal change for an individual needed to be considered real (van Lummel et al. 2016; Weir 2005). The larger the sample, the better the mean and standard deviation of the residuals will approach the real values of the distribution. To see a true change in performance for a group of older individuals, the degree of certainty of 95% LoA may be unrealistic and we therefore recommend looking at the SEM for practical applications. The SEM can be interpreted as the limits for change required to indicate a real increase or decrease for a group of individuals following an intervention (Webber and Porter 2010).

Based on strength measurements collected in our lab before the investigations described in this thesis, a total sample size of 34 (17 per group) seemed sufficient to detect strength differences between two age-groups (α = 0.05 (two-sided), Power = 0.95, Effect size d=1.300063 (G*Power 3.1)). Given the larger age-related declines in muscle power compared to muscle strength as described in the introduction, we expected a similar or even higher effect size for power measures. Therefore, taking into account a possible dropout, we recruited 20 participants (ten men and ten women) per decade (from 20 to 70 years of age) to evaluate changes in muscular function across the life span. With a total of 96 subjects for our last study, we have a data pool that is larger than many other reports within our field of study. However, we experienced that this sample size is not large enough to accurately show non-linear changes with aging across the sample. As demonstrated in figure 1, the lack of older people aged above 65 years and the combination of men and women blunts the expected steeper age-related decline in RPD after 50 years of age. A larger and more heterogeneous sample may have also reduced the effect of the relatively active older subjects included in this study. Therefore, we visualized the average age-related changes in a linear way in **article 3, 4** and **5.** A large scale study in 1387 Flemish Caucasians performed by our research group recently allowed to present non-linear changes in power characteristics and demonstrated that the age-related decline starts around the fourth decade after reaching a plateau around the third decade (Van Roie et al. 2018).

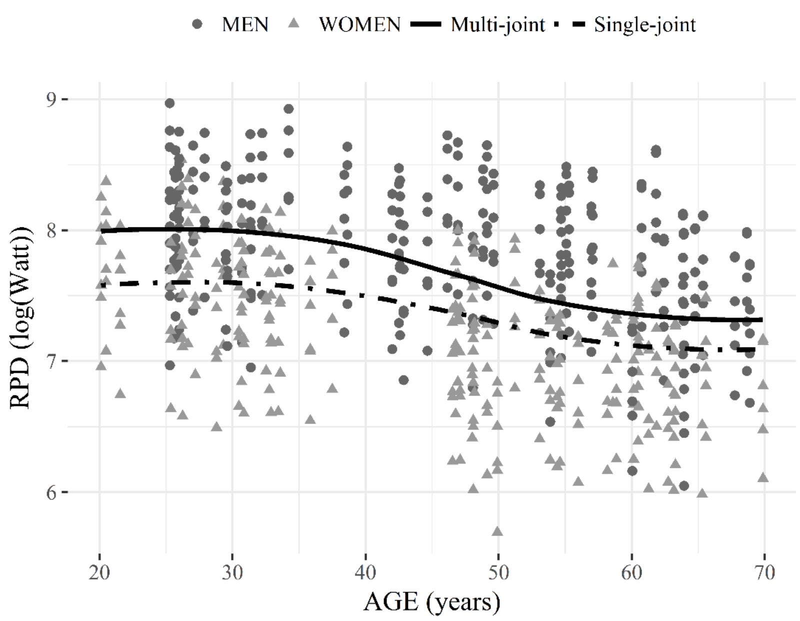

Fig. 1 The rate of power development (RPD) in 96 healthy adults (49 men and 47 women), aged between 20 and 70 years, in single- and multi-joint tests at low, moderate and high speed using a non-linear approach (data from article 3).

2.2.3 Methodology

2.2.3.1 Measuring RPD

To accurately measure time-dependent parameters of muscular function, many factor should be taken into account. In most reports, time-dependent parameters such as RFD are typically measured using isometric testing to control for confounding factors such as angular velocities. RFD is tested in the most standardized way using isolated single-joint approaches such as knee extensions or for more practically relevant outcomes using multi-joint approaches such as squats or leg press. Within our research we tried to accurately measure RPD, taking into account changes in angular velocities, which makes it more representative to many daily activities. Yet, the methodological considerations to accurately measure RFD, may be applicable to RPD.

Compliance of the measurement system may confound the strength measures, in particular for time-dependent measurements. For the measurements in **article 1, 2** and partly **3** we used a Biodex Medical System 3® dynamometer, which is a rigid machine build to safely measure muscle parameters in clinical practice. However, this commercial machine is also designed to test patients in a comfortable way. To illustrate, comfortable seat cushions and a build-in cushion filter that starts braking the movement initiating deceleration early in the motion may influence test results. For research, this way of comfort is in high contrast with accurate measurement needed to answer research questions. A lot of effort was put into the rigidity of the custom-build machine used in **article 3, 4** and **5.** To minimize excess joint movement, low compliant seat cushions, straps, adapted pedals, non-cushioning shoes, extra bolts, frame material, special chain, etc. were used.

Another limitation of the Biodex System is the low sampling frequency of 100Hz to measure time-dependent parameters. However, **article 1** demonstrated good to high reliability for time-dependent measures and **article 2** was able to demonstrate age-related differences. Yet, the sampling frequency of 1000Hz in the custom-build machine allowed for a more accurate measure of for example RPD. To illustrate, a higher sampling frequency allows for a more accurate identification of contraction onset, synchronization with measurements such as EMG and measurement of motor response time such as electromechanical delay.

Instruction is of utmost importance when measuring muscular function. The participants of the studies in this thesis were clearly instructed to push as fast and as hard as possible to elicit an appropriate voluntary explosive contraction with maximal intention. Explanation of the tests and encouragements to the participants allows for the best performance. However, it is important to keep instruction standardized.

Pretension might influence RFD by increasing the initial force, probably due to a change in MU discharge pattern, and decreasing peak RFD (de Ruiter et al. 2006; Van Cutsem and Duchateau 2005). On the other hand, a low-level of pretension is recommended for multi-joint testing to cover the initial compression of soft tissues especially for testing fast actions (Tillin et al. 2013a). Therefore, it is important to standardize pretension across tests and participants to allow for reliable measures as demonstrated in **article 3** and **4.**

2.2.3.2 Multi-joint testing

The main difficulty of multi-joint testing is the higher degrees of freedom. Therefore, the test set-up for **article 3, 4** and **5** aimed to minimize the amount of confounding factors. To illustrate, the foot was fully supported and fixed to the foot plate using a solid strap with the lateral malleolus aligned with the point of force application, provoking a heel thrust to minimize the influence of lower leg muscles and ankle movement. Although this approach could have led to instability around the ankle joint, visual inspection of the measurements refuted this, especially for the first half of the leg extension movements within which muscular function was measured. The positioning was standardized relative to the rotation axis of the in length adaptable lever arm to elicit a standardized range of motion as visualized in **article 3.**

Another limitation of multi-joint testing is the potential initial compliance that is caused by compression of the soft tissues. Therefore, the leg extensor tests could only be initiated after surpassing a low-level of pretension (~ 20-70Nm) as previously recommended (Tillin et al. 2013a).

2.2.3.3 Velocities and accelerations

In **article 1**, maximal knee angular velocities of about 400°/s were measured in a sample of older men and women in single-joint testing on the Biodex. **Article 2** showed that men generally reach higher absolute velocities compared to women and that young and older men were able to reach on average 440°/s and 390°/s against a load of 20% of isometric strength, respectively. Data not included in that article showed that many young individuals can easily reach 500°/s and that higher velocities are not measurable with the Biodex. During usual gait, knee angular velocities can reach 380°/s in young and older adults (Jevsevar et al. 1993). Based on these values, maximal knee angular velocities of 300°/s were chosen for the tests used in **article 3** to allow every participant to successfully complete the isokinetic tests. The knee angular velocities of the multi-joint tests were calculated as the knee joint's range of motion over the time of the particular tests. In **article 4** and **5,** we aimed to evaluate muscular function in response to sudden perturbations. Therefore, we imposed a higher challenge for the participants in terms of different accelerations. Previous reports preprogrammed knee angular acceleration rates till 4000°/s² (Hahn et al. 2017; Tillin et al. 2013b). Given the multi-joint approach and our aim to detect age-related failure, knee angular acceleration rates of about 2000 till 4500°/s² were used. To note, all participants succeeded in performing the high accelerative leg extensor tests without loss of tension during the initial acceleration phases.

2.2.3.4 EMG measurements

As previously acknowledged in the introduction, caution is advised when comparing inter-subject differences in sEMG, because sEMG amplitude is not only determined by MU recruitment or firing rate, but is also influenced by factors such as skin, subcutaneous and fat layers, electrode positioning etc. In this way, a large difference in sEMG measurements could be expected between young and older adults, given their large age-related difference in morphology (Taaffe et al. 2009). A possible solution for this problem is normalization of the sEMG signals to sEMG during a maximal voluntary isometric contraction. However, maximal voluntary isometric activation in the older population could be questioned because of high inter-individual variability (Baggen et al. 2018; Burden 2010). Comparison between acceleration rates in **article 4**, allowed for within-subject normalization, i.e. the tests at high and medium acceleration were normalized to the test at lowest acceleration. This solution avoided the issue of normalization, but limited the results in a way that comparisons could only be made between accelerations and its interaction with age, but not the main effect of age.

A limitation with regard to the EMG measurements in **article 4** is the small number of muscles included. Next to rectus femoris, vastus lateralis and biceps femoris, there are other muscles involved in the leg extensor tests that could have given extra information about the underlying mechanisms of the age-related decline in RPD. Therefore, a more in depth investigation of all the muscles involved in these movements may give additional information.

2.2.3.5 US measurements

Due to the length of the probe, ultrasound images used in **article 5** only visualized part of the fascicles during the tests. Estimation of the absolute fascicle lengths could therefore be erroneous and comparison between individuals is discouraged. Although, relative changes in fascicle lengths within an individual can be determined and compared between individuals as done in **article 5**. However, accuracy of the data could be questioned as our measurement technique only allowed for a sampling frequency of 60Hz. To solve these problems in future research, ultrafast and longer or additional probes could be used to visualize total fascicle lengths.

Furthermore, although some muscle deformation may only be visible in 3D, fascicle measurements for **article 5** were based on two-dimensional ultrasound images. For the analysis, it was assumed that fascicles are represented by straight lines, although it has been shown that this may result in an underestimation of absolute lengths of 2-7% (Finni et al. 2003; Ishikawa et al. 2003). However, these possible systematic errors may not have affected our result, given that we used the same protocol across individuals.

2.2.4 Data analysis

2.2.4.1 Reliability

In order to investigate the effect of training adaptations and the effect of age on muscular function, it is vital that these measures are consistent and free from error. In statistical terms, 'error' refers to the variability that is not attributable to true changes in muscular function. Sources of this error are either intrinsic, including subject-to-subject and trial-to-trial variability or extrinsic, arising from intra-rater variability (Bruton et al. 2000). To estimate the amount of variability that is attributable to error and the amount that represents an accurate value of muscular function, indices of reliability are used. In recent years, several investigators suggested that a combination of indices of reliability should be used in reliability studies compared to a single reliability index (Atkinson and Nevill 1998; Hopkins 2000; Lexell and Downham 2005). Although a consensus has not yet been established, it appears that intraclass correlation coefficients (ICC's) as a relative reliability index together with standard error of measurement (SEM) and limits of agreement (LoA) obtained from Bland-Altman analyses as an absolute reliability index are emerging as the statistical indices of choice (Atkinson and Nevill 1998; Bruton et al. 2000; Rankin and Stokes 1998; Weir 2005). Therefore, these measures were used in all our studies to check reliability in line or partly in line with other reports that investigated measures of muscular function (Arifin et al. 2014; Brown et al. 2005; Drouin et al. 2004; Flansbjer and Lexell 2010; Hartmann et al. 2009; Jenkins et al. 2015; Lund et al. 2005; Power et al. 2011; Tsiros et al. 2011; van Lummel et al. 2016; Webber and Porter 2010).

2.2.4.2 Mixed models

In **article 2,** regular statistics such as t-tests and 2-way ANOVA were used to compare groups of individuals. In **article 3, 4** and **5,** the age-range of 20 to 70 year old adults allowed for an interesting evaluation of age-related changes using a cross-sectional design. However, this unique view across the life span is blunted if separate age-groups would be compared with each other. To take advantage of this whole range of young to older individuals we searched for an applicable tool to statistically compare age-related changes between different conditions. Therefore, mixed-models were built, which allowed for the inclusion of fixed effects such as age, test method, speed of movement or acceleration rate and a random effect (i.e. subject) to correct for the repeated measures design. Although this technique has been limited to other areas of research, the findings in **article 3, 4** and **5** support the use of this kind of design to map age-related changes in muscular function. Large scale investigations across the life-span using this technique or longitudinal designs may improve our understanding of the life course of these changes. This may also be meaningful for clinical practice, as early detection becomes more and more important in the light of prevention.

2.2.4.3 Log-transformation

Comparison of changes is widely used in research and clinical practice. However, large initial values may represent large absolute differences after an intervention, but very small initial values may represent the largest relative differences. Therefore, looking at relative changes is encouraged. However, comparison of relative changes between conditions or groups requires a certain transformation of the data to adjust for the baseline value. Not transforming the data is an underestimated problem that is commonly present in clinical research. In addition, percent change is not a symmetric measure (Harrell 2017). For example, a young men's maximal isometric strength capacity is 200Nm and it declines 10% from 20 to 45 years and a further 10% till 60 years of age, than his maximal strength at 60 is 162Nm and not 160Nm. Therefore, caution is advised when extracting yearly percent changes based on differences between age-groups or based on absolute values and a regression coefficient without adjusting for the baseline value. Yet, many of the studies cited within our research field did not take into account these pitfalls (Edwen et al. 2014; Kennis et al. 2014; Kostka 2005; Skelton et al. 1994). Therefore, we log-transformed the data in **article 3, 4** and **5** to measure the effect of age as independent of the baseline values between different conditions as possible (Törnqvist et al. 1985). Often, log-transformation is used to transform data that does not follow the normal distribution. However, this was not the reason we log-transformed our data. An additional advantage of log-transforming the data is that exponentiated estimates calculated from linear statistical models represent relative percent changes per unit of the independent variable (i.e. per year for the variable age), which are easy to compare between different conditions (Törnqvist et al. 1985).

2.3 Suggestions for future research

Based on the studies presented in this thesis, a number of suggestions for future research are given in the following section.

1. In **paper 1,** absolute indices of reliability are reported to allow other studies to check for real changes that exceed measurement error. Although the sample size in **article 1** was high compared to many other reliability studies, a larger scale reliability study could allow for the calculation of limits of agreement at a 5% significance level to see a true change in performance for an individual that is more relevant to the whole population, which would be useful for clinical practice.
2. Within this thesis, RPD was never directly compared with measures of rapid isometric strength such as RTD/RFD. Direct comparison of RPD with RTD/RFD within the same cohort could give

additional insight into the effects of joint angle, velocity and acceleration and into the underlying mechanisms.

3. In **article 3,** it was suggested that movement complexity resulted in a larger age-related decline of RPD in the multi-joint versus the single-joint tests. However, an in-depth analysis of all the muscles that are involved in the multi-joint leg extension movement could give additional insight into the underlying mechanisms of the larger age-related decline of RPD in multi- versus single-joint.
4. We tried to mimic sudden perturbations in **article 4**. However, a direct link with fall risk could not be made. Implementation of fast accelerative tests in large-scale studies that include investigation of fall incidence could help to detect a direct link between RPD at fast accelerations and fall risk.
5. Although we assume that RPD is more relevant to many activities of daily life compared to pP, we were not able to find any better associations with functional performance in **article 2** and **3**. This was partly explained by the inaccuracy of functional performance tests. With the upcoming of accelerometry, it may be possible to more accurately measure fast and powerful actions during functional tests that can be more directly linked with RPD. However, this should be investigated.
6. **Article 5** suggested that a certain tendon stiffness is required to perform fast actions. However, optimal strategies to improve tendon stiffness should be further investigated as well as its link with improvements in RPD.
7. Intervention studies should elucidate optimal training strategies to improve RPD. The effectiveness of accelerative sprint training on a recline bike as a safe method to improve dynamic, multi-joint RPD should be investigated.
8. It should be noted that the setting to measure RPD multi-joint used in our studies may not be that usable for clinical practice. Future research should create and evaluate methodologies to measure RPD multi-joint in a way that is directly employable, cheap and practical to work with in clinical practice.
9. We were able to capture large age-related declines in **article 2, 3** and **4.** However, we were not able to show that RPD declines earlier during life compared to other measures of muscular function. Future research including large sample sizes should evaluate the declines in muscular function in a non-linear manner.

3 Take home messages

- Time-dependent measures of muscular function should be considered as potential identifiers of muscular aging in research and clinical practice, especially in dynamic multi-joint testing at high accelerations.
- Preventive exercise interventions should not only focus on improving muscle mass and maximal strength, but also neural activation, fiber properties and tendon stiffness.
- Early detection, the underlying mechanisms and appropriate training of rapid power characteristics during aging can be considered as important issues for future research.

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APPENDICES

Appositions – Bijstellingen

Bijstelling 1

Het is belangrijk dat kinderen dagelijks voldoende bewegingskansen krijgen en ook jongeren voldoende gestimuleerd worden om beweging en sport plezant te kunnen vinden.

Bijstelling 2

De overheid moet meer inzetten op een realistischer lichaamsbeeld bij jongeren.

Bijstelling 3

De technologische vooruitgang is op vele vlakken een succesverhaal. Het sociaal contact tussen mensen mogen we echter niet uit het oog verliezen en mag zich niet beperken tot sociale media.

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Personal contribution

The author conceived of the studies in cooperation with the research team. The data of article 1 and 2 were collected by the research team and the data processing methodology was developed by the author. Data for article 3, 4 and 5 were collected in a study that was designed and coordinated by the author. Together with prof. Marc Van Leemputte, mechanical specialist Peter Verstraeten and electronic engineer Paul Meugens, the author constructed and programmed a custom made leg press machine based on the existing isokinetic bicycle of the Department of Movement Sciences. The author performed all measurements, data processing and analysis, interpreted the data and wrote the manuscripts.

Conflict of interest statement

None

Curriculum Vitae

2014 – 2018 PhD student

KU Leuven

Faculty of Movement & Rehabilitation Sciences

Department of Movement Sciences - Physical Activity, Sports & Health Research Group

2009 – 2013 Graduated 'magna cum laude' as Master of Science in Physical Education and Kinesiology

Major Research in Biomedical Kinesiology

KU Leuven

2002 – 2008 Latin-Mathematics

Heilige-Drievuldigheidscollege Leuven

List of publications

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Author affiliations

Corresponding author

Stijn Van Driessche
KU Leuven, Department of Movement Sciences
Physical Activity, Sports & Health Research Group
Tervuursevest 101, B-3001 Heverlee (Belgium)
stijn.vandriessche@kuleuven.be

Co-authors

Evelien Van Roie, dr.
KU Leuven, Department of Movement Sciences
Physical Activity, Sports & Health Research Group
Tervuursevest 101, B-3001 Heverlee (Belgium)
evelien.vanroie@kuleuven.be

Christophe Delecluse, Prof. dr.
KU Leuven, Department of Movement Sciences
Physical Activity, Sports & Health Research Group
Tervuursevest 101, B-3001 Heverlee (Belgium)
christophe.delecluse@kuleuven.be

Benedicte Vanwanseele, Prof. dr.
KU Leuven, Department of Movement Sciences
Human Movement Biomechanics Research Group
Tervuursevest 101, B-3001 Heverlee (Belgium)
benedicte.vanwanseele@kuleuven.be

Ivan Bautmans, Prof. dr.
Vrije Universiteit Brussel, Gerontology Department
Frailty in Ageing Research Group
Laarbeeklaan 103, B-1090 Brussels (Belgium)
ivan.bautmans@vub.ac.be

Marc Van Leemputte, Prof. dr.

KU Leuven, Department of Movement Sciences

Exercise Physiology Research Group

Tervuursevest 101, B-3001 Heverlee (Belgium)

marc.vanleemputte@kuleuven.be