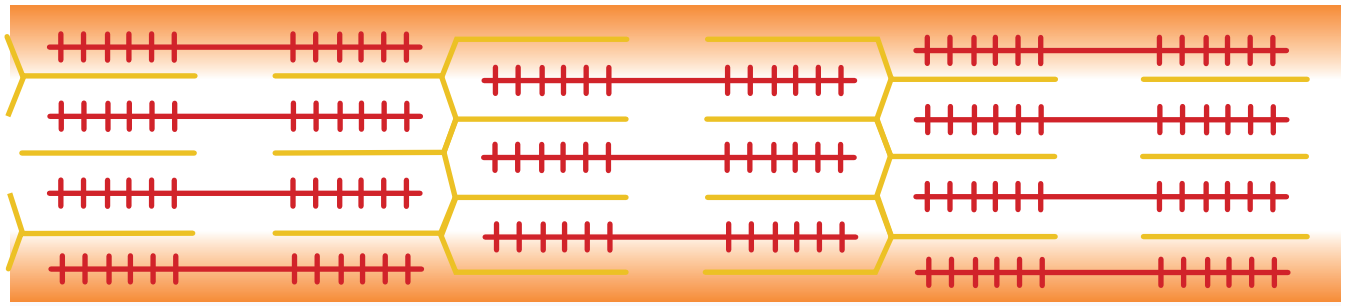
Muscle activation and muscle recruitment in relation to ageing and inflammation

Pauline Arnold



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Colophon

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Muscle activation and muscle recruitment in relation to ageing and inflammation

Pauline Arnold

Thesis submitted to the fulfilment of the requirements for the degree of

Doctor in Gerontological Sciences

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Acknowledgements / Dankwoord

Dankwoord

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CHAPTER 1

General Introduction

Background

"No decline with age is as dramatic or potentially more significant than the decline in lean body mass."

Ian Rosenberg in 1988 was the first to propose the term sarcopenia for the phenomenon he observed, leading to an age-related change in body composition (i.e. muscle loss with changes in adipose tissue mass) and function (Rosenberg 1997). To date sarcopenia is acknowledged as one of the major geriatric syndromes with a prognosis of functional decline, loss of independence and worse physical health-related quality of life (Beaudart and others 2015; Rizzoli and others 2013). Since the nineties research on sarcopenia intensified (Morley and others 2014a) and different research communities aimed at improving the knowledge on sarcopenia and related concepts like, cachexia, pre-cachexia, sarcopenic obesity in aging and chronic diseases (Biolo and others 2014). Evidence for a much more rapid loss of strength compared to loss of muscle mass with aging was found (Clark and Manini 2008; Delmonico and others 2009) attributing to the need for a consensus definition. In 2010 the European Working Group on Sarcopenia in Older People (EWGSOP) provided a working definition on sarcopenia, endorsed by several interest organizations (Biolo and others 2014), as: *a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death*. Based on this definition the prevalence of sarcopenia for community-dwelling older adults is 1-29%, while with increasing age and/or geriatric settings the prevalence of sarcopenia increases (Cruz-Jentoft and others 2014). Given the rapidly aging population the relevance of research on this complex geriatric syndrome needs no argument (Ethgen and others 2017). The more because 70% of community-dwelling elderly might not show sarcopenia. This raises questions how muscle weakness and slowness of movement develop. As long as we do not understand the pathways of declining muscle performance, we will not be able to develop adequate interventions.

The intriguing finding that loss of muscle strength is proportionally higher than loss of muscle mass (Clark and Manini 2008; Delmonico and others 2009; Mitchell and others 2012) points out the need for other explanations than loss of muscle fibres only (Lexell and others 1988), contributing to the etiology of sarcopenia. Age-related changes in the central nervous system result in impairment in muscle activation, contributing to impairment of the force generating capacity of the muscle (Aagaard and others 2010; Clark and Manini 2012; Klass and others 2007; Shield and Zhou 2004). However literature shows conflicting reports regarding the contribution of the neural system in force deficits in elderly (Klass and others 2007).

Another age-related factor influencing muscle weakness is inflammation. The importance of sarcopenia related to inflammation and chronic diseases is becoming increasingly clear (Biolo and others 2014; Morley and others 2014b). Evidence from different investigations show the effect of resistance exercise on strength gains (Borde and others 2015; Csapo and Alegre 2016; Liberman and others 2017; Peterson and others 2010). Also the beneficial effect of physical exercise on inflammation has been reported (Liberman and others 2017), however we do not fully know why and how exercise works.

The aim of our research therefore was to give insight in the mechanisms on the neuromuscular level that contribute to muscle weakness and slowness of movement in elderly.

Muscle activation and muscle recruitment

Definition & concepts

In our research we investigate age-related changes in muscle activation and related mechanisms of force generation. For a good understanding an explanation of some major concepts is provided.

Sarcopenia is defined as age-related loss of muscle mass, muscle strength and physical function (Cruz-Jentoft and others 2010). This *conceptual definition* demonstrates the bio-gerontological perspective of the phenomenon in our studies. Ageing has an effect on muscle mass and strength, affecting all ageing humans. Between the age of 30 and 70 the mean linear loss rates within the musculoskeletal system vary from 0.7% to 1.5% per year (Sehl and Yates 2001). Above the age of 70 years the process accelerates dramatically with losses of strength up to 3.5 % per year (Bautmans and others 2009). The underlying mechanisms are multi-factorial. Contributing factors are age-related, like changes in the endocrine and immune system, loss of motoneurones and denervation of muscle fibres (especially type-II, fast twitch) and increase in non-contractile tissue in muscle. Additional factors contributing to the aggravation of sarcopenia are inactivity or sedentary lifestyle, malnutrition and disease (Bautmans and others 2009; Cruz-Jentoft and others 2010). Not all factors will be present to the same extent in each individual, implying that sarcopenia can have different clinical manifestations in older persons of the same age. In the past decade several clinical criteria have been proposed in order to 'diagnose' sarcopenia in older patients (Cruz-Jentoft and others 2010; Dam and others 2014; Fielding and others 2011; Malmstrom and others 2013). These *operational definitions* for sarcopenia are mainly aimed at identifying older patients with functional deficits that are related to a severe loss of muscle mass and/or strength. However, there is still a lack of international consensus regarding the exact criteria and corresponding cutoff-values (Beaudart and others 2016). In the context of this PhD thesis sarcopenia is considered from the perspective of its conceptual definition, i.e. an age-related bio-gerontological phenomenon.

The concept 'cognition' here is referring to ***cognitive functioning***, including memory, concentration, orientation and executive functioning. In clinical practice the Mini Mental State Examination (MMSE) (Folstein and others 1975) can be used to screen for cognitive decline. It is widely accepted that MMSE-scores of 24/30 or higher can be used to exclude patients suffering from dementia (Folstein and others 1975). In the context of this PhD thesis, we focused on older adults without dementia. Nevertheless, a variability in cognitive functioning can be expected among older persons with a MMSE-score between 24 and 30. However, in this PhD thesis the degree of cognitive capacity has not been assessed in detail, besides the reaction time performance. In fact, one of the many variables of cognitive function is ***reaction time*** (Salthouse 2000). It is generally accepted that reaction time declines with ageing. Reaction time can be assessed using a reaction-time test, in fact measuring processing speed, being a determinant of cognitive function. In this PhD thesis, total reaction time was divided in two components: pre-movement time (i.e. decision time) and movement time. Pre-movement time is defined as the time to process a stimulus and initiate a response, and movement time as the time to execute the response (involving motor activity) (Gorus and others 2006; Roberts and Pallier 2001). Reaction time thus reflects the time from stimulus onset to stimulus offset.

Evidence shows that elderly who are qualified as normal cognitive functioning (i.e. MMSE score >23/30), show variability in their performance during reaction-time tests (Gorus and others 2006). Not only the pre-movement time (considered as the cognitive component of reaction time) showed performance variability, but also did the movement time (considered as the motor component). Previously, several authors have shown that the age-related increase of reaction time in healthy and cognitively intact (i.e. MMSE>23/30) older persons is most pronounced during the movement phase of simple point-to-point reaction time task (Bautmans and others 2011; Gorus and others 2006; Rossit and Harvey 2008; Wolkorte and others 2014). This remarkable finding was the main reason for focusing on the muscular components of increased reaction time in older persons in this PhD thesis.

Movement requires muscle activation, resulting in muscle force. A coordinated movement is the result of an interplay between agonists, antagonists and synergists. The ***agonist(s)*** (prime movers) produce most of the force needed for any particular movement. Synergists assist this action. During a reaction time test described in the first two studies, participants performed an extension movement of the arm, in which the M. Triceps Brachii has been defined as the agonist. ***Antagonists*** also contract, opposing the action of the agonists, thus allowing a controlled movement. During the extension movement of the arm during the reaction time test, the M. Biceps Brachii was considered as the antagonist muscle.

In healthy subjects a smooth, single-joint voluntary movement is usually characterized by a triphasic muscle activation pattern with a typical sequence of muscle recruitment. This pattern consists of an initial burst of agonist muscle activity (AG1), followed by a burst in antagonist muscle activity (ANT) and a second agonist burst (AG2) respectively (Berardelli and others 1996; Hallett and others 1975). It is assumed that AG1 provides the impulsive force to start the movement, that ANT halts the movement at the desired end-point, and that AG2 damps down the effect of ANT at the end of the movement (Berardelli and others 1996). Pfann et al. (Pfann and others 2004) reported that older persons, characterized by slower motor performance consistently show a more biphasic muscle activation pattern (an initial agonist muscle burst followed by an antagonist muscle burst) in point-to-point movements. However, age-related changes in muscle activation patterns are barely understood.

Voluntary muscle activation (VA) is defined as the completeness of skeletal muscle activation during voluntary contractions (Shield and Zhou 2004). VA as the neural driven component, together with local skeletal contractile properties are the two main contributors to force production. Implying that changes, whether or not age related, on many physiological locations could impair force production.

Controlled generation of force and movement, characteristic for human movement, requires the voluntary activity of skeletal muscle. Electrical activity (i.e. action potentials) from the motor cortex descends through the spinal cord to interact with the cell body of an α-motoneuron, located in the anterior horn of the spinal cord. Together with interneurons within the spinal cord and feedback from peripheral receptors, this input (excitatory as well as inhibitory) modulates the input to muscle fibers, via the α-motoneuron and its axon branches, forming the motor unit. How many and which motor units will be activated (i.e. recruited) depends on the force to be delivered. The synaptic connection between the motor axon and muscle fiber is formed by the neuromuscular junction. Here the excitation of the muscle fiber is initiated, among others by calcium (Ca^{2+}), released by the sarcoplasmic reticulum (SR, a storage organel of calcium in the muscle cell). This release in turn is a response to an action potential, causing depolarization of the T-tubular membrane, which is an extension of the muscle fiber surface membrane, into the muscle, connected to the SR (Allen and others 2008). Calcium initiates the cross-bridge cycle (Linari and others 2010), i.e. a cyclical interaction between muscle

proteins (thick myosin and thin actin filaments), given energy by the hydrolysis of adenosine triphosphate (ATP) (Reconditi and others 2011).

Modulation of force is possible by a hierarchically pattern of motor unit recruitment known as the Henneman's size principle (Henneman and others 1974). This principle says that units are recruited in order of their size, from small, slow motor units with type I muscle fibres (being active during low-force contractions) to the fast, large units comprising type II muscle fibres (active during higher-force contractions). Another control mechanism modulating muscle force is known as "frequency or rate coding", referring to the rate at which the motoneuron discharges action potentials. It represents how the neural code is transformed into a mechanical response (force) (Enoka and Fuglevand 2001). The recruitment of motor units and the frequency with which they are activated varies according to muscle characteristics and the type of muscle contraction.

To assess deficits in the ability to completely activate the skeletal muscle the ***twitch interpolation technique*** is commonly used (Merton 1954). The method consists in superimposing a maximal electrical stimulus to a maximal voluntary contraction. When the force output is increased by this superimposed electrical stimulus, the subject's VA (the "completeness" of skeletal muscle activation during voluntary contraction) is considered to be sub-maximal (Shield and Zhou 2004). VA can be calculated as: $[1 - (F_{superimposed\ twitch}/F_{control\ twitch})] \times 100$, where "Fsuperimposed twitch" is the force increment noted during a maximal contraction at the time of stimulation and "Fcontrol twitch" the force evoked by the same electrical stimulation in the relaxed muscle.

Muscle fatigue is any exercise-induced reduction in the ability of a muscle to generate force or power (Gandevia 2001). ***Peripheral muscle fatigue*** is defined as fatigue produced by changes at or distal to the neuromuscular junction (i.e. synapse between a motoneuron and skeletal muscle) (Gandevia 2001). Peripheral fatigue refers to impairment at the level of the muscle. Fatigue-induced peripheral factors contributing to decrease of force are located at the level of the cross-bridge cycle and excitation-contraction coupling mechanism. Fatigue inhibits the interaction of actin and myosin during the cross-bridge-cycle, due to increased release of inorganic phosphate (P_i) and hydrogen ions (H^+). Fatigue slows the release of adenosine diphosphate (ADP) from the cross-bridge, which might limit cross-bridge cycle speed (Kent-Braun and others 2012). Fatigue also influences failure in the excitation-contraction coupling. This can include failure of the propagation of the action potential along the sarcolemma and T-tubular membrane or inhibition of calcium release and re-uptake from the sarcoplasmic reticulum (Allman and Rice 2002; Kent-Braun and others 2012). The oxidative capacity of a muscle, i.e. the ability of the muscle to regenerate ATP, and blood flow also influence peripheral muscle fatigue. In the third study of this PhD thesis peripheral fatigue of a hand muscle was assessed in elderly by interpreting excitability and contractility parameters following a fatigue protocol. Muscle fiber excitability can be assessed using the M-wave, which is a compound action potential recorded with sEMG in response to an electrical stimulus. The amplitude of the M-wave reflects the electrical transmission at the neuromuscular junction and excitability of the muscle fiber membrane (sarcolemma) (Kent-Braun and others 2012). The twitch force (i.e. mechanical force response to an electrical stimulus), rates of force development and relaxation can be used to quantify the contractile properties of the muscle (Kent-Braun and others 2012). ***Central muscle fatigue*** is defined as a progressive reduction in voluntary activation of muscle during exercise (Gandevia 2001), due to processes within the central nervous system (CNS), reducing neural drive to the muscle (Taylor and others 2016). Central fatigue-induced changes concern output of the motor cortex and spinal cord and intrinsic properties of the motoneuron. In fact, the whole pathway within the central nervous system

at which contributions to voluntary activation occur, might affect force production and thus central muscle fatigue. In table 1 the related factors are described in the last column. It must be noted that these factors do not necessarily generate central fatigue. As described in the previous paragraph changes in neural drive to the muscle can be assessed by using the twitch interpolation technique. In the third study in this PhD thesis this method was applied with the objective to assess change in voluntary activation comparing hospitalized patients with an acute infection with community-dwelling elderly controls. The validity of this method measuring central fatigue has been extensively debated (de Haan and others 2009; Taylor 2009). In fact, the extra electrical stimulus, in order to stimulate non-active motor units, is given at the level of the peripheral nerve, implying that the cause of central fatigue, which might be "upstream" remains unclear. However, the debating experts agreed that the method is a valid approach to measure voluntary muscle (in)activation.

New methods of measuring voluntary activation, applying an extra stimulus during fatiguing contractions and reflecting neuromuscular function, have been put forward. Reviewing the force generating process (as previously described) makes clear that the neuromuscular function can be assessed at many sites, see table 1. By comparing muscle responses (measured using EMG) evoked by stimulation of the cortex and spinal cord, the specific influence from cortical and spinal cord processes on force production can be ascertained (Gandevia 2001). However, in this PhD thesis we have not investigated the contribution of spinal and supra-spinal factors in central muscle fatigue.

Site of stimulation	**Stimulation method**	**Muscular response**	**Discriminating factors related to central fatigue, influencing the motoneuron pool**
Cortex	Transcranial magnetic stimulation (TMS)	Motor-evoked potential (MEP) *	Changes in excitability and inhibitability of the motor cortex
Spinal cord / Cervicomedullary region	Transcutaneous electrical or magnetic stimulation	Cervicomedullary motor-evoked potential (CMEP)*	- Changes in descending motor corticospinal tracts - Excitatory and inhibitory intramuscular receptors: • group I, II, III & IV muscle afferents • muscle spindle afferents • Golgi tendon organ afferents
Peripheral nerve / Ia-sensory fibers	Low-intensity transcutaneous electrical stimulation	Hoffmann-reflex	Inhibition of spinal cord
Peripheral nerve / α-motoneuron	Interpolation Twitch method (transcutaneous electrical stimulation)	M-wave	Voluntary muscle activation (spinal + supra-spinal factors)

Table 1: Neuromuscular function related to central fatigue (Kent-Braun and others 2012; Gandevia 2001); *: measured using EMG

Age-related changes in muscle activation & recruitment

Age-related changes in the nervous system result in the inability to fully activate agonist muscles during VA (Klass and others 2007). These changes concern different neural mechanisms: reduced excitability of cortical neurones and motoneurons in the spinal cord, altered motor unit discharge frequency properties (~35-40% lower than in young adults leading to prolonged muscle twitch contraction) and reduced motor unit size and numbers (Clark and Taylor 2011). Especially the larger motoneurons, supplying the fast motor units innervating the type II muscle fibres are most affected by age induced motoneuron cell death (Lexell and others 1988).

Another neural mechanism may inhibit VA of the agonist. With advancing age a decline in reciprocal inhibition is associated with increased co-activation of the antagonistic muscle during voluntary movement (Hortobagyi and Devita 2006). Co-activation of the antagonist muscle might be useful for joint stabilization, but disproportional co-activation can lower the net force exerted by the agonist muscle, as well as inhibit the VA of the agonist muscle.

Age related changes within the peripheral muscle system refer to slowing down of contractile properties. The underlying mechanisms are the above mentioned cross-bridge cycle and excitation-contraction coupling. In particular, impairments in calcium (Ca2+) release from the sarcoplasmic reticulum have been suggested to explain the deficits in the the intrinsic force-generating capacity of aged skeletal muscle relative to its tissue size (Clark and Manini 2012).

In older adults compared to younger adults a re-arrangement of motor units has been reported. The larger motor units (innervating the fast type II muscle fibres) are lost due to denervation. A muscle fiber specific re-innervation process by axonal sprouting (often from type I motor units) has been described (Macaluso and De Vito 2004). This neural adaptation results in larger motor units able to generate high force (Moritani and deVries 1979; Patten and others 2001). As stated by Fling et al. (Fling and others 2009) the size principle of motor unit recruitment seems to be preserved in older adults, which means that at high forces the larger motor units with a slow conduction velocity, but larger number of muscle fibres, are recruited.

Clinical significance

Although evidence for a deficit in VA, tested during isometric contractions, is inconsistent for different muscle groups it is particularly strong for the elbow flexors in elderly. For this muscle group VA is consistently reported as 1%–5% lower in older adults than in young adults (Clark and Taylor 2011). For the knee extensors evidence shows a discrepancy (Clark and Taylor 2011). But from one study it can be concluded that in the very old (aged > 85) who were less physically active, the deficit in VA was reported as 5-15% (Harridge and others 1999). Investigations on the age-related changes in the VA of ankle dorsiflexors showed no differences between old and young participants. There are several studies indicating that elderly have a meaningful level of impairment of voluntary activation (≈ 15%), large enough to explain part of muscle weakness observed (Clark and Manini 2012).

Studies measuring the influence of ageing on co-activation of antagonist muscles during isometric and dynamic contractions also have been reviewed (Klass and others 2007). Co-activation appears to be higher in elderly adults during isometric contractions. During MVC's of knee extensors a difference of ~5% between older and young subjects was reported in co-activation of the m. biceps femoris (Izquierdo and others 1999). Especially for women a difference of ~20% has been reported between older and young women in co-activation of the biceps femoris during knee extension

(Macaluso and De Vito 2004). During (isometric) MVC's of the elbow flexors and extensors, a difference in co-activation of the antagonist muscles of respectively ~5 and 8% was reported (Bautmans and others 2011; Klein and others 2001).

The clinical significance of the above described changes must be related to changes in function over time. The rate of decline will influence the age or time at which a person actually reaches the zone of disability (Rosenberg 1997). A steeper handgrip strength decline after 50 years of age (rate of 0.37 kg/year) has been reported in the general population (Beenakker and others 2010). At the age of 70 most persons will function closer to their limit of maximal strength. Daily activities like rising from a chair or walking the stairs therefore are more challenging given the reduced muscle strength (Hortobagyi and others 2003). Sarcopenic individuals have a greater than threefold increase in falls (Morley and others 2014a), are at higher risk for co-morbidity, hospitalization and institutionalization (Rizzoli and others 2013) and mortality (Chang and Lin 2016) than people without sarcopenia.

Inflammation-induced muscle weakness, muscle activation and muscle recruitment and muscle fatigue

Chronic low-grade inflammatory profile in ageing (CLIP)

Ageing in most people is accompanied by increases in the circulation of inflammatory mediators such as cytokines and acute phase proteins (Krabbe and others 2004). Even in healthy elderly elevations of circulating pro-inflammatory mediators, like Interleukine (IL)-6 en Tumor Necrosis Factor (TNF)-alfa, are found. This phenomenon corresponds to a chronic low-grade inflammatory profile (CLIP) (Beyer and others 2012a; Krabbe and others 2004). Older persons with high serumlevels of IL-6 and TNF-alfa show lower muscle mass and muscle strength (Patel and others 2014; Schaap and others 2006; Visser and others 2002). Sarcopenia can accelerate dramatically in older patients during acute-inflammatory conditions, which are characterised by increased catabolic processes (Bautmans and others 2005a; Beyer and others 2012b).

CLIP & Muscle weakness and muscle fatigue – scientific evidence

Cytokines, like IL-6 and TNF-alpha, are involved in impairing the regulation of skeletal muscle protein turnover (Zoico and Roubenoff 2002). Due to catabolic conditions in skeletal muscle, up-regulation of the ubiquitin-proteasome mechanism (the key component of the proteostasis network to terminate damaged proteins) (Finley 2009) and activation of calpains (calcium dependent regulatory proteases) contribute to muscle protein breakdown (Dargelos and others 2008; Sandri 2013). Recent studies also have shown the influence of TNF-alpha on muscle contractility through an increase in mitochondrial or cytosolic production of Reactive Oxygen Species (ROS) (Zoico and Roubenoff 2002). Recent work of the Frailty in Ageing research group (FRIA) at the Vrije Universiteit Brussel has found that strength training reduces circulating IL-6 and other circulating cytokines in community-dwelling elderly (Bautmans and others 2005b; Forti and others 2014; Forti and others 2016).

Overall the body of literature to date indicates that older individuals develop less muscle fatigue than young individuals, particularly during sustained isometric contractions (Christie and others 2011). Mechanisms that may contribute are differences in blood flow to the working muscles, varying

metabolic responses of the muscle, age-related changes in the mechanical properties of the muscle and differential contributions from central and peripheral factors (Kent-Braun and others 2012). On the other hand, during dynamic contractions older adults develop greater fatigue, related to decline in power (Christie and others 2011). Women have longer endurance times than men during sustained isometric contractions. These sex-based differences might be due to muscle mass or strength, intramuscular pressure and blood flow and neural strategies mediated by metabolic changes during fatigue, however the exact mechanisms remain unclear (Kent-Braun and others 2012).

The FRIA research group has shown that older patients admitted to an acute geriatric ward with inflammation were significantly weaker and showed significantly higher levels of muscle fatigue compared to those without inflammation (Bautmans and others 2005a). In addition, they showed that patients with inflammation had impaired recovery for muscle fatigability, despite medical treatment of the etiology and physiotherapy (Bautmans and others 2005a). This situation can be partially reversed by administration of anti-inflammatory drugs (Beyer and others 2011; Mets and others 2004), demonstrating the causative role of inflammation in the impaired recovery of muscle fatigability in geriatric patients hospitalized with acute infection.

Advanced Glycation End products (AGEs) in CLIP & muscle weakness

Advanced Glycation End products (AGEs) also are known to have pro-inflammatory features (Uribarri and others 2007) and are candidate biomarkers for many age-related inflammatory diseases (Reynaert and others 2016). AGE's are a heterogeneous group of macromolecules formed by the nonenzymatic reaction of proteins, lipids and nucleic acid with glucose (Avery and Bailey 2006; Ott and others 2014). AGE's are produced endogenously, forming cross-links with proteins, but are also present in heated foods, resulting in caramelisation, also known as the Maillard reaction (discovered in 1912 by the French chemist Louis Camille Maillard).

Older adults show an accumulation of AGE's in collagen tissue forming irreversible nonenzymatic glycation cross-links resulting in stiffness of the extracellular matrix (Avery and Bailey 2006; Semba and others 2010a). Besides forming cross-links AGE's increase oxidative stress and inflammation through binding with one of the cell surface receptors for advanced glycation end products (RAGE) (Basta 2008; Uribarri and others 2007). In skeletal muscle the activation of RAGE leads to chronic activation of inflammation, tissue damage and endothelial dysfunction in the microcirculation contributing to exacerbation of sarcopenia with decreasing skeletal muscle strength and physical performance (Dalal and others 2009; Payne 2006; Semba and others 2010a; Semba and others 2010b).

A recent systematic review added evidence for higher levels of AGE's to be independently related to declined walking abilities, inferior ADL, decreased muscle properties (strength, power, mass) and increased physical frailty (Drenth and others 2016).

COHORT	Older community-dwelling subjects n=64, aged 80±6 yrs Young controls n=60, aged 26±3 yrs		Hospitalised patients n=10, aged 82±6 yrs Community-dwelling controls n=19, aged 76±6 yrs	Systematic review + Meta-analysis
Chapter	2	3a	3b	4
Paper	1	2	3	4
Experiment	Reaction time test		Fatigue protocol	-
Muscle activity	M. Triceps Brachii(agonist) M. Biceps Brachii (antagonist)		M. Adductor Pollicis	Ankle dorsal flexors Knee flexors
VA	-	-	M. Adductor Pollicis	Ankle plantar flexors Knee extensors
Inflammation	-	IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-17, CCL2/(MCP-1), CCL3/(MIP-1α), CCL4/(MIP-1β), CCL5/(RANTES), CCL11/(eotaxin), CXCL8/(IL-8), CXCL9/(MIG), CXCL10/(IP-10), TNFα, IFN-α, IFN-γ, and GM-CSF.	IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-17, CCL2/(MCP-1), CCL3/(MIP-1α), CCL4/(MIP-1β), CCL5/(RANTES), CCL11/(eotaxin), CXCL8/(IL-8), CXCL9/(MIG), CXCL10/(IP-10), TNFα, IFN-α, IFN-γ, and GM-CSF.	-
AGE's	-	Pentosidine, Carboxymethyllysine (CML),	-	-

Table 2: Structure of the thesis

Objectives and structure of the thesis

The objectives of this thesis were (1) to provide insight in underlying mechanisms, i.e. age related changes in muscle activation, hypothesized to contribute to muscle weakness and slowness of movement in elderly persons and (2) to review systematically the literature for studies regarding the influence of resistance training on muscle activation in elderly persons.

Table 2 outlines the structure of this thesis, consisting of four studies. Two different cohorts have been studied in order to fulfill the first objective. Since the results of the first three studies showed significant contribution of changes/deficits in antagonist co-activation and voluntary activation in muscle impairment in the aged, the fourth study was aimed at quantifying the available scientific evidence for resistance training to counter these phenomena. The results of the study related to the second objective provide the scientific basis for developing new intervention studies to improve muscle performance in older persons (as described in the paragraph "Future research recommendations" of the General Discussion section).

In **chapter 2 and 3a** we present the investigation of 64 older community-dwelling subjects and 60 young controls, during a simple point-to-point reaction time test of the upper arm. Chapter 2 concerns muscle recruitment and its relation to reaction time, more specifically the activation time of the agonist (M. Triceps Brachii) and antagonist (M. Biceps Brachii) muscles. We hypothesized that an increased antagonist muscle co-activation at the early phase of the reaction time task (Bautmans and others 2011) would be accompanied by an early activation of the antagonist muscle and a delayed agonist muscle activation, thus contributing to a muscle force impairment. Chapter 3a again concerns muscle activation and muscle recruitment of the antagonist (M. Biceps), during the same reaction time test related to the influence of inflammatory circulating cytokines and the possible mediating influence of AGEs. In this study we focused our analyses on muscle activity of the antagonist muscle because its activity showed an aberrant pattern, possibly contributing to slowing of movement, compared to younger persons. We hypothesized that higher levels of pro-inflammatory cytokines and AGEs would relate to slower muscle performance, reflected by reaction time performance.

In **chapter 3b** we present the third experiment investigating 10 hospitalized geriatric patients with acute inflammation and 19 community-dwelling older controls during a fatigue protocol. It explores the role of central (deficit in voluntary activation) and peripheral (local muscle processes) muscle fatigue mediated by circulating markers of inflammation in hospitalized geriatric patients versus elderly controls.

Chapter 4 starts with a paragraph on the relevance of resistance training in ageing, inflammation and muscle weakness. The second paragraph outlines the systematic review and meta-analysis on the influence of strength training on muscle activation in elderly. Literature is consistent about the effect of resistance training to improve muscle strength (Borde and others 2015; Liu and Latham 2009; Peterson and others 2010). Important strength gains (up to >50%) have been reported, already after a relatively short period (i.e. 6–9 weeks) of strengthening exercise, even in very old persons. Given these rapid strength gains, it is accepted that neural adaptations are involved. The respective contribution of changes in voluntary muscle activation and antagonist muscle co-activation in exercise-induced strength gains at higher age have not been systematically reviewed before. The third paragraph contains a discussion with an update of the literature search, the most important findings, clinical implications and conclusion.

In **Chapter 5** a summary, general discussion and future perspectives, proposing further research are described.

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CHAPTER 2

Muscle recruitment and reaction-time performance

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Age-related differences in muscle recruitment and reaction-time performance

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ABSTRACT

Previously, we showed that prolonged reaction-time (RT) in older persons is related to increased antagonist muscle co-activation, occurring already before movement onset. Here, we studied whether a difference in temporal agonist and antagonist muscle activation exists between young and older persons during an RT-test. We studied Mm. Biceps (antagonist muscle) & Triceps (agonist muscle) Brachii activation time by sEMG in 60 young (26 ± 3 years) and 64 older (80 ± 6 years) community-dwelling subjects during a simple point-to-point RT-test (moving a finger using standardized elbow-extension from one pushbutton to another following a visual stimulus). RT was divided in pre-movement-time (PMT, time for stimulus processing) and movement-time (MT, time for motor response completion). Muscle activation time 1) following stimulus onset (PMAT) and 2) before movement onset (MAT) was calculated. PMAT for both muscles was significantly longer for the older subjects compared to the young (258 ± 53 ms versus 224 ± 37 ms, $p = 0.042$ for Biceps and 280 ± 70 ms versus 218 ± 43 ms for Triceps, $p < 0.01$). Longer agonist muscle PMAT was significantly related to worse PMT and RT in young (respectively $r = 0.76$ & $r = 0.68$, $p < 0.001$) and elderly (respectively $r = 0.42$ & $r = 0.40$, $p = 0.001$). In the older subjects we also found that the antagonist muscle activated significantly earlier than the agonist muscle (−22 ± 55 ms, $p = 0.003$). We conclude that in older persons, besides the previously reported increased antagonist muscle co-activation, the muscle firing sequence is also profoundly altered. This is characterized by a delayed muscle activation following stimulus onset, and a significantly earlier recruitment of the antagonist muscle before movement onset.

1. Introduction

Increase of the reaction time (RT) is a factor that contributes to slower motor performance at higher age. RT can be divided into pre-movement time (PMT, the time to process a stimulus and initiate a response) and movement time (MT, the time to execute the response, involving motor activity) (Roberts and Pallier, 2001). Although age-related decreases in cognitive functioning are known to result in slower processing speed and increase in RT, slowing is also observed in cognitively intact elderly persons (Gorus et al., 2006). Previously, Bautmans et al. reported a significantly ($p < 0.001$) longer RT (+32%) in older subjects (80 ± 5 years) compared to young controls (26 ± 3 years) during a simple (upper-limb) point-to-point RT-test. The difference between young and old participants was 2,4-fold higher for MT compared to PMT (Bautmans et al., 2011). This is in line with other RT studies (Gorus et al., 2006; Rossit and Harvey, 2008; Wolkorte et al., 2014) showing that the age-related increase of RT in healthy and cognitively intact older persons is most pronounced during the movement phase of the RT task. Interestingly, Bautmans et al. have shown that in older persons, longer RT was significantly ($p = 0.001$) related to a higher early co-activation of the antagonist muscle during the PMT, i.e. before the start of the movement. On the one hand, a higher co-activation of the antagonist muscle in older persons can improve joint stability as a compensation for age-related muscle weakness (Hortobagyi and DeVita, 2000), but on the other hand it will counteract

Abbreviations: ADL, Activities of Daily Life; bADL, Dependency for basic activities of daily life; iADL, Dependency for instrumental activities of daily life; ADS, Activity Dimensions Summary score; MMSE, Mini Mental State Examination; MVC, Maximal Isometric Voluntary Contraction; MT, Movement time; MAT, Movement activation time; MAT_i, Activation time of the muscle relative to movement onset of the *i-th* MT period; PMT, Pre-movement time; PMT_i, Pre-movement time of the *i-th* RT trial; PMAT, Pre-movement activation time; $PMAT_i$, Activation time of the muscle relative to stimulus onset of the *i-th* PMT period; %PMAT, PMAT expressed as a percentage of PMT; RT, Reaction time; YPAS, Yale Physical Activity Scale.

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and lower the net force exerted by the agonist muscle (Macaluso et al., 2002; Holsgaard-Larsen et al., 2011).

A supplementary element that can contribute to a longer RT in the elderly is an altered firing sequence of agonist and antagonist muscles. In healthy subjects a smooth, single-joint voluntary movement is usually characterized by a triphasic muscle activation pattern, consisting of an initial burst of agonist muscle activity (AG1), followed by a burst in antagonist muscle activity (ANT) and a second agonist burst (AG2) respectively (Hallett et al., 1975; Berardelli et al., 1996). It is assumed that AG1 provides the impulsive force to start the movement, that ANT halts the movement at the desired end-point, and that AG2 damps down the effect of ANT at the end of the movement (Berardelli et al., 1996). Pfann et al. (2004) reported that with slower movement speed older persons consistently show a more biphasic muscle activation pattern (an initial agonist muscle burst followed by an antagonist muscle burst) in point-to-point movements. However, age-related changes in muscle activation pattern are barely understood, and its relation to RT remains unclear. Therefore we investigated the difference in agonist and antagonist muscle activation pattern between elderly and young healthy subjects during a point-to-point RT test. We hypothesized that the increased antagonist muscle co-activation at the early phase of the RT task described previously in older persons (Bautmans et al., 2011) would be accompanied by an early activation of the antagonist muscle, and a delayed agonist muscle activation. Here, we found that in the aged the firing sequence is profoundly altered, characterized by a delayed muscle activation following stimulus onset, and a significantly earlier recruitment of the antagonist muscle before movement onset.

2. Methods

2.1. Participants

Participants and measurement procedures have been described previously in detail (Bautmans et al., 2011). In summary, 124 apparently healthy subjects participated in our study, among whom were 60 young subjects (30 male, 30 female, aged 26 ± 3 years) and 64 community-dwelling elderly (32 male, 32 female, aged 80 ± 6 years). The participants were recruited via the university community, seniors associations, poster and flyer advertisements, and mailings. Subjects were excluded when presenting functional disability of the dominant upper extremity (paresis/paralysis, tremor or recent surgery), cognitive decline (Mini Mental State Examination (MMSE) score < 24/30 (Folstein, Folstein et al., 1975)), neurologic disorders, acute or uncontrolled conditions, or chronic inflammatory pathology. According to the present guidelines (Ferrucci et al., 2004), stable morbidity was not an exclusion criterion per se for older participants. None of the participants was involved in a specific training program or a trained master athlete. In this way a representative older population was obtained. The study was approved by the Medical Ethics Committees of the Universitair Ziekenhuis Brussel (Belgium) and the Erasmus Universitair Medisch Centrum Rotterdam (The Netherlands); and all participants gave written informed consent.

2.2. Measurements

2.2.1. Clinical characteristics

Height and weight were measured, and self-reported morbidity and medication use were recorded. All participants completed the Yale Physical Activity Survey (YPAS) questionnaire and the Activity Dimensions Summary score (YPAS-ADS) was calculated, reflecting the subject's physical activity (vigorous activity, leisure walking, moving, standing and sitting) over the last month on a scale from 0 (no activity at all) to 177 (maximal activity) (Dipietro et al., 1993). For descriptive purposes dependency for basic activities of daily life (bADL) was rated using a 6-item scale (bathing, dressing, transfers, use of toilet, continence and eating) as described by Katz et al. (1963), complemented by orientation in time and place. Each item was scored from 1 (completely independent or no problem in orientation) to 4 (completely dependent or completely disoriented). Dependency for instrumental ADL (iADL) was evaluated using a 9-item questionnaire (telephone use, transportation, shopping, food preparation, housekeeping, handy-man work, laundry, medication use and handling finances) following Lawton et al. (1982). Each item was scored from 1 (completely dependent) to 3 (completely independent). Cognitive functioning was assessed using the Mini Mental State Examination (MMSE) (Folstein, Folstein et al., 1975). MMSE-scores >23/30 were considered as normal.

2.2.2. Reaction time test

A detailed description of the experimental setup can be found in our previous report (Bautmans et al., 2011). The participants performed the RT-test which was preceded by a familiarization session (consisting in 15 trials). Simple, point-to-point RT was assessed using a modified van Zomeren RT-device as described previously (Gorus et al., 2006). Briefly, the device consists of a control panel (connected to a computer) with a central ready button around which eight pushbuttons (that can be illuminated) are arranged in a semicircle. The subject was positioned in front of a horizontally placed control panel with the trunk stabilized to the chair's back support using a belt (eliminating trunk movement). The elbow rested on an articulating elbow support, thus allowing unrestricted elbow extension movement (in a horizontal plane) and maximally reducing postural activity of Mm. Biceps & Triceps Brachii at rest. The position of the control panel was adjusted in order to obtain 60° abduction in the shoulder and 100° elbow extension (when target pushbutton pressed). Movements of the upper arm and hand were monitored using ADXL202 uniaxial piezo-resistive accelerometers (Analog devices, Breda, The Netherlands, adapted by Temec Instruments, Kerkrade, The Netherlands), attached with adhesive tape on the lateral epicondyle (one accelerometer, directed towards the target pushbutton in horizontal plane) and on the processus styloideus of the ulna (three accelerometers, X-axis directed towards the target pushbutton in horizontal plane, Y- and Z-axis perpendicular to respectively X- and Y-axis).

During the RT-test, subjects had to hold down the central ready button to trigger stimulus onset; stimulus offset was attained by pressing the illuminated target button. The RT-assessment protocol in this study consisted in a simple, non-choice RT-test during which always the same target button was used (the fourth or fifth pushbutton for respectively left- and right-handed subjects; 13 cm distance between central ready and target button). Participants were instructed to respond as quickly and accurately as possible and, after response offset, to return immediately to the central pushbutton, thereby triggering the stimulus onset for the next trial. Tasks were made self-paced, meaning that the next inter-stimulus interval (randomly fluctuating between 3 to 6 s) only started after the participant has returned to the central pushbutton. PMT was defined as the interval between stimulus onset and the moment when the subject releases the central button; and MT as the time needed to move the finger to the peripheral response button (using standardized elbow-extension, involving M. Triceps Brachii contraction) (see online Supplementary Material for pictures of the different phases of the RT test). The activity of the central and target pushbuttons were synchronously sampled at 12500 Hz, together with the accelerometers' signals and sEMG of the Mm Biceps & Triceps Brachii (see Fig. 1), and stored on a personal computer for further analysis.

2.2.3. Surface electromyography and signal processing

Self-adhesive pre-gelled electrodes (Ag/Cl, 10 mm diameter, 20 mm inter-electrode distance) were placed over the M. Biceps Brachii Caput Breve, M. Triceps Brachii Caput Longum and one reference electrode on the spinal processus of the seventh cervical vertebra (the skin was cleaned using pure alcohol and shaved when necessary) according to

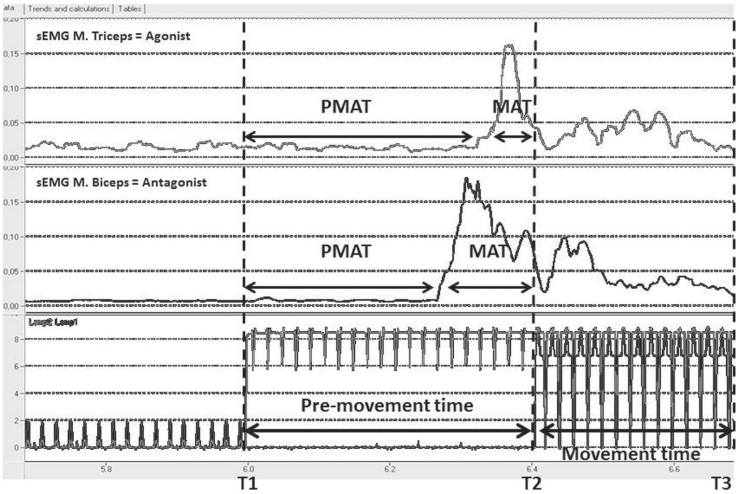

Fig. 1. Signal plot during RT. Representative plot of synchronously sampled sEMG of Mm. Biceps & Triceps Brachii (for illustrative purposes full-wave rectified and RMS-smoothed over 2 ms) and signals of the pushbuttons during a single RT-stimulus in a female participant aged 85 years. PMAT = pre-movement activation time, MAT = movement activation time, T1 = illumination of target pushbutton (visual stimulus, start of PMT), T2 = release of the central ready pushbutton (end of PMT and start of MT), T3 = pressing the target pushbutton (end of MT).

the SENIAM-recommendations (Hermens et al., 2000). sEMG sensors were connected to a universal amplifier (MPAQ, IDEE/Maastricht Instruments, Maastricht, The Netherlands) using shielded wires in order to avoid movement artifacts. All raw sEMG signals were simultaneously sampled at 12500 Hz (Butterworth 4th order, band-pass 10–5000 Hz and notch-filtered) and stored on a personal computer.

Signal processing was performed using data-acquisition software (IdeeQ version 2.9b3, IDEE/Maastricht Instruments, Maastricht, The Netherlands). For the RT-test, 28 stimuli were generated by the test device. When errors occurred (i.e. when MT > 3 s) the system automatically generated a replacement stimulus. Additionally, an observer recorded the wrongly executed trials during the RT-test (e.g. when the subject missed the target pushbutton or made aberrant movements with the arm). The correctly executed trials were confirmed by offline visual inspection of the accelerometer signals. For each participant, at least 23 correctly executed trials (stimuli) were available for data analysis. Median RT, PMT and MT were calculated based on the first available 23 trials, as described previously (Bautmans et al., 2011). The raw sEMG signals of the Mm. Biceps and Triceps Brachii were full-wave rectified and RMS-smoothed over 20 ms. For each RT-trial, the onset of muscle activation was determined as the time point at which the sEMG amplitude exceeded the peak value of the rest sEMG signal (calculated over 250 ms preceding visual onset of the first sEMG burst). For each of the 23 RT-trials, muscle activation time relative to stimulus onset (pre-movement activation time, PMAT), and relative to movement onset (movement activation time, MAT) were calculated (see Fig. 1), and expressed as mean values, computed as:

$$\text{Muscle PMAT} = \frac{1}{23} * \sum_{i=1}^{23} PMAT_i$$

$$\text{Muscle MAT} = \frac{1}{23} * \sum_{i=1}^{23} MAT_i.$$

Similarly, PMAT was expressed as a percentage of PMT (%PMAT) for each of the 23 RT-trials, and expressed as mean value, computed as

$$\text{Muscle \%PMAT} = \frac{1}{23} * \sum_{i=1}^{23} \frac{PMAT_i}{PMT_i}.$$

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS statistics 22.0.0. Differences according to age-groups (young versus old), as well as the interaction with gender, were analyzed for all continuous outcome measures using two-way Analysis Of Variance (ANOVA). Since bADL, iADL and MMSE are expressed on ordinal scales, as well as to reduce potential bias due to possible outliers, Spearman's Rho correlation coefficients were computed to analyze relations of muscle activation with PMT, MT, RT and clinical characteristics. Significance was set a priori at $p < 0.05$.

3. Results

The clinical characteristics of the participants are reported in detail elsewhere (Bautmans et al., 2011). Briefly, none of the older participants showed problematic MMSE or dependency scores and no significant difference was found in physical activity (based on the YPAS-ADS) between both groups (see Table 1).

For both M. Biceps Brachii (acting as an antagonist during the RT-test) and M. Triceps Brachii (acting as an agonist during the RT-test) PMAT was significantly longer in the old subjects compared to the young (258 ± 53 ms versus 224 ± 37 ms, $p = 0.042$ for Biceps and 280 ± 70 ms versus 218 ± 43 ms for Triceps, $p < 0.01$) (see Fig. 2). The elderly thus showed a delayed muscle activation in these muscles compared to the young. Longer M. Triceps Brachii PMAT was significantly related to worse PMT & total RT in young (respectively $r = 0.76$ & $r = 0.68$, $p < 0.001$) and elderly (respectively $r = 0.42$ & $r = 0.40$, $p = 0.001$). For neither M. Biceps nor for M. Triceps Brachii PMAT, MAT and %PMAT, significant relationships were found with cognition (MMSE-score), dependency (bADL and iADL), physical activity (YPAS-ADS), morbidity or medication use; neither in the elderly nor in the young participants separately. M. Biceps Brachii MAT was significantly longer in elderly than in young (65 ± 42 ms versus 50 ± 36, $p = 0.01$) whereas for the M. Triceps Brachii MAT no significant difference was found (43 ± 63 ms in elderly versus 57 ± 27 ms in young, $p = 0.652$) (see Fig. 2). The mean difference in MAT between M. Biceps Brachii and M. Triceps Brachii in the young ones was 6 ±

Table 1
Participants' characteristics.

Parameter	Young subjects (N = 60)	Old subjects (N = 64)
Female	50%	50%
Age (years)*	26.0 ± 3.0	79.6 ± 4.5
MMSE (score: 0–30)	–	28.6 ± 1.5
bADL-dependency (score: 8–32)	–	8.3 ± 0.6
iADL-dependency (score: 9–27)	–	26.0 ± 1.8
YPAS-ADS (score: 0–177)	55.1 ± 20.5	49.6 ± 32.8
PMT (ms)*	269.5 ± 29.1	310.6 ± 41.2
MT (ms)*	176.7 ± 33.6	277.7 ± 73.2
RT (ms)*	450.5 ± 54.2	595.2 ± 102.3

Mean ± SD. *Significant difference between young and old subjects ($p < 0.01$, two-way ANOVA, no significant interaction with gender); MMSE = Mini-Mental-State examination; bADL & iADL = respectively basic and instrumental activities of daily life; YPAS-ADS = Activity Dimensions Summary score of the Yale Physical Activity Survey; PMT = pre-movement time; MT = movement time; RT = total reaction time.

47 ms ($p = 0.311$), whereas for the elderly the difference was −22 ± 55 ms ($p = 0.003$). A positive difference means that the agonist muscle (M. Triceps Brachii) activates first, while a negative one means that the antagonist muscle (M. Biceps Brachii) activates first. No significant interaction with gender was found. The %PMAT (= PMAT/PMT) of M. Biceps Brachii was similar in both groups (80 ± 13% in elderly versus 82 ± 13% in young, $p = 0.321$) whereas the %PMAT of M. Triceps Brachii was significantly higher in elderly compared to young (87 ± 21% versus 79 ± 10%, $p < 0.01$) (see Fig. 3). Since total PMT corresponds to 100%, 87% PMAT of M. Triceps Brachii means that this muscle activates when 87% of the PMT is elapsed. Consequently, in elderly the M. Triceps Brachii activates at a later stage during the pre-movement phase compared with the young.

4. Discussion

In this experiment we explored the difference in agonist and antagonist muscle activation pattern between elderly and young healthy subjects during a point-to-point RT test. We hypothesized that the increased antagonist muscle co-activation at the early phase of the RT task that we described previously in older persons (Bautmans et al., 2011) would be accompanied by an early activation of the antagonist muscle and a delayed agonist muscle activation. Here, we found that in the aged the firing sequence of agonist and antagonist muscles is profoundly altered.

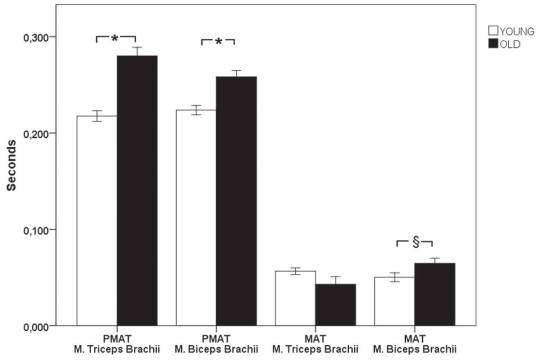

Fig. 2. Pre-movement activation time and movement activation time during point-to-point reaction time test. Significant difference between young and old subjects *$p < 0.01$, §$p < 0.05$ (ANOVA, no interaction with gender); bars represent mean ± SE (based on 23 trials); PMAT = pre-movement activation time; MAT = movement activation time.

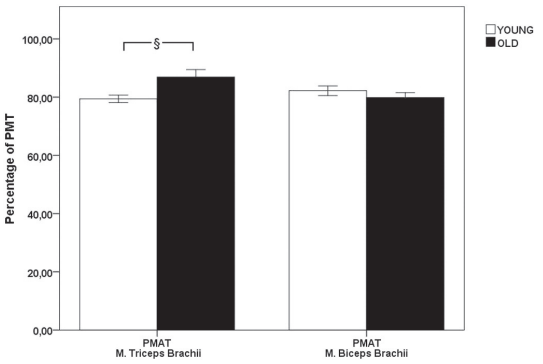

Fig. 3. Muscle pre-movement activation time as percentage of total pre-movement time during point-to-point reaction time test. Significant difference between young and old subjects §$p < 0.05$ (ANOVA, no interaction with gender); bars represent mean ± SE (based on 23 trials); PMAT = pre-movement activation time. PMT = pre-movement time.

A first important observation was a significantly delayed muscle activation following stimulus onset in the older participants. In fact, in the elderly PMAT was significantly longer for M. Biceps and M. Triceps Brachii compared to the young. The temporal delay in pre-movement activation of the agonist muscle (i.e. longer PMAT) confirms the results of Lewis and Brown (1994) who found a significantly longer agonist (in their study the M. Biceps Brachii) muscle activation time which was associated with a longer pre-movement time in elderly compared to younger subjects. We also found that longer agonist PMAT was significantly related to worse PMT and RT. In our RT-test, PMAT represents the time necessary for stimulus reception, integration and decision making in the central nervous system, preparation of the motor program, and sending motor commands to the muscles. Since subjects presenting MMSE-scores < 24/30 were excluded from our study, we believe that our results are not biased by dementia. As previously stated by Salthouse, "nearly all studies with reaction time tasks have found that young adults respond faster than older adults" (Salthouse, 2000); however, the psychophysiological and neurobiological mechanisms are not yet fully understood. In their literature review, Manini et al. (2013) recently described that the age-related alteration in communication from neuron to skeletal muscle can be due to a decline of dopaminergic neurotransmission and impairment of corticospinal excitability. In addition, in elderly persons motor- and cognition-related cortical and subcortical areas are over-activated when performing a motor task (Mattay et al., 2002; Nesselroade and Salthouse, 2004; Heuninckx et al., 2005; Seidler et al., 2010). Also it is observed that in elderly persons, movement preparation leads to additional cortical activity, which is most prominent in the prefrontal cortex (Vallesi et al., 2009; Berchicci et al., 2012). Preparation of movement is suggested to be less optimal in older subjects (Wolkorte et al., 2014).

Secondly, we observed a significantly earlier recruitment of the antagonist muscle before movement onset in the elderly subjects compared to the young. In fact, MAT was significantly longer in the elderly compared to the young for the antagonist muscle (M. Biceps Brachii), but not for the agonist muscle (M. Triceps Brachii). Moreover, we found that %PMAT of M. Biceps was significantly smaller than %PMAT of M. Triceps, which means that in the elderly participants the antagonist muscle activated earlier than the agonist muscle in the pre-movement phase. Reduced reciprocal inhibition through the 1a inhibitory interneuron is a possible underlying mechanism for increased antagonist muscle activity observed in elderly persons (Hortobagyi and Devita, 2006). However this leaves unaddressed the timing issue. It is suggested that inaccuracies in the scaling of flexion, extension and co-activation commands may underlie the altered muscle activation

with aging (Hortobagyi and Devita, 2006). Early activation of the antagonist muscle (M. Biceps Brachii) may prolong the pre-movement phase (i.e. longer PMT). From a biomechanical point of view, the early (co-)activation of the antagonist muscle, before the start of the movement, may hinder the agonist muscle to generate force thus increasing the time necessary to start the movement task. Interestingly, Burke and Kamen (1996) found evidence that during a simple RT-test elderly persons need additional time to activate a sufficient number of alpha motor neurons to initiate a muscle contraction. Several authors have described that, compared to young persons, elderly show different motor strategies and associated brain activity (Bernard and Seidler, 2012; Heetkamp et al., 2014). In fact, the differences in co-activation of antagonist muscles during voluntary motor tasks might be related to age-related changes in activation and inhibition patterns at the cortical level. In a review of Papegaaij et al. (2014) it is speculated that the reduced cortical reciprocal inhibition plays a role in the increased antagonist muscle co-activation seen in elderly subjects. The authors describe that aging causes a reorganization of the cortical control of voluntary movement, which is characterized by an increase in brain activation and a decrease in cortical inhibition.

In our study, the participants had no functional disabilities in ADL. However, it cannot be excluded that this earlier activation of the antagonist muscle is more pronounced in disabled older persons. Future studies including physically impaired older persons are necessary to explore this aspect. However, the relevance of our findings with respect to function in older persons is supported by previous research. A significant relationship between RT-performance and physical functioning, dependency, fall-risk and mortality in elderly persons has been reported (Dhesi et al., 2002; Petrella et al., 2004; Metter et al., 2005). Interestingly, Pijnappels et al. showed that simple point-to-point RT performance (using a light as stimulus and a finger-press as response) was significantly related to balance, choice-stepping RT as well as the occurrence of multiple falls within 1 year follow-up in elderly retirement-village residents (Pijnappels et al., 2010). During the choice-stepping RT-test subjects were instructed to step on an illuminating panel (out of 4 placed in front and aside each foot) as quickly as possible (Pijnappels et al., 2010). Possibly, more pronounced disturbances in agonist–antagonist muscle activation similar to the age-related changes we describe here might be related to increased fall risk in elderly persons.

Although the exact mechanisms of the age-related differences in muscle activation that we observed in our participants remain unclear, we have provided more insight in the presence of altered antagonist muscle co-activation during an RT-test, which might be responsible for increased RT in elderly persons. Since resistance training may decrease antagonist muscle co-activation (Arnold and Bautmans, 2014) and large effect sizes for improvement of response time during and following intermediate intensity exercise were described (McMorris et al., 2011), it would be worthwhile to investigate the effect of physical exercise on these temporal issues in agonist–antagonist recruitment during an RT-test and/or rapid movements.

5. Conclusions

We conclude that in elderly persons the muscle firing sequence is profoundly altered, characterized by a delayed muscle activation following stimulus onset, and a significantly earlier recruitment of the antagonist muscle before movement onset. Since our elderly participants were cognitively intact, the source of these alterations is probably located within the neuromuscular system, and might be a target for exercise interventions.

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CHAPTER 3a

Muscle activation and inflammation

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Reaction Time in healthy elderly is associated with chronic low-grade inflammation and Advanced Glycation End product.

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Abstract

Chronic inflammation and Advanced Glycation End products (AGE) are associated with sarcopenia. Decreased voluntary muscle activation and increased antagonist coactivation can contribute to age-related muscle weakness. The influence of chronic inflammation and AGE in these neuromuscular mechanisms is not clear. We studied whether a relation exists between circulating levels of inflammatory cytokines and AGEs as well as the interplay between agonist and antagonist muscle activation. We studied 64 community-dwelling old subjects, during a maximal isometric voluntary contraction (MVC) and a reaction-time (RT) test of the upper limb. Twenty-five circulating inflammatory biomarkers were determined. Linear regression showed significant relationships between chronic inflammation and six muscle activation parameters. MIP-1β showed a significant negative relation with antagonist coactivation (during MVC) and antagonist muscle activity during pre-movement time (PMT) and movement time (MT) (during RT). A higher level of pentosidine (AGE) was predictive for a longer PMT. We conclude that in older relatively healthy persons antagonist muscle activation is influenced by chronic inflammation, contributing to age-related muscle weakness. Our results also suggest a mechanical and inflammatory influence of pentosidine in upper limb slowing of movement. These findings show novel insight in underlying mechanisms of age-related muscle weakness.

Keywords antagonist coactivation; chronic inflammation; Advanced Glycation End product; aging; cytokines

1. Introduction

A chronic low-grade inflammatory profile (CLIP) is seen in most ageing people (Krabbe and others 2004; Roubenoff 2007). Changes in body composition and decline of the immune system are underlying in complex relationships (Jo and others 2012; Wilson and others 2017). It is well known that CLIP is associated with muscle weakness (Beenakker and others 2010; Beyer and others 2012) and frailty (Wilson and others 2017). Since evidence showed that age-related loss of muscle strength is only weakly associated with the reduction in muscle mass (Clark and Manini 2008; Delmonico and others 2009; Mitchell and others 2012) it is accepted that neuromuscular mechanisms, contribute to age-related muscle weakness (Clark and Manini 2008; Clark and Manini 2012). However, the explanatory mechanisms are not yet fully understood. Neuromuscular mechanisms supposed to be involved are a deficit in voluntary muscle activation and increased antagonist muscle coactivation. The involvement of chronic inflammation in these mechanisms is not clear.

Another factor contributing to the aging process is the low turnover of collagen, resulting in susceptibility to interact with metabolites, allowing the accumulation of non-enzymatic glycation crosslinks, which are irreversible and cause tissue stiffness (Avery and Bailey 2006; Semba and others 2010b). Higher levels of these crosslinks, i.e. Advanced Glycation End products (AGE) are independently related to decreased walking abilities, inferior Activities of Daily Living (ADL), decreased muscle properties (strength, power, mass) and increased physical frailty (Drenth and others 2016). Besides forming of crosslinks, AGE increase oxidative stress and inflammation, through binding with one of the cell surface Receptors for Advanced Glycation End products (RAGE) (Basta 2008; Uribarri and others 2007). This activation of RAGE leads to an exacerbation of decreasing muscle strength and physical performance (Dalal and others 2009; Semba and others 2010a; Semba and others 2010b). The involvement of AGE in voluntary muscle activation is unclear.

We recently found an association between circulating cytokines and contractile muscle properties (twitch force) during a fatigue protocol, in healthy community dwelling elderly (Arnold and others 2017). In another study we provided evidence for the presence of an early antagonist muscle coactivation in community-dwelling elderly during a reaction time (RT) test, using fast dynamic movements (Arnold and others 2015). From a mechanical point of view, this early antagonist coactivation may counteract the agonist muscle, resulting in delay in start of the movement, longer RT and reduced net force production. Our previous findings led to the purpose of this study, which is to answer the question if a relation exists between circulating levels of inflammatory cytokine and AGE and the interplay between muscle activation of agonist and antagonist. Changes in this interplay might be underlying in age-related muscle weakness.

2. Methods

2.1. Participants

This study extends our previous investigations where participants and measurement procedures have been described in detail (Arnold and others 2015; Bautmans and others 2011). Here data from sixty-four community-dwelling elderly (32 males and 32 females, aged respectively 79.6 ± 4.1 and 79.6 ± 4.9 years) were analyzed (see table 1). They were recruited via the University community, seniors associations, poster and flyer advertisements, and mailings. Subjects were excluded when presenting functional disability of the dominant upper extremity (paresis/paralysis, tremor or recent surgery), cognitive decline (Mini Mental State Examination (MMSE) score <24/30 (Folstein and others 1975), neurologic disorders, acute or uncontrolled conditions, or chronic inflammatory pathology. Stable morbidity was not an exclusion criterion per se (Ferrucci and others 2004). None of the participants was involved in a specific training program or was a trained master athlete. The study was approved by the Medical Ethics Committees of the Universitair Ziekenhuis Brussel (Belgium) and the Erasmus Universitair Medisch Centrum Rotterdam (The Netherlands); and all participants gave written informed consent.

2.2. Measurements

2.2.1. Clinical characteristics

Height and weight were measured, and self-reported morbidity and medication use were recorded. All participants completed the Yale Physical Activity Survey (YPAS) questionnaire and the Activity Dimensions Summary score (YPAS-ADS) was calculated, reflecting the subject's physical activity (vigorous activity, leisure walking, moving, standing and sitting) over the last month on a scale from 0 (no activity at all) to 177 (maximal activity) (Dipietro and others 1993). For descriptive purposes dependency for basic activities of daily life (bADL) was rated using a 6-item scale as described by Katz et al. (Katz and others 1963), complemented by orientation in time and place. Each item was scored from 1 (completely independent or no problem in orientation) to 4 (completely dependent or completely disoriented). Dependency for instrumental ADL (iADL) was evaluated using a 9-item questionnaire following Lawton et al. (Lawton and others 1982). Each item was scored from 1 (completely dependent) to 3 (completely independent). Cognitive functioning was assessed using the Mini Mental State Examination (MMSE) (Folstein and others 1975). MMSE-scores >23/30 were considered as normal.

2.2.2. Circulating markers of inflammation and AGEs

Serum levels of 25 different cyto-/chemokines were measured simultaneously by multiplex bead immunoassay (Human Cytokine Twenty-Five-Plex, Biosource International, Nijvel, Belgium) according

to the manufacturer's indications, including: IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, CCL2/(MCP-1), CCL3/(MIP-1α), CCL4/(MIP-1β), CCL5/(RANTES), CCL11/(Eotaxin), CXCL9/(MIG), CXCL10/(IP-10), TNFα, IFN-α, IFN-γ, and GM-CSF. Two different AGEs were measured; Pentosidine en CarboxyMethylLysine (CML). Full names and sensitivities are reported in table 2. Data for samples below the detectable range were imputed as 1 decimal value below the detection limit. When >50% of the samples were below the detection limit, the marker was excluded for statistical analysis (see table 2).

2.2.3. Measurement sequence

First, serum was collected by venepuncture from the non-dominant arm and was frozen at -20°c for later simultaneous determination of circulating cytokines and AGEs. Next, participants' characteristics were assessed and the subjects performed a maximal isometric voluntary contraction (MVC) test of elbow flexion and extension, described by Bautmans et al. (Bautmans and others 2011), in order to calculate the antagonist coactivation. After 5 min. of recovery the participants performed a RT test (Arnold and others 2015; Bautmans and others 2011) which was preceded by a familiarization session (consisting in 15 trials). Both test setups are described in detail in the supplementary material.

2.2.4. Surface electromyography and signal processing

Self-adhesive pre-gelled electrodes (Ag/Cl, 10mm diameter, 20mm inter-electrode distance) were placed over the M. Biceps Brachii Caput Breve, M. Triceps Brachii Caput Longum and one reference electrode on the spinal processus of the seventh cervical vertebra (the skin was cleaned using pure alcohol and shaved when necessary) according to the SENIAM-recommendations (Hermens and others 2000). sEMG sensors were connected to a universal amplifier (MPAQ, IDEE/Maastricht Instruments, Maastricht, The Netherlands) using shielded wires in order to avoid movement artefacts. All raw sEMG signals were simultaneously sampled at 12500Hz (Butterworth 4th order, band-pass 10-5000Hz and notch-filtered) and stored on a personal computer.

Signal processing was performed using data-acquisition software (IdeeQ version 2.9b3, IDEE/Maastricht Instruments, Maastricht, The Netherlands). For the RT-test, 28 stimuli were generated by the test device. When errors occurred (i.e. when movement time>3 seconds) the system automatically generated a replacement stimulus. Additionally, an observer recorded the wrongly executed trials during the RT-test (e.g. when the subject missed the target pushbutton or made aberrant movements with the arm). The correctly executed trials were confirmed by offline visual inspection of the accelerometer signals. For each participant, at least 23 correctly executed trials (stimuli) were available for data analysis.

2.2.5. Muscle activation measures

In this study, the outcome variables were muscle activation measures that in previous studies showed a relation with slowness of movement. Here we investigated 1) antagonist coactivation, calculated from data obtained during the maximal isometric voluntary contraction (MVC), 2) RT, 3) pre-movement time (PMT), 4) movement time (MT), 5) antagonist activity during PMT and 6) antagonist activity during MT, 7) antagonist muscle activation time relative to stimulus onset (PMAT) and 8) antagonist muscle activation relative to movement onset (MAT). Muscle parameters 2 to 8 were calculated from data obtained during the RT test. Measurement procedures and calculations are described in the supplementary material. See figure 1 and the list of abbreviations for an additional explanation of the measures.

2.3. Statistical analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS version 24.0). Differences in clinical characteristics according to gender were analysed using independent t-test. Inflammatory cytokines and AGEs were log(10)-transformed prior to analyses to approximate the normality assumption. Multiple stepwise linear regression was used to determine significant predictor variables that produced the best model for RT measures. Gender, cytokines and AGEs were used as independent variables and eight different muscle activity measures as dependent outcome variables. Potential interaction effects with sex were examined entering all significant factors into the regression model. Cook's distance (>1) and standardized residuals (>4) were checked to determine if cases might be influencing the regression models. Significance was set a priori at $p<0.05$.

3. Results

No significant difference was found between female and male in age, MMSE-score, basic dependency scores, physical activity level, number of medications, number of co-morbidities and pre-movement time (see table 1). Female showed significant higher instrumental dependency scores, but men showed no problematic scores. As expected females showed a significant longer MT and RT than males.

As can be seen in table 2, IL-1β, IL-2, IL-5, IL-6, IL-7, IL-13, IL-15, IL-17, GM-CSF, TNF-α and IFNγ levels were below the detection limit in > 50% of the subjects.

3.1. Antagonist coactivation

Coactivation of the antagonist (M. Biceps) during agonist (M. Triceps) MVC was related to female gender, log MIP-1β and log IL-1RA accounting for 31% of the variability. Female showed higher coactivation. No interaction effect of cytokines and female gender was found.

3.2. Reaction Time

Regression analysis showed log transformed pentosidine to correlate (β = .017, ΔR^2 = .06) significantly with PMT (see Table 3). 24% of the variability in PMT can be predicted by the cytokine pathway expressed by a positive correlation with log IP-10 and a negative correlation with log IL-1R (see Table 3). MT was significantly correlated with female gender and log MIG in which log MIG explains 8%. No relation was found between cytokines or AGEs and RT. Female showed longer MT. No interaction effect of cytokines, pentosidine and female gender was found.

3.3 Antagonist muscle activity

Muscle activity of the antagonist during PMT and MT showed significant negative associations with log MIP-1β (β= -.4.648 and -4.763 respectively) whereas female showed higher muscle activity. No interaction effect of cytokines and female gender was found.

3.4. Antagonist muscle activation time

No relation was found between cytokines or AGEs and the activation time of the antagonist during the pre-movement-time (PMAT). Activation time of the antagonist related to movement onset (MAT) showed a significant negative association with log IL-2R (β = -.053, R^2 = .123).

4. Discussion

This exploratory study for the first time shows the relation between the chronic low-grade inflammation profile (CLIP), reflected by inflammatory cytokines, and different muscle activation parameters, probably contributing to slowing of muscle performance. The most noticeable finding was the significant negative relation between MIP-1β and 1) coactivation of the antagonist muscle during an isometric MVC and 2) muscle activity of the antagonist muscle during PMT and MT during a fast dynamic contraction, i.e. the RT test. In addition, a higher level of pentosidine seems to be predictive for a longer PMT.

Markers of chronic low grade inflammation were significantly related with the degree of antagonist coactivation during maximal voluntary isometric contraction, especially MIP-1β and IL-1RA with respectively a negative and a positive association. These associations show the involvement of chronic inflammation in peripheral antagonist muscle coactivation during an isometric MVC. Our previous research has already shown the correlation between contractile properties (twitch force) of the M. adductor pollicis (acting as agonist muscle) and MIP-1β and IL-1RA during an isometric contraction in a population of relatively healthy elderly (Arnold and others 2017). MIP-1β proteins mediate their biological function by binding to cell receptors and induce intracellular effects leading to chemotaxis, degranulation and phagocytosis. Thus they play a key role in the induction and modulation of inflammatory responses (Maurer and von Stebut 2004). MIP-1β also plays a key-role in muscle regeneration following muscle injury, due to intensive resistance exercise (Mathers and others 2012;

Yahiaoui and others 2008). IL-1RA is a cytokine receptor acting as cytokine binding protein, which can down regulate the effects of circulating cytokines (anti-inflammatory). Cytokine receptors tend to have longer half-lives than their target cytokines, and as their secretion appears to parallel that of the cytokine, they are good markers of chronic cytokine activity (Morley and Baumgartner 2004). Coactivation has been found to be higher in older adults compared to younger persons, during isometric contractions (Izquierdo and others 1999; Macaluso and others 2002; Rozand and others 2017). However studies regarding the influence of ageing on antagonist coactivation during isometric contractions in the upper limb, by comparing young and old subjects, show contrasting results (Klass and others 2007). The negative association between MIP-1β and antagonist coactivation in our participants most probably indicates an impairment mechanism, since the major function of antagonist muscle activation in elderly is to add to joint stabilization, as a compensatory mechanism (Hortobagyi and Devita 2006; Klein and others 2001). Here we found an effect of gender on coactivation of the antagonist muscle, indicating a higher level of coactivation in females than males. Gender differences during isometric contractions have been described related to accuracy of movement and antagonist coordination (Brown and others 2010; Yoon and others 2009), however the tasks performed in those studies were different. The gender difference might be explained by the lower mean muscle strength in females compared to men, suggesting that the higher coactivation is used as a compensation strategy for maintaining joint stabilization, during isometric contractions.

PMT and MT, together reflecting RT, also showed significant positive associations with the cytokines IP-10 and MIG, and IL-1RA showed an inverse relation with PMT. In addition, pentosidine showed a positive association with PMT. Both findings suggest that either by the chronic inflammatory- or by the AGE-pathway PMT may be influenced. Although the contribution of pentosidine in predicting PMT was small, this was in line with our initial hypothesis that accumulation of cross-linking AGE would contribute to slowing of muscle function. Our finding confirms the research by Haus et al (2007) who showed that glycation-related cross-linking of intramuscular connective tissue may contribute to altered muscle force transmission and decreased muscle function in healthy aging elderly, explained by changes in the endomysial collagen tissues (Haus and others 2007). The stiffness of passive collagen tissues seems to hinder processing time. From a mechanical point of view increased muscle activity of the antagonist gives resistance to the agonist to generate force and the time to start the movement, resulting in decreased force output and delay of the start of the movement. Apparently CML, which is a non-cross-linking AGE, can be considered less influential on the biomechanics of muscle tissue. Our findings in previous research showed that the antagonist muscle activity during PMT was significantly higher compared to the muscle activity in young people (Bautmans and others 2011). Here also an inverse association was found between the antagonist muscle activity during PMT and MT and the pro-inflammatory marker MIP-1β. The association means that more inflammatory response, reflected by

MIP-1β, is related to lower antagonist muscle activity. This negative association probably indicates an impairment of antagonist coactivation during dynamic movements in elderly and in fact indicates an impairment of the joint stabilizing mechanism. The effect of gender on muscle activity during PMT and MT might be related to lower muscle strength and rate of force development (RFD) known in females compared to males (Wu and others 2016) during dynamic contraction.

Previous work showed that additional to the higher muscle activation of the antagonist, the recruitment time of the antagonist during the RT test of the upper limb (expressed as movement activation time (MAT)), is longer in elderly compared to young participants (Arnold and others 2015). Here we found no association between CLIP and antagonist PMAT (i.e. the time necessary for stimulus reception, integration and decision-making in the central nervous system, preparation of the motor program, and sending motor commands to the muscles) and a negative association between IL-2R (a cytokine receptor) and MAT. This association accounts only for 12% of the variability in antagonist MAT. Several authors described age-related changes in activation and inhibition patterns at the cortical level in elderly influencing the delay of muscle activation (Bernard and Seidler 2012; Burke and Kamen 1996; Heetkamp and others 2014; Papegaaij and others 2014). Our findings suggest that CLIP, as another mechanism, is involved in altered muscle recruitment patterns in elderly.

The complex interrelation and mediating role of inflammation-related markers and its association with declining muscle quality and physical functioning has been known for many years (Calvani and others 2017; Peake and others 2010). Cytokines that affect muscle function can be produced in the muscle intrinsically or by neutrophils, macrophages, fibroblasts, vascular smooth muscle cells and vascular endothelium (Zoico and Roubenoff 2002). In addition, also senescent cells can contribute to low-grade inflammation, by an increase in the secretion of pro-inflammatory cytokines which has been defined as the senescence associated secretory phenotype (SASP) (Davalos and others 2010; Sikora and others 2014). In our study we determined the most prominent SASP-related biomarkers, including IL-8, IL-6, IL-1, MCP-1, eotaxin and MIP-1α (related to MIP-1β) (Davalos and others 2010). Since our participants were relatively healthy and well-functioning, we expected that high-sensitivity C-reactive protein (hs-CRP) - a common marker of inflammation which is used frequently in clinical practice to identify patients with chronic inflammation - would be very low in most subjects. Therefore, we choose not to determine hs-CRP, but a large set of cyto/chemokines including both pro- and anti-inflammatory biomarkers. It is beyond the scope of this study to explain the individual function of each factor. More information about muscle protein degradation pathways related to cytokine elevations can be found in the review of Saini et al. (Saini and others 2009). Our findings show that in healthy elderly CLIP is involved in voluntary activation and coactivation of the antagonist, and should motivate clinicians to consider it as targets for therapeutic interventions. The

more because exercise as a strong anti-inflammatory strategy has been proven to be effective (Mathur and Pedersen 2008; Pedersen and Saltin 2015).

Our findings show positive as well as negative relationships between the inflammatory markers and muscle activity. The interplay between pro-inflammatory cytokines (negative relations with MIP-1β, IP-10, MIG, IL-2R) and anti-inflammatory ones (positive relations with IL-1RA) in our regression model, suggests that a balance between pro- and anti-inflammatory signaling is involved in muscle activity.

The relationship between the antagonist muscle activation parameters and cytokines and AGEs has not been investigated before. Exploring the possible relationships between the complex interrelated cytokines and AGEs, and the muscle outcomes of interest by using the regression method revealed relations contributing to age-related changes in muscle activation.

Pentosidine was included as an independent predictor together with inflammatory cytokines. Since AGE's can have both a mechanical and inflammatory action on muscle performance, the impact of pentosidine on slowing of movement might have been underestimated. Probably this was not the case as no significant correlations between the cytokines and pentosidine were found, which legitimates to interpret pentosidine as an independent variable in the model.

Since the presence of stable comorbidities was not an exclusion criterion per se, it cannot be excluded that other factors related to chronic disease or treatment might have influenced muscle performance in our participants. However, the number of medication was very low, with a mean of 2.6. All participants were free of functional limitations in the dominant arm. It is well known that cholesterol-reducing medication such as statins can have adverse effects including myalgia (Iwere and Hewitt 2015). However only six subject (<10%) used statins and none reported muscle pain. Therefore, it is very unlikely that our results were affected by statin use. By allowing participation of subjects with stable chronic conditions we were able to recruit a representative sample of well-functioning older adults and thus our results are more likely to be generalizable than when we would have selected older persons completely free of any comorbidity and medication use. In our study, neither number of medications nor comorbidities showed significant relationships with muscle activity outcomes (data not shown). However, the impact on muscle performance of chronic conditions and commonly used medication at older age merits further investigation.

The scores of the YPAS-ADS also have been entered in the regression models as a covariate. The result showed the subject's physical activity level to be predictive for movement time. Lower activity level was associated with longer movement time. However, the association must be interpreted as negligible ($\beta = -0.001$, $p = 0.016$).

Research in this domain allows qualifying a sample size of 64 as "a high number". However, given the large number of variables in the study, we cannot completely exclude that some associations

– although statistically significant -were identified by chance. This first exploration should therefore be followed by research in a larger sample in order to confirm the relationships. However, the number of independent predictors retained in the regression models were restricted to 3 or less, thus the sample size of our study is likely to be sufficient (at least n=20 per predictor) to obtain valid analyses. The relatively high mean age (79.6 years) of our elderly participants suggests that age-related changes in the neuromuscular system have taken place, thus the sample size is representative, contributing to the relevance of our findings.

5. Conclusions

We can conclude that regression analysis showed significant relationships between circulating cytokines and AGE (pentosidine) and muscle activation parameters during isometric MVC and fast dynamic contractions of the upper arm muscles in community-dwelling elderly. These findings are the first to provide evidence for the involvement of the chronic low-grade inflammatory profile in antagonist muscle activation, contributing to age-related muscle weakness. The results also suggest a mechanical and inflammatory influence of the cross-linking AGE, pentosidine, in slowing of movement. More research is necessary to determine causal relations. However our results show novel insight in underlying mechanisms of age-related muscle weakness and likely contribute to developing more targeted interventions, aimed at countering muscle weakness in elderly.

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Conflict of interest statement

The authors have no conflicts of interest to disclose.

List with abbreviations

RT = Reaction Time: pre-movement time + movement time (msec.)

PMT = pre-movement time: time for stimulus processing (msec.)

MT = movement time: time for motor response completion (msec.)

Antagonist coactivation = M. Biceps muscle activation during M. Triceps contraction, as a percentage of the maximal M. Biceps activation during MVC

Antagonist activity during PMT = M. Biceps average muscle activation during pre-movement time, expressed as percentage of activation during MVC

Antagonist activity during MT = M. Biceps average muscle activation during movement time, expressed as percentage of activation during MVC

Antagonist PMAT = M. Biceps muscle activation time relative to stimulus onset (msec.)

Antagonist MAT = M. Biceps muscle activation time relative to movement onset (msec.)

IP-10 = interferon gamma inducible protein 10

IL-1RA = interleukin 1 receptor antagonist

IL-2R = interleukin 2 receptor

MIG = monokine induced by interferon gamma

MIP-1β = macrophage inflammatory protein-1β

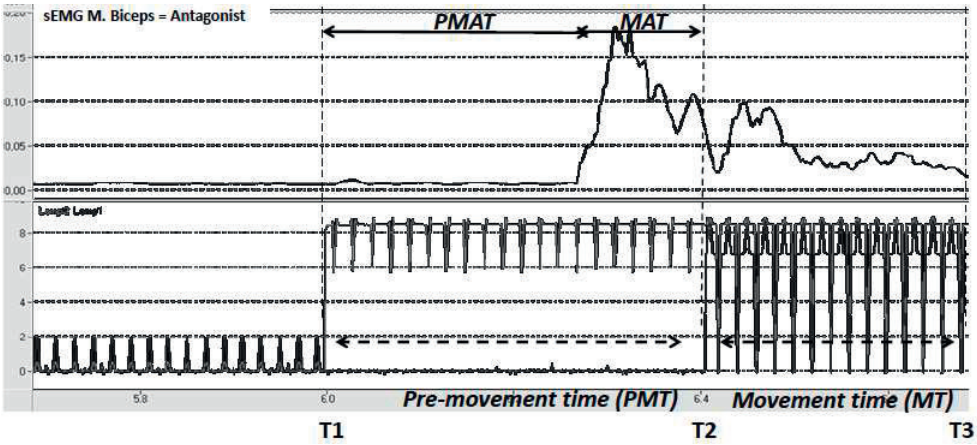

Figure 1: **Signal plot during Reaction Time test.** Plot of sEMG of antagonist muscle (Mm. Biceps) (for illustrative purposes full-wave rectified and RMS-smoothed over 2ms) and signals of the pushbuttons during a single RT-stimulus in a female participant aged 85 years. T1=illumination of target pushbutton (visual stimulus, start of PMT i.e. processing time), T2=participant releases the central pushbutton (end of PMT and start of MT), T3=participant presses the target pushbutton (end of MT). PMAT=pre-movement activation time, MAT=movement activation time.

Table 1 Participants characteristics

Characteristic	Female (N=32)	Male (N=32)
Age (years)	79.6 ± 4.9	79.6 ± 4.1
MMSE (score 0-30)	28.6 ± 1.6	28.6 ± 1.4
bADL-dependency (score 8-32)	8.3 ± 0.5	8.3 ± 0.6
iADL-dependency (score 9-27)	26.6 ± 0.7†	25.3 ± 2.3
YPAS-ADS (score 0-177)	51.9 ± 39.1	47.3 ± 25.3
MVC-triceps/agonist (N)	117.7 ± 39.2†	156.9 ± 49.0
Medication (number)	2.6 ± 3.0	2.6 ± 1.9
Co-morbidity* (number)	1.3 ± 1.4	1.9 ± 1.5
PMT (ms)	310.6 ± 39.6	311.5 ± 43.2
MT (ms)	302.8 ± 73.3†	252.5 ± 64.8
RT (ms)	618.6 ± 89.2†	571.8 ± 77.0

Mean ± SD; †=significant different from male ($p<0.05$, independent t-test); MMSE=Mini-Mental-State examination; bADL & iADL=respectively basic and instrumental activities of daily life; YPAS-ADS= Activity Dimensions Summary score of the Yale Physical Activity Survey; MVC = maximal voluntary contraction; N = Newton, PMT=pre-movement time; MT=movement time; RT=total RT; *Stabilized (chronic) conditions including hypertension, chronic heart failure, diabetes type-2, chronic obstructive pulmonary disease, osteoarthritis, antecedents of cancer, antecedents of depression, elevated cholesterol.

Table 2 Circulating markers of inflammation

Cyto/chemokine	**sensitivity**	**N=64**	
pg/mL		Undetectable (N)	Median ± IQR
IL-1β	<15	39	14.9±24.1
IL-1RA	<20	7	210.0±256.0
IL-2	<15	47	14.9±0.1
IL-2R	<40	1	192.0±103.0
IL-4	<5	23	6.0±8.1
IL-5	<5	61	4.9±0.0
IL-6	<5	35	4.9±6.1
IL-7	<25	54	24.5±0.0
IL-8	<3	2	36.5±32.8
IL-10	<3	23	3.0±3.1
IL-12	<6	-	144.0±73.3
IL-13	<6	41	5.9±23.1
IL-15	<25	41	24.5±9.0
IL-17	<20	49	19.9±0.0
GM-CSF	<5	41	4.9±57.1
TNF-α	<5	54	4.9±0.0
IFN-α	<25	12	40.0±34.5
IFN-γ	<2	33	1.9±3.1
MCP-1	<8	-	520.0±322.5
MIP-1α	<15	8	34.5±27.8
MIP-1β	<10	4	90.5±83.5
RANTES	<20	-	>1100
Eotaxin	<5	-	85.5±58.8
MIG	<20	20	66.5±105.1
IP-10	<5	-	35.0±29.5
Pentosidine (ng/ml)	<0.8	2	7.2±17.2
CML*	<16	2	135.2±122.4

pg/ml = picogram per milliliter; ng/ml = nanogram per milliliter; * = N=54; IQR= interquartile deviation calculated as P75-P25; IL= interleukin; IL-1RA= IL-1 receptor antagonist; GM-CSF= granulocyte macrophage colony-stimulating factor; TNF-α= tumor necrosis factor alpha; IFN= interferon; IL-2R= IL-2 receptor; IP-10= interferon γ-inducible protein 10; MCP= monocyte chemoattractant protein; MIG= monokine induced by interferon gamma; MIP= macrophage inflammatory protein; RANTES= Regulated up-on Activation Normal T-cell Expressed and Secreted; CML = carboxymethyllysine; When >50% of samples in the group was below the detection limit (shaded) the cyto/chemokine was excluded for statistical analysis.

Table 3: Relationships between cytokines, AGEs and muscle parameters

Independent variables	**Dependent variable**	
	antagonist coactivation	
	β	R^2
(constant)	33.534**	0.312
Female gender	9.850**	
Log MIP-1β†	-21.075**	
Log IL-1RA†	11.363*	
	pre-movement time (PMT)	
	β	R^2
(constant)	0.231***	0.301
Log IP-10	0.083***	
Log IL-1RA	-0.030**	
Log Pentosidine	0.017*	
	movement-time (MT)	
	β	R^2
(constant)	0.171***	0.216
Female gender	0.054**	
Log MIG†	0.046*	
	antagonist activity during PMT	
	β	R^2
(constant)	12.724**	0.230
Female gender	4.883**	
Log MIP-1β†	-4.648*	
	antagonist activity during MT	
	β	R^2
(constant)	14.061***	0.274
Log MIP-1β†	-4.763**	
Female gender	3.662**	
	antagonist activation during MT	
	β	R^2
(constant)	0.190***	0.123
Log IL-2R	-0.053*	

* p<0.05, ** p<0.01, *** p<0.001; p-values are two-sided; R^2 = for model;
† = no interaction with female gender

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Supplementary material

Maximal isometric voluntary contraction (Bautmans and others 2011)

The subject was seated on a chair with the shoulder of the dominant arm adducted and neutrally rotated, elbow flexed at 90° and forearm in neutral position. The forearm was stabilized using a custom-made arm rest supporting the proximal third of the ulna, and the distal part (at the processus styloideus) was firmly attached to a strength gauge (Tedea-Huntleigh model 615, Cardiff, United Kingdom, capacity=200 kg, total error b0.02% related load). The subject was instructed to push (elbow extension) or pull (elbow flexion) to the gauge as hard as possible under verbal encouragement and to maintain that effort for five seconds. The highest developed strength plateau out of three consecutive trials was considered as MVC. The signals of the strength gauge were synchronously sampled (at 12500 Hz, Butterworth 4th order, lowpass 1 Hz and notch-filtered) together with the surface electro myography (sEMG) of the Mm Biceps and Triceps Brachii and stored on a personal computer for further analysis.

Root-Mean-Square amplitude (RMS) of Mm. Biceps and Triceps Brachii sEMG signals was calculated over 2 s corresponding to the highest maximal strength plateau obtained during the MVC. **Antagonist coactivation** was calculated (and normalised) as:

$$100 * RMS_{Antagonist(MVCagonist)} / RMS_{Antagonist(MVCantagonist)}$$

Reaction time test (Arnold and others 2015; Bautmans and others 2011)

Simple, point-to-point Reaction Time (RT) was assessed using a modified van Zomeren RT-device as described previously (Gorus and others 2006). Briefly, the device consists of a control panel (connected to a computer) with a central ready button around which eight pushbuttons (that can be illuminated) are arranged in a semicircle. The subject was positioned in front of a horizontally placed control panel with the trunk stabilized to the chair's back support using a belt (eliminating trunk movement). The elbow rested on an articulating elbow support, thus allowing unrestricted elbow extension movement (in a horizontal plane) and maximally reducing postural activity of Mm. Biceps and Triceps Brachii at rest. The position of the control panel was adjusted in order to obtain 60° abduction in the shoulder and 100° elbow extension (when target pushbutton pressed). Movements of the upper arm and hand were monitored using ADXL202 uniaxial piezo-resistive accelerometers (Analog devices, Breda, The Netherlands, adapted by Temec Instruments, Kerkrade, The Netherlands), attached with adhesive tape on the lateral epicondyle (one accelerometer, directed towards the target pushbutton in horizontal plane) and on the processus styloideus of the Ulna (three accelerometers, X-axis directed towards the target pushbutton in horizontal plane, Y- and Z-axis perpendicular to respectively X -and Yaxis).

During the RT-test, subjects had to hold down the central ready button to trigger stimulus onset; stimulus offset was attained by pressing the illuminated target button. The RT-assessment protocol in this study consisted in a simple, non-choice RT-test during which always the same target button was used (the fourth or fifth pushbutton for respectively left- and right-handed subjects; 13 cm distance between central ready and target button). Participants were instructed to respond as quickly and accurately as possible and, after response offset, to return immediately to the central pushbutton, thereby triggering the stimulus onset for the next trial. Tasks were made self-paced, meaning that the next inter-stimulus interval (randomly fluctuating between 3 and 6 s) only started after the participant has returned to the central pushbutton. **Pre-movement time (PMT)** was defined as the interval between stimulus onset and the moment when the subject releases the central button; and **movement time (MT)** as the time needed to move the finger to the peripheral response button (using

standardized elbow-extension, involving M. Triceps Brachii contraction). The activity of the central and target pushbuttons were synchronously sampled at 12500 Hz, together with the accelerometers' signals and sEMG of the Mm Biceps and Triceps Brachii, and stored on a personal computer for further analysis.

For the RT-test, 28 stimuli were generated by the test device. When errors occurred (i.e. when MT>3 sec) the system automatically generated a replacement stimulus. Additionally, an observer recorded the wrongly executed trials during the RT-test (e.g. when the subject missed the target pushbutton or made aberrant movements with the arm). The correctly executed trials were confirmed by offline visual inspection of the accelerometer signals. For each participant, at least 23 correctly executed trials (stimuli) were available for data analysis. **Median RT, PMT and MT** were calculated based on the first available 23 trials, as described previously (Gorus et al., 2006). RMS of Mm. Biceps and Triceps Brachii were calculated over PMT and MT periods of each of the 23 trials, and **average muscle activation during PMT and MT** (see fig. 1) was expressed as percentage of activation during MVC, computed as:

$$\text{Muscle activity during PMT} = \left(\frac{100}{23 * RMS_{MVC}}\right) * \sum_{i=1}^{23} RMS_{PMTi}$$

$$\text{Muscle activity during MT} = \left(\frac{100}{23 * RMS_{MVC}}\right) * \sum_{i=1}^{23} RMS_{MTi}$$

For each RT-trial, the onset of muscle activation was determined as the time point at which the sEMG amplitude exceeded the peak value of the rest sEMG signal (calculated over 250 ms preceding visual onset of the first sEMG burst). For each of the 23 RT-trials, muscle activation time relative to stimulus onset (**premovement activation time, PMAT**), and relative to movement onset (**movement activation time, MAT**) (see fig. 1) were calculated, and expressed as mean values, computed as:

$$\text{Muscle PMAT} = \frac{1}{23} * \sum_{i=1}^{23} PMAT_i$$

$$\text{Muscle MAT} = \frac{1}{23} * \sum_{i=1}^{23} MAT_i$$

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CHAPTER 3b

Muscle activation and inflammation

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Peripheral muscle fatigue in hospitalised geriatric patients is associated with circulating markers of inflammation

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ABSTRACT

Geriatric patients with acute infection show increased muscle weakness and fatigability but the relative contribution of central and peripheral factors is unclear. Hospitalised patients with acute infection (82 ± 6 years, N = 10) and community-dwelling controls (76 ± 6 years, N = 19) sustained a maximal voluntary isometric contraction of the M. Adductor Pollicis until strength dropped to 50% of its maximal value. Voluntary muscle activation (VA) was assessed before and at the end of the fatigue protocol using twitch interpolation method and muscle activity was monitored using surface electromyography. Twenty-five circulating inflammatory biomarkers were determined. At pre-fatigue, no significant difference in VA was found between groups. VA decreased to similar levels (~50%) at the end of the fatigue protocol with no association with inflammatory biomarkers. In geriatric patients, muscle activity decreased significantly ($p < 0.05$) during the fatigue protocol, whereas it increased in the controls (time * group interaction $p < 0.05$). The decrease in muscle activity was significantly related to higher levels of inflammation. Although slower muscle contraction and relaxation were significantly related to higher levels of inflammation, no statistical differences were found between groups. Our results confirm that muscle activity is significantly altered in older patients with acute infection and that local processes are involved.

1. Introduction

Muscle atrophy and weakness are typical characteristics of biological ageing, originally defined as sarcopenia (Rosenberg, 1989). Sarcopenia is a key-element in the physical frailty phenotype (Fried et al., 2001), and both conditions are tightly related to inflammatory processes (Bauer and Sieber, 2008; Baylis et al., 2013). Sarcopenia can accelerate dramatically in older patients during inflammatory conditions, which are characterised by increased catabolic processes. Previously, we have reported that older patients admitted to an acute geriatric ward with inflammation were significantly weaker and showed significantly greater levels of muscle fatigability (i.e. susceptibility to fatigue) compared to those without inflammation (Bautmans et al., 2005). In addition, we demonstrated that patients with inflammation had impaired recovery of muscle fatigability, despite medical treatment of the aetiology and physiotherapy (Bautmans et al., 2005). This situation can be partially reversed by administration of anti-inflammatory drugs (Beyer et al., 2011; Mets et al., 2004), showing the causative role of inflammation in the impaired recovery of muscle fatigability in geriatric patients hospitalised with acute infection. In a first randomized single-blinded controlled study (Mets et al., 2004), we have demonstrated that muscle fatigability was significantly (>60%) reduced following treatment with a selective COX-2 inhibitor (Celecoxib). In a second double-blinded and placebo-controlled study (Beyer et al., 2011; Beyer et al., 2012b), we confirmed this previous finding by demonstrating significant reduction of muscle fatigability in hospitalised geriatric patients with acute infection following treatment with Piroxicam. Unfortunately, given the numerous contra-indications and side effects, standard non-steroidal anti-inflammatory treatment cannot be systematically recommended to counteract inflammation-induced weakness and muscle fatigue in those patients.

Evidence has been found for rapid strength gains following resistance exercise in elderly persons (Peterson et al., 2010), mainly due to improvements of voluntary muscle activation (Arnold and Bautmans,

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2014; Penzer et al., 2015). However, physical exercise remains extremely challenging for hospitalised patients, especially when targeting sufficiently high exercise intensity and volume. In a recent systematic review, Kosse et al. reported that <50% of the hospitalised patients meet the inclusion criteria to start an exercise program, of whom 3%–19% are unwilling to participate because "*they felt unwell or did not feel like exercising*" (Kosse et al., 2013). These latter symptoms are most likely related to ongoing inflammation, and reflect a sickness behaviour, a well-known behavioural phenomenon induced by pro-inflammatory cytokines acting in the brain during acute inflammatory pathology (Dantzer and Kelley, 2007; Dantzer et al., 2008). This behaviour is a physiological state in which the organism sets priority to recover from infection. Fatigue is one of the major sickness symptoms as described by Dantzer and Kelley (2007).

Muscle fatigue, defined as the decrease in force or power production in response to contractile activity (Kent-Braun et al., 2012) may find its cause at various sites. Central factors (output of the motor cortex, spinal excitability, motor unit recruitment) as well as peripheral factors (metabolic processes, excitation-contraction coupling) are reported to contribute to muscle fatigue, as comprehensively reviewed by Kent-Braun et al. (2012). Muscle fatigue related to impairment of the central nervous system shows a decline in voluntary muscle activation (VA). One of the approaches to assess the level of VA is the twitch interpolation method (Merton, 1954). The method consists to superimpose a maximal electrical stimulus to a maximal voluntary contraction. When the force output is increased by this superimposed electrical stimulus, the subject's VA (the "*completeness*" of skeletal muscle activation during voluntary contraction) is considered to be sub-maximal (Shield and Zhou, 2004). Peripheral factors – at the level of the muscle itself – contributing to muscle fatigue include alterations of the actin-myosin interactions, excitation-contraction coupling and sarcoplasmic reticulum function (Kent-Braun, 1999; Kent-Braun et al., 2012). To assess peripheral excitability of the muscle membrane, the amplitude of the M-wave (muscle compound action potential) is often used. The M-wave is recorded with surface electromyography (sEMG) reflecting the motor response evoked by electrical stimulation of the motor axons (Kent-Braun, 1999).

The influence of central and peripheral factors to muscle fatigue mediated by circulating markers of inflammation in hospitalised geriatric patients has not been examined before. Understanding these mechanisms will help to develop more targeted therapeutic interventions to counteract the inflammation-induced muscle atrophy in those patients. Therefore, the aim of this study was to determine the relation of central and peripheral contributions to the development of muscle fatigue during a fatiguing test in inflammatory hospitalised patients compared with community-dwelling older controls.

2. Methods

2.1. Participants

Twenty-nine older persons, among whom 10 hospitalised geriatric patients with acute inflammation (2 male, 8 female, aged 82 ± 6 years) and 19 community-dwelling older controls (10 male, 9 female, aged 76 ± 6 years) participated in this study (see Table 1). The geriatric patients were recruited within the first 3 days after admission to the geriatric ward of the "Universitair Ziekenhuis Brussel". To be included in the study, patients had to be admitted for acute-infection and present serum levels of C-reactive protein of >10 mg/L. Patients presenting inflammation of non-infectious origin or who had a neurological disease, dementia or cognitive or musculoskeletal deterioration interfering with the test procedures were excluded. The community-dwelling older controls were recruited via the university community, seniors associations, poster and flyer advertisements, and mailings. They were screened by interview and excluded when presenting functional disability of the dominant upper extremity (paresis/paralysis, tremor or recent surgery), cognitive decline (Mini Mental State Examination (MMSE) score < 24/30) or neurologic disorders (including Parkinson's disease, Multiple Sclerosis or Cerebro-Vascular Accident), chronic inflammatory pathology, and use of medication with anti-inflammatory effect (corticosteroids or NSAID). The study was approved by the Medical Ethics Committee of the "Universitair Ziekenhuis Brussel" (IRB O.G. 016, Belgium) and all participants gave written informed consent.

2.2. Measurements

2.2.1. Anthropometric characteristics

Height and weight were measured and body mass index (weight/height^2 expressed in kg/m^2) calculated.

Table 1
Participants' characteristics.

Parameter	Geriatric patients N = 10			Older controls N = 19		
	Male N = 2	Female N = 8	Total	Male N = 10	Female N = 9	Total
Age (years)	80.6 ± 9.5	82.3 ± 5.4[†,a]	82.0 ± 5.7[†,b]	76.1 ± 5.3	74.9 ± 7.4	75.5 ± 6.2
Height (m)	1.75 ± 0.13[*,a]	1,57 ± 0.08	1.61 ± 0.12	1.74 ± 0.05[*,a]	1.55 ± 0.06	1.65 ± 0.10
Weight (kg)	71.0 ± 1.4	62.4 ± 9.3	64.15 ± 9.0	76.3 ± 8.8[*,a]	57.7 ± 6.4	67.5 ± 12.2
BMI (kg/m^2)	23.3 ± 2.9	26.3 ± 5.9	25.6 ± 5.3	25.2 ± 2.8	24.0 ± 3.5	24.7 ± 3.1
MVC (N)	47.2 ± 8.6[†,a]	52.7 ± 20.2[†,a]	51.5 ± 18.2[†,b]	105.3 ± 24.5[*,a]	67.3 ± 15.6	87.3 ± 28.1
Medications (n)[c]	4.5 ± 6.4	5.5 ± 5.2	5.3 ± 5.1	4.0 ± 3.1	3.6 ± 1.8	3.7 ± 2.5
Comorbidity (n)[c]	2.0 ± 2.8	2.3 ± 2.1	2.2 ± 2.0	2.2 ± 0.6	1.8 ± 0.7	2.0 ± 0.7
Osteoporosis	0	1	1	0	5	5
Arterial hypertension	1	4	5	8	6	14
COPD	0	2	2	1	0	1
Peripheral arterial insufficiency	1	2	3	3	1	4
Gout	0	0	0	2	0	2
Chronic heart failure	1	3	4	4	1	5
Gastrointestinal disorder	1	3	4	4	2	6
Diabetes mellitus	0	2	2	0	1	1
Macular degeneration	0	1	1	0	0	0

Data represent mean ± SD; BMI = body mass index; MVC = maximal voluntary contraction; COPD = Chronic Obstructive Pulmonary Disease.
[*] Significantly different from female $p < 0.05$.
[†] Significantly different from older controls $p < 0.05$.
[a] Mann-Whitney *U* test.
[b] Independent samples *t*-test.
[c] Home medication or pre-existing comorbidities (i.e. before hospitalisation for the geriatric patients).

2.2.2. Measurement sequence

First, serum was collected by venepuncture from the non-dominant arm and was frozen at −20 °C for later simultaneous determination of circulating markers of inflammation. Next, participants' characteristics were assessed and finally the muscle strength and fatigue assessments were performed.

2.2.3. Circulating markers of inflammation

Serum levels of 25 different cyto-/chemokines were measured simultaneously by multiplex bead immunoassay (Human Cytokine Twenty-Five-Plex, Biosource International, Nijvel, Belgium) according to the manufacturer's indications, including: IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-17, CCL2/(MCP-1), CCL3/(MIP-1α), CCL4/(MIP-1β), CCL5/(RANTES), CCL11/(eotaxin), CXCL8/(IL-8), CXCL9/(MIG), CXCL10/(IP-10), TNFα, IFN-α, IFN-γ, and GM-CSF. Full names and sensitivities are reported in Table 2. Data for samples below the detectable range were imputed as 1 decimal value below the detection limit. When >50% of the samples in both groups were below the detection limit, the marker was excluded for statistical analysis (see Table 2).

2.2.4. Experimental setup for strength and muscle fatigue assessment

Subjects were seated on a chair with the dominant forearm resting on a custom-made ergometer. The forearm and hand, with stretched fingers, were placed in supination in a thermoplastic open cast. Fingers, wrist and forearm were fixed by Velcro tape, avoiding excessive pressure on blood vessels. The thumb was abducted and placed in a rigid plastic ring, connected to a strength transducer (TC 2000-100; Kulite, Basingstoke, UK) by a non-extendible wire (see Fig. 1). The output of the strength transducer was connected to a universal amplifier (MPAQ, IDEE Maastricht Instruments, Maastricht, The Netherlands).

2.2.5. Surface electromyography and signal processing

Two self-adhesive pre-gelled Ag/Cl electrodes (Silvertrace P40Cl, 10 mm diameter), recording sEMG activity of the M. Adductor Pollicis, were placed between the motor point of the M. Adductor Pollicis (located by electrical stimulation showing the best visual contraction of the thumb) and the metacarpophalangeal joint. A reference electrode was placed on the Os Pisiforme (see Fig. 1). The sEMG sensors were connected to the MPAQ amplifier using shielded wires in order to avoid movement artefacts. Signal processing was performed using data-acquisition software (IdeeQ version 2.9b3, IDEE Maastricht Instruments,

Table 2
Circulating markers of inflammation.

Cyto/chemokine	Sensitivity	Geriatric Patients N = 10		Older Controls N = 19	
pg/mL		*Undetectable*	*Median ± IQR*	*Undetectable*	*Median ± IQR*
		n		*n*	
CRP	<1	–	26.2 ± 98.0#	–	–
IL–1β	<15	9	–	18	–
IL–1RA	<20	0	276.0 ± 390.0*	3	85.0 ± 144.0
IL–2	<15	9	–	19	–
IL–2R	<40	0	431.0 ± 458.8*	0	213.0 ± 179.0
IL–4	<5	0	8.0 ± 5.5	1	7.0 ± 2.0
IL–5	<5	9	–	18	–
IL–6	<5	3	10.5 ± 17.1*	16	4.9 ± 0.0
IL–7	<25	10	–	17	–
IL–8	<3	0	127.0 ± 95.8*	0	37.0 ± 18.0
IL–10	<3	0	7.0 ± 15.5	0	4.0 ± 5.0
IL–12	<6	0	200.5 ± 178.8*	0	98.0 ± 84.0
IL–13	<6	5	–	14	–
IL–15	<25	6	–	17	–
IL–17	<20	9	–	17	–
GM–CSF	<5	6	–	10	–
TNF–α	<5	10	–	19	–
IFN–α	<25	6	–	14	–
IFN–γ	<2	0	7.0 ± 2.0	0	7.0 ± 1.0
MCP–1	<8	0	568.0 ± 421.8*	0	374.0 ± 391
MIP–1α	<15	1	42.0 ± 48.0*	10	14.9 ± 19.1
MIP–1β	<10	0	142.0 ± 161.5*	0	43.0 ± 57.0
RANTES	<20	0	3935.5 ± 1302.0	0	3674.0 ± 1342.0
Eotaxin	<5	0	70.5 ± 56.3	0	70.0 ± 54.0
MIG	<20	1	49.0 ± 119.5	5	29.0 ± 29.1
IP–10	<5	0	39.5 ± 67.5	1	29.0 ± 19.0

pg/mL = picogram per millilitre; IQR = interquartile deviation calculated as P75-P25; CRP = C-reactive protein (only measured in patient group); #) reported in mg/L; IL = interleukin; IL-1RA = IL-1 receptor antagonist; GM-CSF = granulocyte macrophage colony-stimulating factor; TNF-α = tumor necrosis factor alpha; IFN = interferon; IL-2R = IL-2 receptor; IP-10 = interferon γ-inducible protein 10; MCP = monocyte chemoattractant protein; MIG = monokine induced by interferon gamma; MIP = macrophage inflammatory protein; RANTES = Regulated up-on Activation Normal T-cell Expressed and Secreted. When >50% of samples in both groups were below the detection limit (shaded) the cyto/chemokine was excluded for statistical analysis.
* Significantly different from older controls ($p < 0.05$).

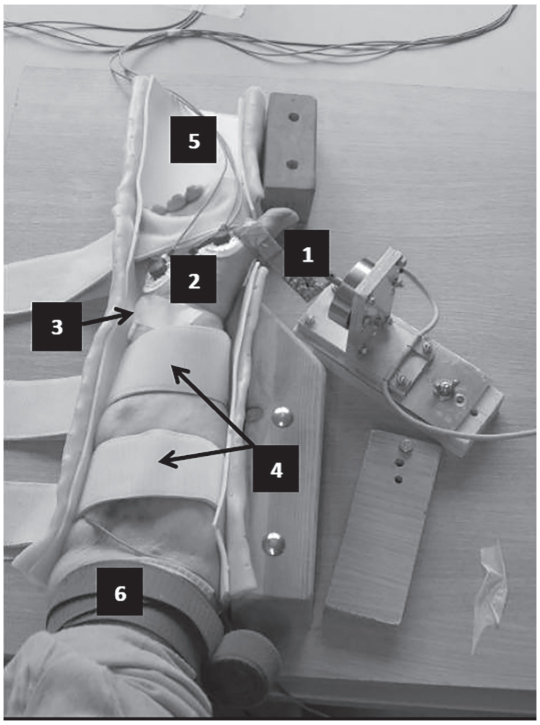

Fig. 1. Experimental setup: 1 = rigid plastic ring, connected to a strength transducer by a non-extensible wire; 2 = sEMG electrodes; 3 = stimulation electrode (cathode); 4 = Velcro straps; 5 = thermoplastic open cast; 6 = stimulation electrode (anode) on M. Biceps Brachii.

Maastricht, The Netherlands). The sEMG signals of the M. Adductor Pollicis were simultaneously sampled (at 12.500 Hz, Butterworth 4th order, band-pass 10–5000 Hz and notch-filtered) together with the strength signal (at 12.500 Hz, Butterworth 4th order, low-pass 20 Hz and notch filtered) and stored on a personal computer (see Fig. 2).

2.2.6. Maximal voluntary contraction and fatigue protocol

Assessment of VA was done by the twitch interpolation technique (Shield and Zhou, 2004) consisting in applying a supramaximal electrical stimulus during a maximal voluntary contraction (MVC). The M. Adductor Pollicis was activated by stimulating its motor nerve (N. Ulnaris stimulation) by a single square monophasic pulse of 200 μs delivered through a constant-current stimulator (Endomed 582, Enraf Nonius). The cathode was placed proximal to the wrist (see Fig. 1) and the anode on the M. Biceps Brachii. The supramaximal intensity was determined at rest prior to superimposition. Therefore stimuli at increasing intensities were administered to the N. Ulnaris until the amplitude of the M-wave (compound muscle action potentials) and twitch force reached a plateau. All interpolated stimuli were delivered at an intensity of 130% of the intensity that produced maximal M-wave and twitch force.

2.2.6.1. Pre-fatigue MVC. First, subjects were asked to perform 3 MVCs of the M. Adductor Pollicis (a preload of 2 N was imposed to the thumb) with an interval of 5 s to get familiar with the procedure. After 1 min rest, a new MVC was performed and the interpolated twitch was applied when MVC strength plateaued. Immediately after relaxation, a supramaximal stimulus (control twitch) was delivered to the relaxed muscle (in order to calculate the interpolated twitch ratio (Shield and Zhou, 2004)).

2.2.6.2. Fatigue protocol. To assess muscle fatigability, subjects performed a sustained MVC in a similar setup. Care was taken that the strength produced by the subject at the start of the fatigue test was similar than during the MVC test. Subject was instructed to maintain the contraction until her/his strength dropped to 50% of its pre-fatigue value

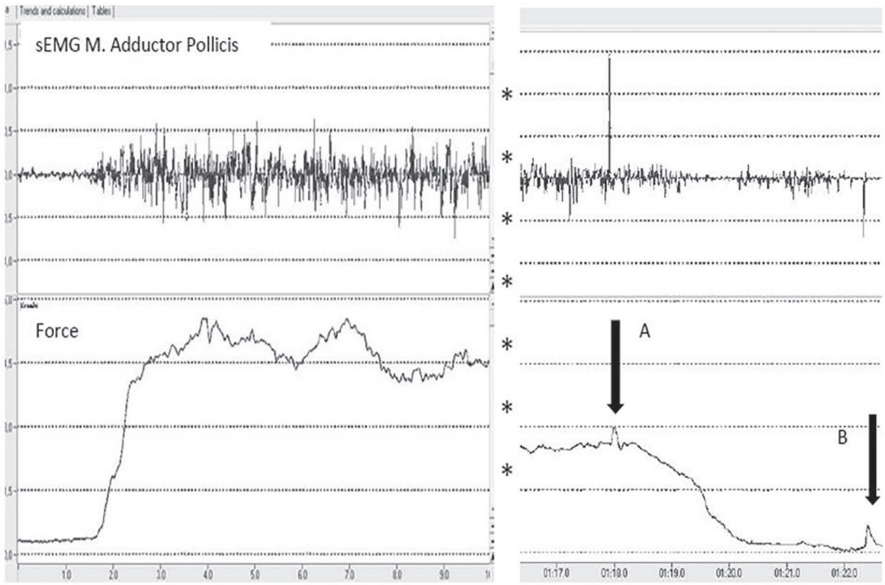

Fig. 2. sEMG and voluntary force recordings of M. Adductor Pollicis at the start (left panel) and end of the fatigue protocol (right panel). Arrow A = superimposed force elicited by the interpolated twitch method when force declined to 50% of MVC; Arrow B = force elicited by the control twitch in relaxed muscle following the fatigue protocol.

(as observed by the investigator based on the force output of the strength transducer). At this stage, before (interpolated twitch) and immediately after relaxation (control twitch), a supramaximal electrical stimulus was delivered. During the MVC test and throughout the fatigue test subjects were verbally encouraged to produce maximal effort.

2.3. Calculations and statistical analysis

Voluntary activation (VA) was calculated as follows: $[1 - (F_{superimposed\ twitch} / F_{control\ twitch})] \times 100$ with F = force increment due to stimulation (Shield and Zhou, 2004). The muscle activity of the M. Adductor Pollicis was calculated as the Root-Mean-Square (RMS) amplitude of the EMG signals over a time window of 2 s during the MVC test (pre-fatigue), and at 1/4, 2/4, 3/4, and at the end of the fatigue test. RMS sEMG activity was normalized to the M-wave peak-to-peak amplitude of the control twitch (i.e. after the pre-fatigue MVC, and after the fatigue test for the measurements during the fatigue protocol), and expressed as sEMG/M-wave ratio as described by Duchateau et al. (2002). Since raw sEMG data are difficult to interpret due to the strong interindividual variability induced by a multitude number of factors (see Farina et al. (2004) for overview) we report only on normalized sEMG data. Contractile properties in pre-fatigue condition and after the fatigue protocol were determined (Hicks et al., 1989) by measuring twitch force (TF), mean rate of force development (RFD) and rate of force relaxation from maximum to 50% (RFR), based on the control twitch respectively after pre-fatigue MVC and after the fatigue test. Mean rate of force development and relaxation were obtained by respectively dividing TF by contraction time and TF/2 by half-relaxation time. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (version 23.0). Independent samples *t*-tests, Chi-Square tests, Mann-Whitney *U* test and Analysis of Covariance (ANCOVA, with age as covariate) were used to assess differences between groups. Changes from pre-fatigue to post-fatigue (i.e. during or at the end of the fatigue protocol) were analysed by repeated measures ANCOVA with group (patients versus controls) as between-subjects factor and age as covariate. For analysis of changes within each group separately, repeated measures ANOVA was used. Bonferroni correction was used to adjust for multiple testing on group-specific time contrasts. Data for the cytokines were log(10) transformed in order to normalize data distribution. Partial correlations (corrected for age) were computed to analyse the relationship between different muscle parameters and levels of cyto/chemokines. Significance was set a priori at $p < 0.05$.

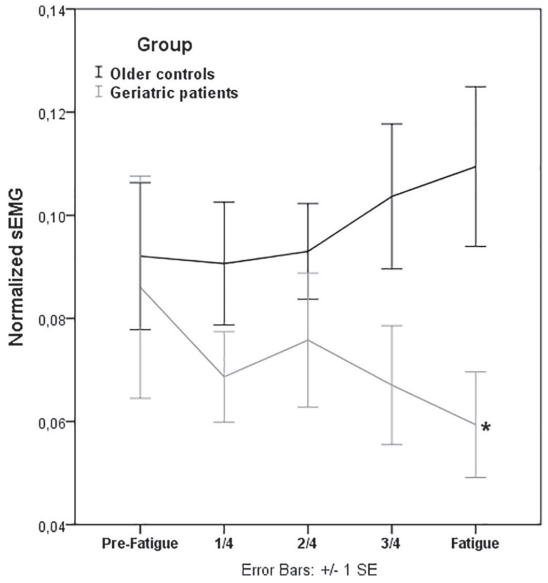

Fig. 3. Normalized sEMG during the fatigue protocol. Muscle activity decreased significantly in the geriatric patients during the fatigue protocol (repeated measures ANOVA p = 0.046). In the older controls muscle activity tended to increase, but this was not statistically significant (repeated measures ANOVA p = 0.193). Significant time * group interaction was observed when muscle activity at the end of the fatigue protocol was compared to pre-fatigue levels (repeated measures ANCOVA corrected for age p = 0.014*).

3. Results

The geriatric patients were significantly older and weaker compared to the older controls (see Table 1 for age and MVC). Females showed significantly smaller height (for both groups) and weaker MVC (in older controls only) compared to males. No other significant differences between the groups were found.

3.1. Voluntary activation & muscle activity

As can been seen in Table 3 no significant overall change (p = 0.098) was found in VA following the fatigue protocol. When analysed

Table 3
Voluntary activation level and electrical and contractile properties of M. Adductor Pollicis before and after a fatiguing contraction.

Parameter		Geriatric patients N = 10	Older controls N = 19	Group difference[a]	Time effect[b]	Time * group effect[b]
VA (%)	Pre-fatigue	62.4 ± 32.5	77.3 ± 13.7	p = 0.178	p = 0.098	p = 0.824
	Fatigue	49.0 ± 17.6	49.9 ± 26.9*			
	p-Value*	0.424	0.002			
M-wave amplitude (mV)	Pre-fatigue	4.23 ± 3.14	4.50 ± 2.38	p = 0.811	p = 0.342	p = 0.838
	Fatigue	3.36 ± 2,20	3.55 ± 2.05*			
	p-Value*	0.150	0.024			
Twitch force (N)	Pre-fatigue	5.8 ± 2.2	9.9 ± 4.3	p = 0.075	p = 0.017	p = 0.106
	Fatigue	4.4 ± 1.9	5.2 ± 3.5*			
	p-Value*	0.202	<0.001			
RFD (N/s)	Pre-fatigue	69.4 ± 32.0	126.1 ± 68.4	p = 0.145	p = 0.072	p = 0.092
	Fatigue	60.5 ± 34.0	68.8 ± 56.9*			
	p-Value*	0.866	<0.001			
RFR (N/s)	Pre-fatigue	44.7 ± 16.3	73.5 ± 34.2	p = 0.100	p = 0.035	p = 0.137
	Fatigue	30.4 ± 12.3*	34.1 ± 25.0*			
	p-Value*	0.048	<0.001			

Pre-fatigue = before the start of the fatigue protocol; Fatigue = at the end of the fatigue protocol (i.e. when strength dropped to 50% of its maximum); VA = voluntary muscle activation; RFD = rate of force development; RFR = rate of force relaxation from maximum to 50%; significantly different from pre-fatigue (*paired *t*-test with Bonferroni correction).
[a] ANCOVA (corrected for age) for pre-fatigue levels.
[b] Repeated measures ANCOVA corrected for age.

separately, VA decreased significantly in the older controls after the fatiguing protocol, whereas it did not differ significantly for the geriatric patients. However, no significant time * group interaction was found.

Muscle activity (expressed as sEMG/M-wave) decreased significantly in the geriatric patients during the fatigue protocol (repeated measures ANOVA $p = 0.046$, see Fig. 3). In the older controls, muscle activity tended to increase, but the difference was not statistically significant (repeated measures ANOVA $p = 0.193$, see Fig. 3). Moreover, a significant time * group interaction was observed when muscle activity at the end of the fatigue protocol was compared to pre-fatigue condition (repeated measures ANCOVA corrected for age ($p = 0.014$)).

3.2. Muscle membrane excitability

Overall, M-wave amplitude was not significantly modified following the fatigue protocol ($p = 0.342$, see Table 3) and changes did not differ between geriatric patients and older controls (see Table 3). However, when analysed separately, M-wave amplitude decreased significantly in the older controls ($p < 0.05$) and showed a trend to decrease in the geriatric patients ($p = 0.075$).

3.3. Muscle contractile properties

Overall, TF decreased significantly following the fatigue protocol ($p = 0.017$, see Table 3) without significant difference in the change between both groups (see Table 3). When analysed separately, this decrease remained statistically significant in the older controls ($p < 0.001$), but not in the geriatric patients ($p = 0.101$). For RFD, an overall trend to decrease was observed following the fatigue protocol, but this was not statistically significant ($p = 0.072$, see Table 3). In the older controls, RFD decreased significantly, contrary to the geriatric patients in whom no significant change was observed. RFR was significantly lower following the fatigue protocol ($p = 0.035$, see Table 3), this remained statistically significant when geriatric patients and older controls were considered separately (see Table 3).

3.4. Circulating levels inflammatory markers

As can be seen in Table 2, IL-1β, IL-2, IL-5, IL-7, IL-13, IL-15, IL-17, GM-CSF, TNF-α and IFNα levels were below the detection limit in >50% of the subjects in each group. IL-1RA, IL-2R, IL-6, IL-8, IL-12, MCP-1, MIP-1α and MIP-1β were significantly higher in geriatric patients compared to older controls. VA was not significantly related to levels of inflammatory markers, except for IL-10 at pre-fatigue ($p < 0.05$, see Table 4).

Likewise, no significant relationship with muscle membrane excitability was found (except with IL-12 at the end of the fatigue protocol). In contrast, higher levels of inflammatory markers were significantly related to worse muscle contractility (see Table 4). Especially MCP-1 was significantly associated with all muscle contractility outcomes at both pre- and post-fatigue levels. A same pattern was found for IL-1RA, but not all correlation coefficients reached statistical significance. The decrease in muscle activity during the fatigue protocol was significantly related to higher levels of IL-2R, MCP-1, MIP-1α and MIP-1β (see Table 4). Since MCP-1 correlated with all muscle contractility outcomes we also analysed whether these relationships remained significant in each group separately. For the community-dwelling controls post-fatigue TF, RFD and RFR remained significantly related with MCP-1 ($r = -0.61$, $p = 0.003$, $r = -0.58$, $p = 0.006$, $r = -0.54$, $p = 0.12$ respectively); in the geriatric patients only the decrease in muscle activity during the fatigue protocol was significantly related to higher levels of MCP-1 ($r = -0.72$, $p = 0.008$).

4. Discussion

In this study we explored the involvement of central and peripheral neuromuscular factors of muscle fatigability during a fatigue protocol in hospitalised geriatric patients with acute inflammation compared with community-dwelling older controls.

We hypothesized that geriatric patients would show an impaired ability to voluntarily activate their muscles, due to the ongoing inflammation. Our expectation was based on one of our earlier studies showing that muscle fatigability was significantly improved after a relatively short period of anti-inflammatory treatment in hospitalised geriatric patients with acute infection (Beyer et al., 2011; Mets et al., 2004). From that study, we assumed that muscle fatigability was mainly driven by a deficit in central activation rather than by local muscular impairments. However, contrary to our hypothesis, current results indicate that geriatric patients showed a somewhat lower, but not statistically different, VA compared to older controls (mean difference −14%, $p > 0.05$). It must, however, be noted that the older controls were unable to achieve complete VA (77 ± 14%) in pre-fatigue condition. This is in line with previously described age-related impairments in VA, ranging from 5% to 20% (Clark and Manini, 2012; Clark et al., 2015; Klass et al., 2007; Manini and Clark, 2012; Shield and Zhou, 2004). At the end of the fatigue protocol, VA further decreased and reached a similar level in both geriatric patients and older controls (49 ± 18% and 50 ± 27% respectively, $p > 0.05$). Since in pre-fatigue, VA was slightly higher in the control group, this fatigue-induced decrease was statistically significant in the controls, but not in the geriatric patients. Our results indicate that

Table 4
Correlation coefficients between circulating markers of inflammation and voluntary activation level, muscle electrical and contractile properties.

Parameter		IL-1RA	IL-2R	IL-4	IL-6	IL-8	IL-10	IL-12	IFN-γ	MCP-1	MIP-1α	MIP-1β	RANTES	Eotaxin	MIG	IP-10
VA	Pre-fatigue	−0.02	0.06	−0.07	−0.13	−0.15	**−0.47***	0.14	−0.38§	0.01	−0.17	−0.33	0.14	0.04	0.02	0.22
	Fatigue	−0.06	0.02	0.10	−0.17	−0.09	−0.15	−0.04	0.20	−0.18	−0.21	−0.19	0.18	0.02	−0.08	−0.06
M-wave	Pre-fatigue	−0.28	−0.20	0.08	−0.23	−0.02	−0.12	−0.34	0.10	−0.14	0.04	0.02	−0.13	0.01	−0.20	−0.28
amplitude	Fatigue	−0.32	−0.20	0.04	−0.12	−0.06	0.05	**−0.40***	−0.20	−0.09	0.05	0.02	−0.21	−0.02	−0.25	−0.26
Twitch force	Pre-fatigue	**−0.54†**	**−0.40***	−0.15	−0.23	−0.30	**−0.46***	**−0.51†**	−0.07	**−0.59†**	**−0.39***	**−0.51†**	−0.31	−0.32	**−0.53†**	−0.37§
	Fatigue	**−0.41***	−0.22	−0.13	0.02	−0.13	−0.12	**−0.44***	−0.01	**−0.54†**	−0.13	−0.36	**−0.38***	**−0.39***	−0.20	-0.38§
RFD	Pre-fatigue	**−0.41***	−0.22	−0.12	−0.07	−0.23	−0.35	−0.32	−0.30	**−0.46***	−0.20	−0.36	−0.15	−0.19	−0.31	−0.30
	Fatigue	−0.38§	−0.14	−0.07	−0.10	−0.10	−0.01	**−0.39***	0.09	**−0.45***	0.05	−0.28	−0.31	−0.34	−0.08	**-0.43***
RFR	Pre-fatigue	**−0.39***	−0.30	0.01	−0.22	−0.31	−0.37§	−0.36	0.02	**−0.50†**	−0.27	**−0.39***	−0.21	−0.22	**−0.39***	−0.34
	Fatigue	−0.37§	−0.24	−0.05	−0.08	−0.16	−0.12	−0.38§	0.10	**−0.47***	−0.08	−0.25	−0.27	−0.35	−0.16	**−0.44***
Δ sEMG pre-fatigue/fatigue		−0.34	**−0.45***	−0.15	−0.37§	−0.36	−0.21	−0.32	−0.03	**−0.46***	**−0.41***	**−0.56†**	0.01	−0.20	−0.23	−0.28

Data represent partial correlation coefficients corrected for age; in order to meet criteria for parametric testing cytokine data were log(10)-transformed; pre-fatigue = before the start of the fatigue protocol; fatigue = at the end of the fatigue protocol (i.e. when strength dropped to 50% of its maximum); VA = voluntary muscle activation; RFD = rate of force development; RFR = rate of force relaxation from maximum to 50%; Δ sEMG pre-fatigue/fatigue = change in muscle activity from pre-fatigue to fatigue; IL = interleukin; IL-1RA = IL-1 receptor antagonist; IFN = interferon; IL-2R = IL-2 receptor; IP-10 = interferon γ-inducible protein 10; MCP = monocyte chemoattractant protein; MIG = monokine induced by interferon gamma; MIP = macrophage inflammatory protein; RANTES = Regulated up-on Activation Normal T-cell Expressed and Secreted. Significant coefficients are presented in bold.

* $p < 0.05$.

† $p < 0.01$.

§ $0.06 > p > 0.05$.

sustained isometric MVC induced similar central fatigue in both the geriatric patients and the controls (around 50%) at the end of the fatigue protocol. It cannot be excluded, however, that the relatively high variance for VA might have induced a type-2 error. However, in absence of significant relationships between VA and circulating markers of inflammation (except a negative correlation at pre-fatigue with IL-10), it is unlikely that the inflammatory status was the main influencing factor for central fatigue in the geriatric patients. Most probably, other factors located at supra-spinal (i.e. the drive of the motor cortex to motor neurones) and spinal (i.e. mechanisms that modulate the responsiveness of motor neurones) levels are involved (for a detailed review of these mechanisms see refs (Gandevia, 2001; Taylor et al., 2016; Taylor and Gandevia, 2008).

The geriatric patients showed a significant decrease in muscle activity during the fatigue protocol, which was not observed in the older controls. Moreover, the change in muscle activity from pre-fatigue to fatigue level was significantly different between both groups (repeated measures ANCOVA corrected for age $p = 0.014$). Likewise, the decrease in muscle activity during the fatigue protocol was significantly related to higher levels of several circulating markers of inflammation (IL-2R, MCP-1, MIP-1α and MIP-1β). Previously, higher levels of IL-2R have been shown to be related to higher loss of muscle strength in postmenopausal women (Rolland et al., 2007).

In our study, we also found indications for the involvement of impaired muscle excitability and contractility in the occurrence of muscle fatigability after a sustained MVC. In fact, TF and RFR showed an overall significant decrease, whereas there was no change in M-wave amplitude. The M-wave amplitude reflects electrical transmission at the neuromuscular junction and excitability of the muscle fiber membrane, i.e. the Na^+-K^+ pump mechanism (Kent-Braun et al., 2012). We found no significant decline in M-wave amplitude following the fatigue protocol neither for both groups together, nor for the hospitalised patients separately. However, in the older controls the decline was statistically significant ($p < 0.05$). A decrease in twitch force induced by fatigue, without a change in the M-wave amplitude may indicate a failure of the excitation-contraction coupling (ECC) (Kent-Braun et al., 2012), suggesting that ECC failure may be responsible for part of the loss of force. However, and although the reduction in VA during the fatiguing task did not change significantly between the two groups, we cannot rule out that VA contributed to a slightly greater part in the drop in MVC force in the older controls compared to the geriatric patients. It must be noted that in pre-fatigue condition, the hospitalised patients showed already a lower twitch force (5.8 ± 2.2 N) than the controls (9.9 ± 4.3 N), even if this difference was not statistically significant ($p = 0.075$). Moreover, twitch force in the controls dropped following the fatigue protocol to levels that are comparable to pre-fatigue values in the patients (5.2 ± 3.5 N), which might be an indication that ECC was already altered in the hospitalised patients before starting the fatigue protocol. The lack of statistical significance in pre-fatigue twitch force between the patients and the controls might have been due to a type-2 error and additional studies are needed to confirm our results. The finding that the decline in M-wave showed no significant difference between both groups suggests that the decline in neuromuscular propagation in geriatric patients and older controls is not influenced by inflammatory processes. In addition, no significant relation was found between M-wave amplitude and serum levels of cytokines (except for IL-12 at the end of the fatigue protocol).

The force response to a single electrical stimulation (muscle twitch) was measured to quantify the contractile properties of the muscle. Twitch force was measured at rest, after the MVC (pre-fatigue) and when strength had dropped to 50% of its maximum (post-fatigue). This measure together with RFD reflects changes due to alterations in ECC mechanisms and metabolic processes within the muscle. These metabolic processes among others are associated with the production of inorganic phosphate (P_i) and hydrogen (H^+) ions and ATP hydrolysis. Fatigue-induced increases in P_i and H^+ decrease isometric force due to a reduced transition from the weak- to strong binding state of the actin-myosin cross-bridge cycle (Kent-Braun et al., 2012; Linari et al., 2010) and reduced Ca^{2+} sensitivity in the sarcoplasmic reticulum. The adenosine triphosphate (ATP) hydrolysis during contraction, causing adenosine diphosphate (ADP) accumulation, is thought to rather limit cross-bridge cycle speed (Kent-Braun et al., 2012). Another important metabolic factor is the production of mitochondrial reactive oxygen species (ROS) responsible for tissue degeneration, especially affecting skeletal muscle (Supinski and Callahan, 2007). The Ca^{2+} release channels of the sarcoplasmic reticulum are one of the targets for oxidative damage, thus influencing Ca^{2+} release and force generation capacity. ROS also activates the caspase/calpain pathway. These enzymes have been shown to alter contractile proteins as part of the inflammation-induced catabolic processes, causing myofilament degradation (Powers et al., 2007; Saini et al., 2009; Supinski et al., 2009). Our study shows a significant correlation between the electrically-induced force and different circulating markers of inflammation in pre-fatigue as well as in post-fatigue condition. This observation suggests that muscle force generating capacity is likely affected by local processes influenced by the ongoing inflammation. Geriatric patients seemed to show slower contractile- and relaxation speed in pre-fatigue condition compared to the older controls, but this difference was not statistically significant. The fact that RFR decreased significantly following the fatigue test strengthens the hypothesis that local metabolic processes are involved in the occurrence of muscle fatigue in our participants. Although slower muscle contraction and relaxation were significantly related to higher levels of several inflammatory markers, we found no statistically significant differences between hospitalised patients and controls. However, it must be noted that for RFD the values of the controls at the end of the fatigue test (68.8 ± 56.9 N/s) were significantly decreased compared to pre-fatigue condition, and comparable to those of the hospitalised patients at pre-fatigue (69.4 ± 32.0 N/s) in whom no significant change was observed. The correlation between MCP-1 and voluntary muscle activation, muscle electrical and contractile properties also were analysed for groups separately. The results show a significant relation between higher level of MCP-1 and lower post-fatigue contractile muscle properties in community-dwelling elderly. This finding is confirmed by previous studies (Bautmans et al., 2007; Bautmans et al., 2008) pointing out the importance of muscle fatigue, probably more than muscle force, in the presence of the chronic low-grade inflammation profile in elderly persons. In the geriatric patients higher levels of MCP-1 correlated significantly with decrease in muscle activity from pre-fatigue to fatigue, suggesting the involvement of this cytokine in acute inflammation-induced loss of strength, confirmed by Beyer et al. (2012a).

The strength of our study is the evaluation of muscle fatigability with simultaneous sEMG monitoring and the use of the twitch interpolation technique in frail, acutely ill and hospitalised geriatric patients. It must be mentioned that this patient population was not often tested by electrophysiological methods, previous studies focusing mainly on muscle performance. Our study, therefore, provides unique data in these geriatric patients, on muscle weakness and fatigability, a condition that is often neglected in clinical decision making. Another strength is the large number of inflammatory markers that were used, allowing to detect the cyto-/chemokines related to muscle fatigue in these patients. However, our study has also some limitations. Unfortunately, the levels of several inflammatory biomarkers were below the detection limit. Since our experimental protocol was challenging for ill geriatric patients with poor mobility, the sample size was relatively low, which might have influenced the statistical power of our analyses. In this context, some fatigue-induced changes in VA, M-wave amplitude and RFD were found in the old controls separately, despite non-significant overall ANCOVA analysis; consequently, these results must be interpreted carefully. It must be noted that there is also a difference in the number and age (although used as covariate in the statistical analyses) of subjects in the two groups and the proportion between female and

male subjects. However, no significant sex interactions were found with the difference in changes in TF ($F = 0.395$, $p = 0.535$), RFD ($F = 0.806$, $p = 0.378$) and RFR ($F = 0.132$, $p = 0.719$) between patients and controls during the fatigue protocol. Therefore, splitting the analyses for sex is not to be considered; especially given the relatively small sample size in our study. The absence of sex-based interaction is in line with previous studies of our research group in which also no interaction with sex was found for (changes in) muscle fatigue and/or performance in hospitalised patients with inflammation (Bautmans et al., 2005; Beyer et al., 2012a; Mets et al., 2004). It cannot be excluded that the lack of statistically significant differences for TF and RFD might have been due to a type-2 error. However, despite the relatively low number of participants, and correction for covariates in our statistical models, we were able to demonstrate significant differences between patients and healthy controls as well as significant relationships with inflammatory biomarkers. On the other hand, multiple correlation analysis might also have induced a type 1 error; however, several relationships with MCP-1 remained significant when analysed for each group separately. Another limitation is the fact that we studied the M. Adductor Pollicis, which is a small muscle of the hand and caution is required when extrapolating our findings to other muscle groups such as muscles involved in locomotion. On the other hand, our study showed that electrophysiological experiments with ill geriatric patients are feasible and the fact that we choose for a small hand muscle implicates that also those patients who were e.g. unable to perform muscle tests on large test devices were eligible to participate in the study. It should also be noted that muscle performance – especially fatigability – can change rapidly during hospitalisation in older patients (Bautmans et al., 2005), therefore the hospitalised patients were assessed within the first 3 days after admission in order to limit bias due to resolution of the infection by the treatment. Finally, it cannot be excluded that other factors such as chronic low-grade inflammation - already existing before admission of the hospitalised patients - might have influenced our results.

5. Conclusions

Overall, the results of our study indicate that geriatric patients with acute infection show substantially altered muscle activity and support the hypothesis that local processes are involved. Contrary to our initial hypothesis, we found less evidence of the involvement of voluntary activation deficit in geriatric patients with acute inflammation. Our previous work showed that NSAID treatment significantly improves muscle fatigability in hospitalised geriatric patients with acute infection (Beyer et al., 2011; Mets et al., 2004), but in these studies we did not assess electrophysiological outcomes. Future studies should confirm our findings and explore whether these inflammation-related muscle impairments can be reversed by anti-inflammatory treatment.

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CHAPTER 4

Exercise and muscle activation

Relevance of resistance training in ageing, inflammation & muscle weakness

Arnold P, Bautmans I. The influence of strength training on muscle activation in elderly persons: A systematic review and meta-analysis. Exp Gerontol 2014; 58: 58–68 (IF_{2015} 3.485, Q1)

Update literature search, clinical implications & conclusion

Relevance of resistance training in ageing, inflammation & muscle weakness

The relative risk of poor physical performance, functional limitation or physical disability in older adults with low muscle strength (dynapenia) or muscle mass (sarcopenia) has been reported as 2.20 (95%CI 1.50-3.10) and 1.37 (95%CI 0.87-2.00) respectively (Manini and Clark 2012). Thus the risk for older adults with low muscle strength to become functional limitated is more than two fold higher than for older people with high muscle strength.

Strength gains must be attributed to muscle hypertrophy as well as neuromuscular adaptations. Narici et al. have been reporting strength gains due to resistance training up to 37% in a population of the oldest old (85-97 yrs) related to a change in the cross sectional area of 10% (Narici and others 2004). In a meta-analysis of Stewart et al. training adaptations in elderly aged >75 years of + 1.5% - 15.6% increase in muscle size are reported due to hypertrophy (Stewart and others 2014). A recent meta-analysis (Peterson and others 2010) has shown the efficacy of high intensity resistance training (RT) as prevention or treatment strategy for age-related loss of muscle strength. For example the pooled estimate of mean strength change for leg press from baseline to postintervention, combining data from 51 treatment cohorts, was 31.63 kg (95% CI, 27.59-35.67 kg) ($p < 0.001$) (Peterson and others 2010).

The relationship between the intensity of training and strength improvement has also been systematically reviewed. Borde et al. (Borde and others 2015) confirmed the effectiveness of resistance training on upper and lower extremity muscle strength in healthy elderly. They also report dose–response relationships for training variables (i.e., volume, intensity, rest). The resistance training is characterized by a high external load of 70-80% of the one-repetition maximum (1RM). However this training intensity can not always be recommended in the elderly and clinicians hesitate to prescribe the high load programs in elderly. Low intensity RT-programs also have shown efficacy in increasing muscle volume and basic strength (Van Roie and others 2013; Watanabe and others 2014). Van Roie et al. emphasize the importance of achieving maximal effort, i.e. a muscle fatigue, during training.

Recent studies have revealed the beneficial effects of physical exercise in suppressing the chronic low-grade inflammation profile (CLIP) (Beyer and others 2012; Petersen and Pedersen 2005). Contracting skeletal muscle secretes myokines (among which Interleukin (IL)-6) (Peake and others 2015; Pedersen and Fischer 2007) which have anti-inflammatory effects. RT-induced increases in IL-6 at each exercise session and its accompanying release of inflammation-reducing cytokines are believed to reduce CLIP (Forti and others 2016). This beneficial effect recently has been confirmed in a systematic review (Liberman and others 2017). The exercise-induced myokine production seems to be maintained at a higher age (Jankord and Jemiolo 2004).

While literature is consistent about the effect of resistance training to improve muscle strength in elderly, conflicting evidence consists on alterations in the central nervous sytem affecting the capacity to fully activate the muscle during maximal voluntary contraction at older age (Klass and others 2007; Manini and Clark 2012).

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The influence of strength training on muscle activation in elderly persons: A systematic review and meta-analysis

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ABSTRACT

Age-related muscle weakness is only partially related to muscle atrophy, due to neuromuscular changes including reduced voluntary muscle activation and antagonist muscle co-activation. The respective contribution of these mechanisms in exercise-induced strength gains at higher age is unclear. Here the literature was systematically reviewed for studies reporting exercise-induced effects on voluntary muscle activation and antagonist muscle co-activation in elderly persons. Seventeen relevant studies were identified, 4 investigated voluntary muscle activation, 8 antagonist muscle co-activation and 5 studies investigated both. Meta-analysis showed an exercise-induced improvement in voluntary activation in plantar flexors (weighted mean difference (WMD) +8.8%, $p < 0.001$), and knee extensors (WMD +1.8%, $p < 0.001$), with greater gains in activation capacity obtained in subjects with lower voluntary activation level prior to the onset of training. We found no significant overall effect of strength training on antagonist co-activation during ankle plantar flexion (WMD +0.6%, $p = 0.686$) or knee extension (WMD −1.1%, $p = 0.699$ for the RCT's and −1.8%, $p = 0.516$ for the non-controlled trials). Based on our results we can conclude that there is evidence for exercise-induced increase in voluntary activation related to strength gains in the lower extremities in elderly persons. The results for exercise-induced effects on antagonist co-activation are inconsistent and more research is necessary to determine its contribution to strength gains following resistance training in elderly persons.

1. Introduction

Sarcopenia, defined as the age-related loss of skeletal muscle mass and resulting in an important change in body-composition and function in elderly persons (Rosenberg, 1997), has been extensively described in the literature (Bautmans et al., 2009; Cruz-Jentoft et al., 2010; Fielding et al., 2011; Rosenberg, 2011). Due to differences in approaching sarcopenia in epidemiological studies, the reported prevalence rates vary widely (Bautmans et al., 2009). Recently, clinical criteria for diagnosing sarcopenia-related disability have been proposed (Cruz-Jentoft et al., 2010; Fielding et al., 2011), based on a combination of muscle atrophy, muscle weakness and reduced physical function. Intriguingly, age-related loss of muscle strength is only weakly associated with the reduction in muscle mass (Clark and Manini, 2008; Delmonico et al., 2009; Mitchell et al., 2012). In fact, the decrease in muscle strength is much more rapid compared to loss of muscle mass (Delmonico et al., 2009). The mechanisms explaining this age-related muscle weakness are not yet fully understood. Since sarcopenia originally refers to the age-related muscle atrophy, the term dynapenia has been proposed to describe the age-related loss of muscle strength and power (Clark and Manini, 2008, 2012). Neuromuscular mechanisms that are supposed to be involved in dynapenia are a deficit in maximal voluntary muscle activation and increased antagonist muscle co-contraction. Muscle weakness due to age-related changes in myocyte properties (e.g. muscle fibre atrophy, and Ca^{2+} dysregulation) is beyond the scope of this review and is extensively described in the recent work of Russ et al. (2012).

Age-related changes at the level of the motor cortex and the spinal cord can influence the voluntary muscle activation (Manini and Clark, 2012; Russ et al., 2012). Conflicting evidence exists on alterations in the central nervous system affecting the capacity to fully activate the muscle during maximal voluntary contraction (MVC) at older age (Klass et al., 2007; Manini and Clark, 2012). The twitch interpolation technique is commonly used to assess deficits in the ability to completely activate the skeletal muscle (Merton, 1954). During (usually an isometric) MVC, electrical stimuli are superimposed at the level of the peripheral nerve, thus stimulating the motor axons of the contracting muscle. When the force output is increased by these superimposed

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electrical stimuli, the subject's voluntary activation (the *"completeness"* of skeletal muscle activation during voluntary contraction) is considered to be sub-maximal (Shield and Zhou, 2004). In general, two methods are used to quantify voluntary activation (Shield and Zhou, 2004). One method is to compute the interpolated twitch (IT)-ratio as:

$$IT(\%) = [1-(\text{superimposed twitch}/\text{control twitch})] \times 100 \quad (1)$$

where "superimposed twitch" is the force increment noted during a maximal contraction at the time of stimulation and "control twitch" the force evoked by the same electrical stimulation in the relaxed muscle.

An alternative approach is to express MVC force as a percentage of the total force produced during superimposed stimulation (Kent-Braun and Le Blanc, 1996). This index is known as the central activation ratio (CAR), calculated as:

$$CAR = MVC/(MVC + \text{stimulated force}) \quad (2)$$

where "stimulated force" is the total force generated during the superimposed stimulation.

Another mechanism that may contribute to dynapenia in elderly persons is the co-activation of antagonist muscle(s) during agonist muscle contraction. Co-activation of the antagonist muscle might be useful for joint stabilization, but disproportional co-activation can lower the net force exerted by the agonist muscle, as well as inhibit the voluntary activation of the agonist muscle. The primary spinal coordinator of agonist–antagonist muscle activity is the disynaptic reciprocal inhibition through the Ia inhibitory interneuron (Hortobagyi and Devita, 2006). When agonist Ia afferents are activated, inhibition of the antagonist motor neurons occurs by Ia inhibitory interneurons, causing a smooth movement. A decline in reciprocal inhibition with advancing age is associated with increased antagonistic muscle activity during voluntary movement (Hortobagyi and Devita, 2006). The magnitude of co-activation of the antagonist muscle is most often approached by expressing the EMG activity of the antagonist muscle during agonist contraction, as a percentage of the maximal antagonist muscle EMG activity (i.e. during a maximal contraction) (Kellis, 1998). Studies that measured the influence of ageing on antagonist muscle co-activation during isometric and dynamic contractions have been reviewed previously (Klass et al., 2007). Co-activation appears to be higher in elderly adults during isometric contractions. During MVC's of knee extensors a difference of ~5% between old and young subjects was reported in co-activation of the m. biceps femoris (Izquierdo et al., 1999). A difference of ~20% between older and young women in co-activation of the biceps femoris during knee extension also has been reported (Macaluso and De Vito, 2004). During (isometric) MVC's of the elbow flexors and extensors, a difference in co-activation of the antagonist muscles of respectively ~5 and 8% ($p < 0.01$) was reported (Bautmans et al., 2011; Klein et al., 2001).

Strong evidence shows that resistance training is the most effective strategy to counter and prevent age-related muscle weakness (Liu and Latham, 2009; Macaluso and De Vito, 2004; Peterson et al., 2010). Important strength gains (up to >50%) have been reported, already after a relatively short period (i.e. 6–9 weeks) of strengthening exercise, even in very old persons. Given the rapid strength gains, it is widely accepted that neural adaptations are involved. To date, the respective contribution of changes in voluntary muscle activation and antagonist muscle co-activation in exercise-induced strength gains at higher age remains unclear. The purpose of this study was to review systematically the literature for studies regarding the influence of resistance training on voluntary muscle activation and antagonist muscle co-activation in elderly persons.

2. Material and methods

2.1. Literature search

Pubmed and Web of Knowledge were screened (last search on November 20, 2013) using the following keywords: *(aged [Mesh] OR aged, 80 and over[Mesh] OR frail elderly[Mesh]) AND (resistance training[Mesh] OR exercise[Mesh] OR strength training) AND (muscle, skeletal[Mesh]) AND (voluntary activation OR twitch interpolation OR co-activation OR co-contraction OR antagonist)* for PubMed and *Topic = (elderly) AND (Topic = (resistance training) OR Topic = (exercise) OR Topic = (strength training)) AND (Topic = (muscle) OR Topic = (skeletal muscle)) AND (Topic = (voluntary activation) OR Topic = (twitch interpolation) OR Topic = (co-activation) OR Topic = (co-contraction) OR Topic = (antagonist))* for Web of Knowledge. This action resulted respectively in 84 and 69 articles (Fig. 1). For these articles, titles, keywords and abstracts were screened for relevance. Studies were included if they met the following criteria: written in English, reporting training interventions in healthy subjects aged >60 years (mean age), and outcomes for muscle activation (measured with the twitch interpolation technique or electromyography) and/or calculation of antagonist muscle co-activation. Training intervention was defined as a strength training regimen using external resistance. Papers were excluded if the training intervention did not meet these criteria and if the study population had a specific impairment or medical condition. Randomised as well as semi-randomised controlled trials and non-controlled experimental studies were included. Inclusion and exclusion criteria were applied independently by two reviewers. Disagreement was resolved by discussion and consensus method. This procedure resulted in 17 relevant articles (see Fig. 1).

2.2. Quality assessment

Randomised controlled trials (RCT) investigating the effect of training interventions were assessed using the methodology checklist for RCT's from the National Institute for Health and Clinical Excellence (NICE, Appendix D, 2009). This checklist is designed to assess the internal validity of the study and contains four sections (A–D), each of which addresses a potential source of bias. It concerns selection bias (A), performance bias (B), attrition bias (C) and detection bias (D). All assessments were performed by two independent reviewers. Scores were attributed here as "yes", "no", "unclear" or "not applicable" (Table 1). Papers for which quality assessment resulted in disagreement between raters were reassessed and a consensus based final score was attributed.

2.3. Data extraction

Study populations' characteristics (gender, mean age and range or standard deviation) were identified. Although in some studies young participants were compared to old, the data concerning the older (mean age >60 years) subjects were the main focus in this review. The following data were extracted: training programme (type of exercise, duration, number and frequency of training sessions and repetitions), assessment method of outcome measure, muscle group investigated, exercise-induced changes in the level of voluntary activation and/or antagonist muscle co-activation.

2.4. Data analysis

For data of voluntary activation and antagonist co-activation obtained in (randomised) controlled studies, weighted mean differences between groups (WMD, with 95% confidence interval [95% CI]) were calculated. For data of voluntary activation and antagonist co-activation obtained in non-controlled trials, treatment mean differences (TxMD, change score pre- and post-training with 95% CI) were calculated. Analyses were conducted in OpenMeta[Analyst] software for

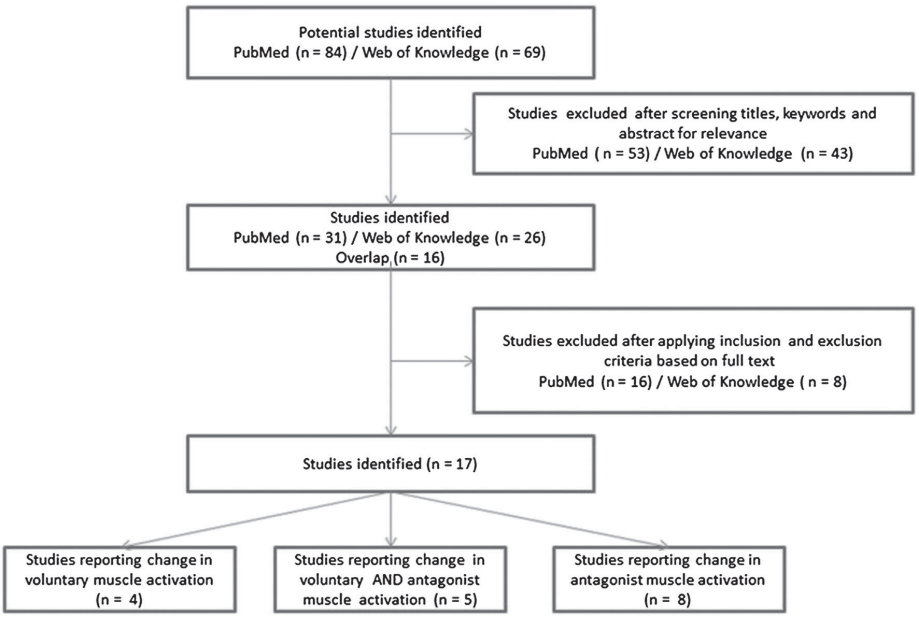

Fig. 1. Flow chart study selection.

advanced meta-analysis from Brown University Evidence Based Practice Center (Wallace et al., 2009) using the Random-Effects method and heterogeneity (τ^2) calculation according to DerSimonian and Laird (1986). Pooling was done based on subgroups according to 1) study design, 2) assessment method and 3) muscle group investigated. When standard errors were reported, these were re-calculated to standard deviation values (standard error = standard deviation multiplied by square root of the sample size). The standard deviation of the difference in change was needed to calculate the weighted mean difference. The pre- and post-intervention standard deviations were used as well as the within-participant bivariate correlation of the outcome measures in the following equation:

$$SD_{diff} = SQRT(VAR(pre) + VAR(post) - 2 * CORR(pre, post) * SD(pre) * SD(post))$$

where VAR = variance (SD^2) and CORR = within-participant bivariate correlation (estimated at 0.5 when no data were available).

Lacking data in the original publications were requested by contacting the authors of the papers. Unfortunately, some data from the experiments in the studies reported by Hakkinen et al. (experiment A [isometric unilateral] and experiment B, (Hakkinen et al., 2000) and dynamic bilateral (Hakkinen et al., 1998)) and by de Boer et al. (2007) (co-activation during dorsal flexion) could not be obtained and thus not included in the meta-analyses.

3. Results

3.1. Study characteristics

All studies had the purpose to investigate the neuromuscular pathway by which resistance training enhances muscle strength, in the lower limb muscles. Publication dates ranged from 1992 to April 2011. Within the literature published in the last 5 years, only one study was identified which met the inclusion criteria. Several studies were excluded since these investigated other types of exercise interventions

Table 1
Quality assessment randomised controlled trials.

Reference	Appropriate method of randomisation A1	Adequate concealment of allocation A2	Groups comparable at baseline A3	Groups received same care apart from the intervention(s) studied B1	Participants blind to treatment allocation B2	Individuals administering care blind to treatment allocation B3	Groups were followed up for an equal length of time C1	Participants that did not complete treatment in each group C2a
Holsgaard-Larsen et al. (2011)	+	?	+	?	-	?	+	4 (total)
LaRoche et al. (2008)	+	?	−	?	−	?	+	−
Morse et al. (2007)	+	+	?	?	−	?	+	2 (TrN)
Simoneau et al. (2007)	+	?	+	−	−	?	+	−
Simoneau et al. (2006)	+	?	+	−	−	?	+	?
Morse et al. (2005)	+	+	?	?	−	?	+	−
Reeves et al. (2005)	+	?	−	?	−	?	+	?
Reeves et al. (2004a, 2004b)	+	?	−	?	−	?	+	?

A = selection bias, B = performance bias, C = attrition bias, D = detection bias, + = Yes, − = No, ? = Unclear (not/not clearly reported), TrN = training group, N/A = not applicable.
[a] Definition of method used to quantify % muscle activation.

(tai-chi, cycling, balance training, walking) or focused on persons with specific medical conditions (central nervous system diseases such as stroke, M. Parkinson or Multiple Sclerosis) or following surgery (knee or hip arthroplasty). In nine studies, participants were randomly assigned to a training intervention or a control group. One study was a not-randomised controlled experiment and seven were non-controlled experimental studies (see Tables 2–4). Four studies investigated the change in voluntary muscle activation and eight studies reported data on changes in antagonist muscle co-activation (see Fig. 1). In five studies, both aspects were investigated.

3.2. Quality assessment of randomised controlled trials

Internal validity of the nine RCT's was assessed with the NICE methodology checklist for RCT's. For all nine studies the four sections (A–D) could be a potential source of bias (see Table 1). Unknown risk of bias is qualified to the RCT's since only five criteria were clear for all. All studies used an appropriate randomisation method and a non-blind treatment allocation. Groups were followed up for an equal length of time, outcomes (except for the study of Morse et al., 2007) were defined accurately and outcome determination was valid and reliable in all studies.

3.3. Participants

A total of 336 subjects were included in the seventeen studies, which all investigated lower extremity muscle groups. Subjects were healthy community-dwelling older and/or young volunteers, except for those included in the study of Harridge et al. ($n = 11$), who were recruited from a geriatric day-hospital and needed some assistance in Activities of Daily Living (Harridge et al., 1999). All participants were naïve for strength training and were not involved in physical training other than recreational physical activities prior to the intervention. Medication use was described in only four studies (Cannon et al., 2007; Hakkinen et al., 1998, 2000, 2001).

3.4. Training intervention

As can be seen in Tables 2–4, training volume and intensity varied among the included studies. Length of the training ranged from 6 weeks to 1 year, frequency from 2 to 3 times per week and intensity from 50% to 85% of 1 RM (Repetition Maximum, i.e. the maximal load that can be displaced in one movement). Some studies used 3 (Simoneau et al., 2006, 2007), 5 (Reeves et al., 2004a, 2004b, 2005) or 8 RM (Morse et al., 2005, 2007) to determine the exercise intensity. The number of sets per session ranged from 1 to 6, with 8 to 15 repetitions per set. The number of exercises varied from a single muscle group to a whole body approach.

3.5. Voluntary muscle activation

Five RCT's reported data about exercise-induced change in voluntary activation. Three assessed ankle muscles (Morse et al., 2005, 2007; Simoneau et al., 2006) and two investigated knee extensors (Reeves et al., 2004a, 2004b). Three non-controlled experimental studies described the effects of strength training on voluntary muscle activation in knee extensor muscles (Cannon et al., 2007; Harridge et al., 1999; Knight and Kamen, 2001) and one in plantar flexor muscles (Scaglioni et al., 2002).

3.5.1. Exercise-induced change of VA in plantar flexor muscles

Morse et al. (Table 2) showed that one year training significantly ($p < 0.05$) increased plantar flexor muscle activation from 88 ± 2% to 96 ± 4% (Morse et al., 2007). This 8% increase was significantly different from the control group ($p < 0.05$), which remained stable with values of 82 ± 7% and 81 ± 7% respectively pre- and post-one year follow-up. After correspondence with the author it was clarified that IT-ratio was used for calculating voluntary activation. In 2005, Morse et al. reported earlier data from a similar study investigating the effects of the same training intervention on voluntary activation of plantar flexor muscles (Morse et al., 2005). The pre-training muscle activation level was 84 ± 11.0%, which increased significantly after one year training to 92 ± 8%. Significant difference in change from the control group was noted ($p < 0.05$), whose mean activation level was 80 ± 13% at baseline and 79 ± 9% after 12 months follow-up. Also in this study IT-ratio was used for quantification of voluntary muscle activation. Simoneau et al. (see Table 2) found a significant increase ($p < 0.05$) in IT-ratio of plantar flexors after six month training (from 66 to 100% at baseline to 81–100% after 6 months) (Simoneau et al., 2006). The authors reported that at baseline, the mean plantar flexor muscle activation was significantly lower than 100%, but not anymore after 6 month training, suggesting a 'complete voluntary activation' after the exercise intervention. In the control group, IT-ratio remained unchanged (from 89 ± 15% at baseline to 88 ± 12% after 6 months).

Scaglioni et al. (see Table 2) in a non-controlled study, investigated the IT-ratio of plantar flexors in 14 men and found a small (4 ± 10%) but statistically significant ($p = 0.03$) within group increase from 95 ± 7% to 98 ± 2% after 16 weeks of training (Scaglioni et al., 2002).

As shown in Fig. 2, data of three RCT's could be pooled. No statistical heterogeneity was found ($I^2 = 0\%$). After 26 to 52 week resistance training, voluntary activation of plantar flexor muscles increased significantly (overall effect (WMD) = +8.8%, $p < 0.001$).

3.5.2. Exercise-induced change of VA in knee extensor muscles

Reeves et al. (see Table 2) used CAR for quantification of voluntary activation of knee extensors and reported a significant ($p < 0.05$)

Groups comparable for treatment completion	Participants in each group for whom were no outcome data available	Groups comparable with respect to the availability of outcome data	Study had an appropriate length of follow-up	Study used a precise definition of outcome	Valid and reliable method was used to determine the outcome	Investigators blind to participants exposure to intervention	Investigators blind for confounding and prognostic factors
C2b	C3a	C3b	D1	D2	D3	D4	D5
no	?	?	N/A	+	+	?	?
+	0	+	N/A	+	+	?	?
no	2 (TrN)	?	N/A	−[a]	+	?	?
+	0	+	N/A	+	+	?	?
?	?	?	N/A	+	+	?	?
+	0	+	N/A	+	+	?	?
?	?	?	N/A	+	+	?	?
?	?	?	N/A	+	+	?	?

Table 2
Change in maximal voluntary activation of plantar flexor and knee extensor muscles in response to resistance training.

Study details		Subjects			Intervention details				Outcome		
Author, year	Design	N	Age	Gender	Duration (weeks)	Intensity	Volume (series × repetitions)	Frequency (per week)	Muscle-group	Measurement	Change in voluntary activation (%) WMD[a] or TxMD[b] [95%CI]
Morse et al. (2007)	RCT	TrN: 13 CTR: 8	73 ± 3 74 ± 4	M M	52	80-100% of 8 RM	3 × 10	3	PF	IT-ratio	+8.4[a] [3.1, 13.7]
Morse et al. (2005)	RCT	TrN: 13 CTR: 8	73 ± 12 74 ± 5	M M	52	80–100% of 8 RM	3 × 10	3	PF	IT-ratio	+9.4[a] [−0.2, 19.0]
Simoneau et al. (2006)	RCT	TrN: 11 CTR: 9	78 ± 3 76 ± 3	6F/5M 4F/5M	26	55–75% of 3 RM	3 × 10	3	PF	IT-ratio	+9.6[a] [−1.4, 20.5]
Scaglioni et al. (2002)	NCET	TrN: 14	68 (65–80)	M	16	50%–80% of 1 RM	2 × 10	3	PF	IT-ratio	+2.9[b] [0.04, 5.8]
Reeves et al. (2004a, 2004b)	RCT	TrN: 9 CTR: 9	74 ± 4 67 ± 2	5F/4M 5F/4M	14	60–80% of 5 RM	2 × 10−15	3	KE	CAR	+7[a] [−3.6, 17.6]
Harridge et al. (1999)	NCET	TrN: 11	85–97	8F/3M	12	50–80% of 1 RM	3 × 10	3	KE	IT-ratio	+3[b] [−2.3, 8.3]
Cannon et al. (2007)	NCET	TrN: 8	70 ± 7	F	10	50–75% of 1 RM	3 × 10	3	KE	IT-ratio	+2.1[b] [1.3, 2.9]
Knight and Kamen (2001)	NCET	TrN: 7	67–81	1F/6M	6	85% of 1 RM	3 × 10	3	KE	CAR	+1.3[b] [0.2, 2.5]

Values for age represent mean + SD or range, RCT = randomised controlled trial, NCET = non-controlled experimental trial, TrN = training group, CTR = control group (i.e. no exercise intervention), F = female, M = male, RM = repetition maximum, PF = plantar flexors, IT-ratio = interpolation twitch ratio, WMD = weighted mean difference (intervention versus control), TxMD = treatment mean difference (intervention group only).

increase of 5% after 14 week training. In the control group a non-significant decrease of 2% was seen (Reeves et al., 2004a, 2004b). Harridge et al. (see Table 2) investigated 11 very old (>85) individuals (Harridge et al., 1999). A twelve week resistance training programme failed to increase voluntary activation of the knee extensors. The IT-ratio was used for quantification. Cannon et al. (see Table 2) failed to demonstrate a significant increase in IT-ratio of the knee extensors after a 10 week training programme in elderly women (+2 ± 1%) (Cannon et al., 2007). However, it must be noted that baseline IT-ratio values were already very high (96 ± 2% in the old participants).

Knight and Kamen (see Table 2) compared the effects of 6 week training in a group of old individuals (Knight and Kamen, 2001). They reported a significant ($p < 0.01$) increase of 1.7% in voluntary activation of the knee extensors. The central activation ratio (CAR) was used for quantification.

Data of three non-controlled experimental trials could be pooled. No significant statistical heterogeneity was found ($I^2 = 0$, see Fig. 3). Subgroup analysis was stratified by measurement method (IT-ratio or CAR). A significant overall improvement of voluntary activation in knee extensors following 6 to 12 week resistance training was found (overall effect (WMD) = +1.8%, $p < 0.001$).

3.6. Antagonist muscle co-activation

Nine RCT's (Holsgaard-Larsen et al., 2011; LaRoche et al., 2008; Morse et al., 2005, 2007; Reeves et al., 2004a, 2004b, 2005; Simoneau et al., 2006, 2007), one non-randomised controlled trial (de Boer et al., 2007) and three non-controlled experimental studies (Hakkinen et al., 1998, 2000, 2001) reported data on exercise-induced changes of antagonist muscle co-activation.

3.6.1. Exercise-induced change in antagonist co-activation during plantar flexion

As shown in Table 3, Morse et al. found no significant change in antagonist muscle co-activation during plantar flexor MVC after 52 week strength training (whole body approach including leg press and 'sitting calf resistance weight machines') (Morse et al., 2005, 2007). Pre-training values for the trained groups were 10 ± 3% (Morse et al., 2005) and 9 ± 3% (Morse et al., 2007), and post-training 11 ± 5% (Morse et al., 2005) and 11 ± 5% (Morse et al., 2007). The control group showed pre-training values of 10 ± 7% (Morse et al., 2005, 2007) and post-training 12 ± 10% (Morse et al., 2005, 2007). Simoneau

Table 3
Change in antagonist co-activation during plantar flexion[a] in response to resistance training of ankle plantar flexor muscles.

Study details		Subjects			Intervention details				Outcome		
Author, year	Design	Training	Age	Gender	Duration (weeks)	Intensity	Volume (series × repetitions)	Frequency (per week)	Muscle activity	Measurement (EMG)	Change in antagonist co-activation (%) WMD [CI]
Morse et al. (2007)	RCT	TrN: 13 CTR: 8	73 ± 3 74 ± 4	M M	52	80–100% of 8 RM	3 × 10	3	DF[a]	Isom aa: −20°	−1.0[−7.7, 5.7]
Morse et al. (2005)	RCT	TrN: 13 CTR: 8	73 ± 12 74 ± 5	M M	52	80–100% of 8 RM	3 × 10	3	DF[a]	Isom aa: −20°	−1.8[−8.5, 4.9]
Simoneau et al. (2007)	RCT	TrN: 12 CTR: 11	79 ± 3 76 ± 4	7F/5M 5F/6M	52	55–75% of 3 RM	3 × 10	3	DF[a]	Isom aa: 90°	+0.8[−3.3, 4.8]
de Boer et al. (2007)	NRCT	TrN: 12 CTR: 8	74 ± 3 74 ± 4	F F	52	80–100% of 8 RM	3 × 10	3	DF[a]	Isom aa: −20°–30°	+5.9[−14.1, 25.9]
Simoneau et al. (2006)	RCT	TrN: 11 CTR: 9	78 ± 3 76 ± 3	6F/5M 4F/5M	26	55–75% of 3 RM	3 × 10	3	DF[a]	Isom aa: 90°	+11.3[−0.8, 23.3]

Values for age represent mean + SD. NRCT = non-randomised controlled trial, TrN = training group, CTR = control group (i.e. no exercise intervention), F = female, M = male, RM = repetition maximum, DF = dorsal flexors, EMG = electromyography, Isom = isometric contraction, aa = ankle angle (−20° = foot in dorsal flexion, 90° = the footplate of the dynamometer perpendicular to the tibia, −20°–30° = 6 different angles −20°, −10°, 0°, 10°, 20°, 30°), WMD = weighted mean difference, CI = 95% confidence interval.

Table 4
Change in antagonist co-activation during knee extension or stair ascent in response of resistance training.

Study details		Subjects			Intervention details (strength training)				Outcome		
Author, year	Design	N	Age	Gender	Duration (weeks)	Intensity	Volume (series × repetitions)	Frequency (per week)	Muscle activity	Measurement (EMG)	Change in antagonist co-activation (%) WMD[a] or TxMD[b] [95%CI]
Reeves et al. (2005)	RCT	TrN: 9 CTR: 9	74 ± 4 67 + 2	5F/4M 5F/4M	14	60–80% of 5 RM	2 × 10–15	3	KF	Isom ka: 90°–10°	−1[a][−24.9, 22.7]
Reeves et al. (2004a)	RCT	TrN: 9 CTR: 9	74 ± 4 67 + 2	5F/4M 5F/4M	14	60–80% of 5 RM	2 × 10–15	3	KF	Isom ka: 90°–10°	−2[a][−26.5, 22.5]
Reeves et al. (2004b)	RCT	TrN: 9 CTR: 9	74 ± 4 67 + 2	5F/4M 5F/4M	14	60–80% of 5 RM	2 × 10−15	3	KF	Isom ka: 90°–10°	−0.4[a][−26.7, 25.0]
Holsgaard-Larsen et al. (2011)	RCT	TrN: 12 CTR: 11	70 ± 3 70 ± 3	F F	12	75–80% 1 RM	3 × 8–10	2	KF + KE (stair ascent)	Ascending stair at freely chosen velocity	5.7[a][−3.7, 15.1]
LaRoche et al. (2008)	RCT	TrN: 12 CTR: 12	71 ± 6 74 + 5	F F	8	Isokinetic: LV/HL + HV/LL	3 × 8	3	KF	Isom ka: 105°	−6.4[a][−14.7, 1.8]
Hakkinen et al. (2000)	NCET	TrN: 10 TrN: 7	62–77 63–68	5M/5F 3M/4F	A: 24–3 (de-training)–21 B: 24–24 (de-training)	50–80% of 1 RM	4–6 × 6–12 3 × 10–15	2	KF	Dyn/bilat ka: 70°–180° Isom/unilat ka: 90°	A: −9[b][−28.9, 10.9] B: no change A: no change B: no change
Hakkinen et al. (2001)	NCET	TrN: 11 TrN: 10	72 ± 3 67 ± 3	M F	26	50–80% of 1 RM	3 × 10–15	2	KF	Dyn/bilat ka: 70°–160° Isom/unilat ka: 107°	M: 2[b][−9.9, 13.8] F: −7[b][−28.6, 14.6] M: 5[b][−6.0, 16.0] F: −10[b][−29.1, 9.1]
Hakkinen et al. (1998)	NCET	TrN: 11 TrN: 10	72 ± 3 67 ± 3	M F	26	50–80% of 1 RM	3 × 10–15	2	KF	Dyn/bilat ka: 70°–180° Isom/unilat ka: 90°	Sign. change/no data M: −3[b][−14.8, 8.8] F: −7[b][−22.3, 8.3]

Values for age represent mean ± SD or range, NCET = non-controlled experimental trial, TrN = training group, CTR = control group (i.e. no exercise intervention), F = female, M = male, RM = repetition maximum, LV = low velocity, HV = high velocity, HL = high load, LL = low load, KF = knee flexors, KE = knee extensors, EMG = electromyogram, Isom = isometric contraction, ka = knee angle, Dyn = dynamic concentric contraction, bilat = bilateral, unilat = unilateral, ka = knee angle, WMD = weighted mean difference, TxMD = treatment mean difference, CI = 95% confidence interval.

et al. (see Table 3) reported in 2006 data after 6 month training and in 2007 after 1 year training intervention for the same study population (Simoneau et al., 2006, 2007). A significant increase of ~12% in antagonist muscle co-activation during isometric plantar flexor MVC was found after the first six months, which fell back to baseline levels after the next six months of training. In the control group no significant changes were observed for any of the antagonist co-activation parameters during the whole study period. In a not-randomised controlled study, de Boer et al. found a significant increase of 7% in the tibialis anterior muscle co-activation during isometric plantar flexor MVC after 12 month training (from 12 ± 8% to 19 ± 11%) (de Boer et al., 2007) (see Table 3). During isometric dorsal flexor MVC, training resulted in a decreased (−4%, $p < 0.01$) co-activation of the gastrocnemius lateralis muscle, but not of the gastrocnemius medialis muscle (−2%, $p > 0.05$). No significant changes were found in the control group.

Data of four RCT's and one non-randomised controlled study investigating dorsal flexor activity during plantar flexion could be pooled. After 26 to 52 week strength training no significant overall effect on antagonist co-activation during ankle plantar flexion was found (WMD = +0.6% [−2.3, 3.6], $p = 0.686$). No significant statistical heterogeneity was found ($I^2 = 0$, see Fig. 4).

3.6.2. Exercise-induced change in antagonist co-activation during knee extension

As can be seen in Table 4, Reeves et al. found no change in antagonist muscle co-activation during isometric knee extension MVC after neither 14 weeks of training nor in the control group (Reeves et al., 2004a, 2004b, 2005). Also Holsgaard-Larsen et al. (see Table 4) found no significant change in knee extensor and flexor co-activation during freely chosen velocity stair-ascent in elderly women after 12 week (24 sessions) explosive isokinetic strength training of the lower limb muscles (Holsgaard-Larsen et al., 2011). On the contrary, LaRoche et al. (see Table 4) found a significant decrease (−6%, $p < 0.02$) of antagonist (knee flexors) co-activation during isometric knee extension in the training group (8 weeks of explosive isokinetic resistance training of knee extensors and flexors) compared with a control group (LaRoche et al., 2008).

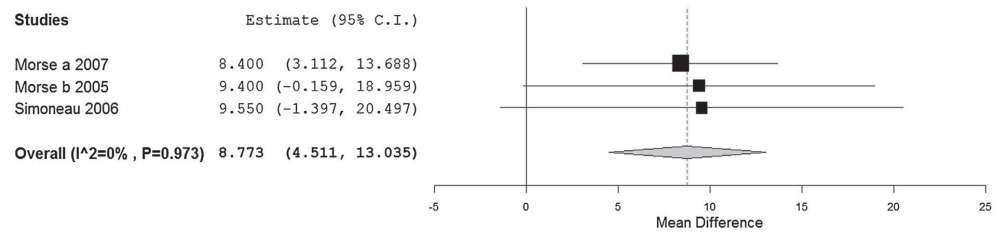

Fig. 2. Forest plot of three RCT's studying the effect of strength training on voluntary activation of plantar flexor muscles as measured by IT-ratio. Voluntary activation increased significantly following resistance training with an overall effect (WMD) of +8.773% ($p < 0.001$). I^2 = % heterogeneity and corresponding p-value.

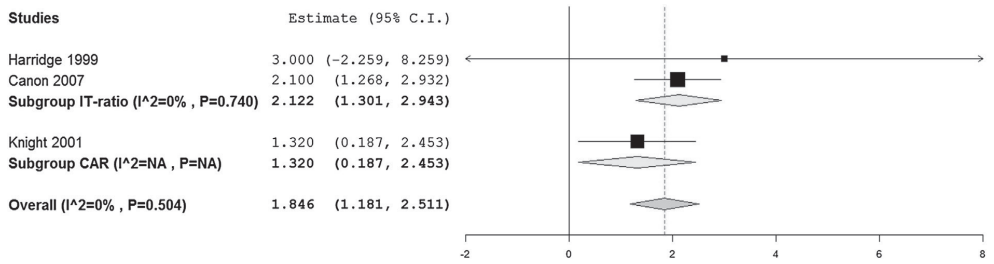

Fig. 3. Forest plot of three non-controlled studies investigating the effect of strength training on voluntary activation of knee extensor muscles measured by either IT-ratio or CAR. Voluntary activation increased significantly following resistance training with an overall effect (WMD) of +1.846%, ($p < 0.001$). I^2 = % heterogeneity and corresponding p-value.

Häkkinen et al. (see Table 4) investigated co-activation of the biceps femoris muscle during knee extensor MVC following different training protocols (Hakkinen et al., 2000). Experiment A (24 week training/3 week detraining/21 week re-training) and experiment B (24 week training/24 week detraining) were applied to two groups of middle aged and old subjects. In experiment A the biceps femoris co-activation during *unilateral isometric leg extension* decreased slightly but not significantly in both age groups, and no change was seen in experiment B. Biceps femoris muscle co-activation during *bilateral dynamic knee extension* decreased significantly in the older group (from 41 ± 11% to 32 ± 9%, $p < 0.05$) after the first 8 weeks in experiment A with no further changes thereafter; no other significant changes were observed in any of the experiments. Häkkinen et al. also investigated four different groups, based on sex and age, which were all assessed after a 1-month control period, followed by 6 month resistance training (Hakkinen et al., 1998, 2001) (see Table 4). The biceps femoris muscle co-activation during *dynamic knee extension* remained unaltered in all groups (Hakkinen et al., 2001), although in their previous paper (Hakkinen et al., 1998) a significant decrease ($p < 0.05$) was reported for the older women after training. No training-induced changes were reported for biceps femoris muscle co-activation during *isometric knee extension*, except for the right leg in old female (pre = 42 ± 34%, post = 32 ± 26%, $p < 0.05$ (Hakkinen et al., 2001); in their previous paper (Hakkinen et al., 1998) reported as pre = 31 ± 9%, post = 24 ± 4%, $p < 0.05$) and the left leg in old male ((Hakkinen et al., 1998): pre = 24 ± 6%, post = 21 ± 6%, $p < 0.05$). No significant changes for any of the antagonist co-activation parameters were observed after the 1-month control period.

Data of five RCT's could be pooled. A subgroup analysis was done based on testing method, i.e. isometric or dynamic (ascending stair at free chosen velocity). No significant overall effect of resistance training on antagonist co-activation was found (overall effect (WMD) = −1.121%, $p = 0.699$). Meta-analysis on the available data from the studies of Häkkinen et al. also showed no significant overall effect on antagonist co-activation (of knee flexors) during knee extension following resistance training (overall effect (TxMD) = −1.791%, $p = 0.516$). No significant statistical heterogeneity was found ($I^2 = 0$, see Figs. 5–6).

3.7. Relationship between training-induced neuromuscular adaptations and strength gains

As shown in Table 5 all studies reported significant strength gains following resistance training. In only two out of the seventeen studies the relationship between neuromuscular adaptations and training induced strength gains was reported. Simoneau et al. found a significant positive correlation between the training-induced gains in plantar flexor MVC torque and the gains in *voluntary activation* capacity ($r = 0.63$, $p = 0.05$) (Simoneau et al., 2006). Also, a lower baseline value of voluntary activation level was related with a greater gain in activation capacity ($r = -0.81$, $p = 0.006$) and gain in MVC torque ($r = -0.69$, $p = 0.027$). Scaglioni et al. also found a negative correlation ($r = -0.81$, $p < 0.001$) between baseline *voluntary activation* and the training effect, i.e. a greater deficit of voluntary activation at baseline is related to a higher increase after training (Scaglioni et al., 2002). Harridge et al. found, although no overall gain in voluntary activation was seen in the eleven (very old) subjects after the training period, a correlation of $r = 0.92$ ($p < 0.005$) between change in *voluntary activation* and change in MVC of knee extensors (Harridge et al., 1999).

4. Discussion

The purpose of this study was to review systematically the literature for studies regarding the influence of resistance training on voluntary muscle activation and antagonist muscle co-activation in elderly persons. We found evidence for training-induced neuromuscular adaptations in relation to strength gains following resistance training in elderly persons. Exercise-induced increase in voluntary activation of plantar flexor muscles was found in three RCT's (Morse et al., 2005, 2007; Simoneau et al., 2006) and in one non-controlled experimental

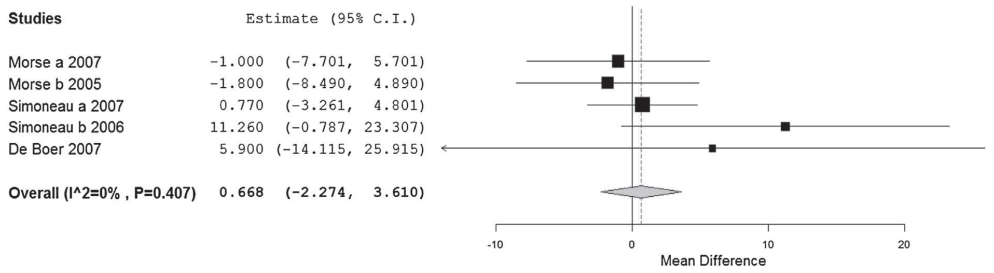

Fig. 4. Forest plot of four RCT's and one non-randomised controlled trial studying the effect of strength training on antagonist co-activation (of ankle dorsal flexors) during isometric plantar flexion MVC as measured by sEMG. Antagonist co-activation showed no significant overall change following resistance training (overall effect (WMD) = +0.668%, $p = 0.656$). I^2 = % heterogeneity and corresponding p-value.

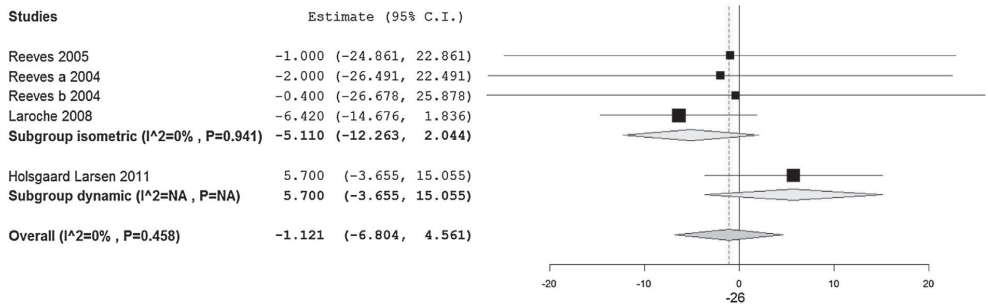

Fig. 5. Forest plot of five RCT's investigating the effect of strength training on antagonist co-activation (of knee flexor muscles) during knee extension, as measured by either isometric or dynamic contractions. No significant overall effect of resistance training on antagonist co-activation was found (overall effect (WMD) = −1.121%, p = 0.699). I^2 = % heterogeneity and corresponding p-value.

study (Scaglioni et al., 2002). The pooled effect estimate (+8.8% [4.5, 13.0], p < 0.001) may be interpreted as clinically relevant. Two RCT's (Reeves et al., 2004a, 2004b) and after pooling, three non-controlled studies, reported similar effects for the knee extensor muscles (Cannon et al., 2007; Harridge et al., 1999; Knight and Kamen, 2001). Based on these results we can conclude that voluntary muscle activation in ankle plantar flexors and knee extensors can be improved by strength training in elderly persons. The direct relationship between training-induced improvement in muscle activation and strength gain should be confirmed by future studies, since this has been investigated and demonstrated in only two papers (1 for knee extensors and 1 for ankle plantar flexors). The pooled effect estimates for change in antagonist co-activation during plantar flexion and knee extension as a result of resistance training did not show significant changes.

Increase in firing rate of motor units (as a major factor for maximal force production) contributes to the strength gains in the early phase of resistance training (Gabriel et al., 2006). Training seems to decrease the activation threshold of fast-twitch motor units and increase their initial firing rate (Van Cutsem et al., 1998). The contribution of changes in neural drive to exercise-induced strength gains seems to decrease after 6 week training (Gabriel et al., 2006). In later phases of the resistance training the training induced increase in voluntary muscle activation in elderly persons is hypothesized to be related to the re-innervation of de-nervated muscle fibres (mainly type II, due to age-related processes) by axonal sprouting (often from type I motor-units) (Macaluso and De Vito, 2004). This adaptation results in larger motor units able to generate higher force (Moritani and deVries, 1979; Patten et al., 2001). As stated by Fling et al. (2009) the size principle of motor unit recruitment seems to be preserved in older adults, which means that at high forces the larger motor units with a slow conduction velocity, but larger number of muscle fibres, are recruited. Until about the eighth week of training, the anabolic processes in muscles are stimulated, which means that the rate of muscle protein synthesis is higher compared to the degeneration rate (Saini et al., 2009). Mid-test data points of change in voluntary activation in the studies with longer duration included in our review were not available. Therefore it stays unclear which training period, e.g. how many weeks, is necessary in order to obtain changes in voluntary activation following strength training. Factors that influence the balance between anabolism and catabolism of muscle are believed to be mediated by the actions of growth factors and cytokines (Saini et al., 2009). Complex biochemical and genetic processes also play a role in whether muscle is gained or lost and are described extensively by Saini et al. (2009). Morse et al. suggest that hypertrophy and muscle activation of plantar flexors each accounted approximately for half of the increase in muscle strength following training (Morse et al., 2005, 2007). The authors presumed that the increase in voluntary muscle activation observed in their study was due to a low level of voluntary activation capacity prior to the onset of training in the elderly who were investigated. This hypothesis was enforced by Simoneau et al. (2006) and Scaglioni et al. (2002) who found that a lower baseline value of voluntary activation level was related with a greater gain in activation capacity after training (r = −0.81, r = −0.90 [reported as r^2 = 0.82], respectively) and gain in MVC torque (r = −0.69, Simoneau et al., 2006).

The included studies investigating voluntary activation of the knee extensors all lasted less than 14 weeks. Reeves et al. (2004a, 2004b, 2005) and Knight and Kamen (2001) suggested that the observed training induced strength gains in the knee extensors were due to increased

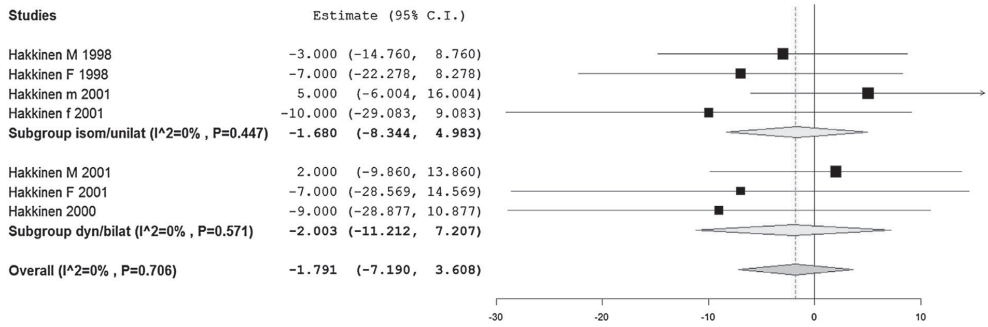

Fig. 6. Forest plot of three non-controlled experimental trials investigating the effect of strength training on antagonist co-activation (of knee flexor muscles) during either isometric/unilateral or dynamic/bilateral knee extension. M = male, F = female. No significant overall effect on antagonist co-activation (of knee flexors) during knee extension was found following resistance training (overall effect (TxMD) = −1.791%, p = 0.516). I^2 = % heterogeneity and corresponding p-value.

Table 5
Relationships between training-induced changes in muscle strength and neuromuscular adaptations.

	Exercise-induced change in muscle strength	Voluntary activation		Antagonist co-activation	
		Exercise-induced change in the training group	Relation with change in muscle strength	Exercise-induced change in the training group	Relation with change in muscle strength
Morse et al. (2007)	PF ↑	PF ↑	NR	DF no change	NR
Morse et al. (2005)	PF ↑	PF ↑	NR	DF no change	NR
Simoneau et al. (2006)	PF & DF ↑	PF↑	PF $r = 0.63$, $p = 0.05$	–	–
Scaglioni et al. (2002)	PF ↑	PF ↑	NR	–	–
Reeves et al. (2004a, 2004b)	KE ↑	KE ↑	NR	KE no change	NR
Harridge et al. (1999)	KE ↑	KE no change	KE $r = 0.92$, $p < 0.005$	–	–
Cannon et al. (2007)	KE ↑	KE no change	NR	–	–
Knight and Kamen (2001)	KE ↑	KE ↑	NR	–	–
Simoneau et al. (2007)	PF & DF ↑	–	–	First 6 months: DF ↓, PF↑ Second 6 months: PF↓, DF no change	NR
de Boer et al. (2007)	PF↑, DF↓	–	–	DF ↓, PF ↑	NR
Reeves et al. (2005)	KE ↑	–	–	KF no change	NR
LaRoche et al. (2008)	KE ↑	–	–	KF ↓	NR
Holsgaard-Larsen et al. (2011)	KE & KF ↑	–	–	KE & KF no change	NR
Hakkinen et al. (2000)	KE ↑	–	–	Isometric KF: no change Dynamic KF ↓ (in older group)	NR
Hakkinen et al. (1998, 2001)	KE ↑	–	–	Isometric & dynamic KF ↓ (in older subjects)	NR

NR = not reported, ↑ = significant increase (within group effect as reported in the original papers), ↓ = significant decrease (within group as reported in the original papers), KE = knee extensors (for antagonist co-activation: during knee extensor contraction), KF = knee flexors (for antagonist co-activation: during knee extensor contraction), PF = plantar flexors (for antagonist co-activation: during plantar flexion contraction), DF = dorsal flexors (for antagonist co-activation: during dorsal flexor contraction).

neural drive, i.e. increased motor unit recruitment and/or increased firing rate, of the agonist muscles, although only small changes were found in voluntary activation of knee extensor muscles. Cannon et al. suggested that the inability to find a significant change may be due to methodological issues rather than a lack of neural adaptation (Cannon et al., 2007). The interpolated twitch technique was possibly insensitive to detect the small neural adaptation, since the subjects under investigation were capable of achieving the near-complete (~95%) muscle activation before training. A significant increase in EMG amplitude was observed, which was interpreted by Cannon et al. as evidence for neural adaptation, i.e. increased motor unit recruitment and/or motor neuron firing rate. Also Harridge et al. found no effect of a 12 week resistance training on muscle activation of the knee extensors, despite a close relationship ($r = 0.92$; $P < 0.005$) was observed between the change in voluntary muscle activation and the change in MVC (Harridge et al., 1999). The authors' explanation for the lack of improved voluntary activation is related to the specific adaptation of muscles to the mode of training. Dynamic resistance training was employed whilst the muscle contractions during the tests of voluntary activation were isometric. This factor influencing the results in twitch interpolation studies was also confirmed in other studies and discussed in the review of Shield and Zhou (2004). Different methodological issues related to the method used to quantify voluntary activation may explain inconsistent outcomes in the included studies. Scaglioni et al. described a non-linear relationship between interpolated twitch amplitude (due to motor unit recruitment and/or firing frequency) and muscle force beyond 65% MVC, thus causing the inability of the interpolated twitch technique to detect the very small changes >65% MVC (Scaglioni et al., 2002). Also Taylor (2009) and de Haan et al. (2009) discussed this issue. The relationship between voluntary force and superimposed response seems to depend (besides other factors) on the muscle group under investigation and the type of stimulation used (single, doublets or pulse trains). Especially in the high force range, values will vary between muscle groups. Another concern is the fact that the CAR-method can be sensitive for bias. As described earlier (Eq. (2)) MVC force is expressed as a percentage of the total force produced during the superimposed evoked response. However MVC force is determined by a couple of synergists, whilst only the stimulated muscles give the force increments (Shield and Zhou, 2004). Even though maximal force results from different muscles, the superimposed twitch, if elicited by nerve stimulation, should activate all the quadriceps muscles (femoral nerve stimulation) and soleus + gastrocnemii (tibial nerve stimulation). As a matter of fact, the twitch is not reflecting a single muscle activation. In respect to the quantification method of voluntary activation level, there seems to be a consensus in the literature that the electrically evoked force added to the isometric voluntary contraction is a measure for the quality (i.e. motor unit recruitment and firing rate) of muscle activation. Given these issues, we have stratified our pooled analyses according to the method used (IT-ratio or CAR).

Most studies investigated training induced adaptations measuring maximal strength development during isometric contractions (no change in muscle length), because of difficulties measuring electrophysiological muscle parameters when movement is involved. In fact, all nine studies that investigated training induced effects on voluntary muscle activation used isometric muscle testing, whilst the training protocol involved dynamic muscle contractions. Only in one study (Knight and Kamen, 2001) also isometric training was included in the training protocol. Specificity of adaptation to the training intervention may have biased the outcomes. During dynamic (heaviest weight that can be lifted) or isokinetic (maximal torque) strength testing, the speed of movement influences the strength that can be developed (Macaluso and De Vito, 2004). The literature is not clear regarding the possible role of voluntary muscle activation deficits in strength development at very high velocities (Klass et al., 2007). Elderly people, as a consequence of the preferential atrophy of type II fibres with ageing (Lexell, 1995), usually show a limited capacity to carry out movements at high velocities.

Another mechanism contributing to strength gains by training is the spinal inhibitory pathway reflected by decrease in co-activation of the antagonist muscle. A decrease in antagonist co-activation should allow more net force production of the agonist muscle. It is well-known that increase in antagonist co-activation is important for maintaining the integrity of the joint (Baratta et al., 1988) and in elderly persons this co-activation is larger compared to young ones (Hortobagyi and Devita, 2006). Thus far, it is not clear what the central nervous system will attempt to optimise: force production or joint integrity (Gabriel et al., 2006). This might explain the variability in study results related to exercise-induced effects on antagonist co-activation in ankle plantar

flexors and knee extensors. However, the relevance of antagonist co-activation during isometric contraction – i.e. to stabilize the joint during mechanically constrained isometric contraction – may not be that relevant per se. Also a learning effect has been suggested as an explanation for the decrease in antagonist muscle co-activation after resistance training, as seen both in young and older people (Hakkinen et al., 1998). The learning effect is assumed to occur typically in the first 1–2 weeks of training, and is the result of a learning process in which the correct sequence of muscle contractions is laid down as a motor pattern in the central nervous system (Rutherford and Jones, 1986). However, Simoneau et al. (2007) attributed the fact that the initial significant increase of antagonist co-activation (during the first six months of training) decreased back to baseline levels after the second six months to a learning effect.

The contribution of the exercise-induced decrease of antagonist co-activation to strength gains remains unclear. The included studies investigating training-induced changes in antagonist co-activation of knee or ankle joint muscles report an increase as well as a decrease. The joint targeted may be a factor, as well as the type of contraction (e.g. isometric testing) during the assessments. As stated by Hortobagyi and Devita (2006) the generation of high levels of voluntary force requires the co-activation of flexors and extensors to stabilize the joint. Häkkinen et al. found that before training elderly women had significantly higher levels of co-activation than younger ones (Hakkinen et al., 1998, 2001). After training the magnitude of hamstring co-activation during knee extension was reduced, reaching levels observed in the other groups. It may be assumed that the initial higher hamstring co-activation provided increased stabilization of the leg, because of uncertainty about the movement task. Holsgaard-Larsen et al. suggested a "safety mechanism" to help ensure joint control during a motor task (such as stair climbing), which would be responsible for an elevated antagonist co-activation after training (Holsgaard-Larsen et al., 2011). Also other authors referred to the contribution of joint stability as a possible explanation as to why co-activation remains unchanged following training (de Boer et al., 2007; Morse et al., 2005; Reeves et al., 2004a, 2004b, 2005). Gabriel et al. (2006)) refer to the study of Carolan and Cafarelli (1992) who studied the effect of an 8-week training intervention of the knee-extensors on sEMG activity of the vastus lateralis and biceps femoris muscles. The study gives strong support for increased agonist muscle force (vastus lateralis muscle) due to a reduction in antagonist co-contraction (biceps femoris muscle) in young men. However in older individuals evidence exists for decreasing spinal reciprocal inhibition with age that might be responsible for the increased antagonist muscle activation (Hortobagyi and Devita, 2006).

Evidence shows that a dose–response relationship exists between the training intervention and the training induced strength gain (Liu and Latham, 2009). Actually, 3 sets of 10 repetitions with an intensity of 70–80% of 1 RM, 3 times per week during a minimum of 8 week training is recommended to achieve a significant effect (Chodzko-Zajko et al., 2009; Garber et al., 2011). All included studies met this criterion.

Although two literature databases have been carefully screened, it cannot be excluded that relevant papers were missed. Unfortunately, due to the large methodological differences between the included studies, an overall meta-analysis could not be performed. Finally, it must be acknowledged that many of the included papers showed different methodological shortcomings (see Table 1), as well as relatively low sample sizes. It cannot be excluded that this might have led to a type-II error in these studies.

The results of this review are not in accordance with the conclusions from an earlier review (Shield and Zhou, 2004) describing eight studies that assessed training induced changes in voluntary muscle activation assessed by the twitch interpolation technique in healthy adults. They concluded that most studies suggested that voluntary muscle activation does not increase after resistance training, although there were three exceptions, from which two investigated older people (Knight & Kamen, 2001; Scaglioni et al., 2002).

5. Conclusion

The results of this systematic review support the widely accepted hypothesis that neuromuscular adaptations are involved in the rapid training-induced strength gains in the lower extremities seen in elderly people. We found evidence for exercise-induced increase in voluntary activation related to strength gains in the lower extremities in elderly persons. On the other hand, the results for exercise-induced effects on antagonist co-activation are inconsistent and did not reached pooled statistical significance. The results described here could be different in other muscle groups, especially in the upper limb. A lower level of voluntary activation capacity prior to the onset of training results in a greater gain in activation capacity. Specific adaptation of muscles to the mode of training, static or dynamic, must be taken into account when interpreting the lack of improvement in voluntary activation. A learning effect is suggested as an explanation for the decrease in antagonist muscle co-activation after resistance training in older people. However, increased antagonist co-activation in ankle muscles is reported after training, which supports the hypothesis that antagonist muscle co-contraction has a beneficial effect on joint stabilization and acts as a safety mechanism. More research is necessary to further unravel the neuromuscular pathways by which strength gains are obtained following strength training in elderly persons, as well as the dose–response relationships. This will support the clinical decision making in prescribing exercise interventions to counter muscle weakness and related physical dependency in elderly persons.

Acknowledgements

None.

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Update literature search, clinical implication & conclusion

An update of the systematic literature review was done by screening Pubmed and Web of Science last date on the 1st of february 2017, corresponding the strategie previously reported in our systematic review (Arnold and Bautmans 2014). The search resulted in 23 new articles in PubMed and 23 in Web of Science, since november 2013. Seven articles showed overlap. After applying the in- and exclusion criteria and reading the abstracts only two articles were relevant, one in PubMed (Walker and Hakkinen 2014) and one in Web of Science (Stragier and others 2016).

The study of Walker&Häkkinen is a non-randomised controlled trial (NRCT) investigating resistance exercise induced change (10 weeks training program) in voluntary activation (VA) of the knee extensors (KE) and antagonist co-activation of the knee flexors (KF) during knee extension. The twitch interpolation technique was used for quantification of VA of the KE. An increase of 2.0 % ($p<0.05$) was seen in the training group of older men (N=26, age 64±8) after 10 weeks training. Lacking data in the publication for the control group were requested by contacting the authors, in order to calculate the weighted mean differences between groups, required to execute the meta-analysis. In the older control group (N=11, age 65±3) also an increase of 2.4 % was seen, resulting in no difference in change between groups. In our previously published meta-analysis the studies of Reeves (Reeves and others 2004a; Reeves and others 2004b) were included. These two studies and the study of Walker&Hakkinen were pooled. No significant overall effect of the strength training on VA of KE was found (WMD = +1.8% [-4.3, 7.9], p=0.560), see figure 1. Our previous conclusion showed a weighted mean difference (intervention vs. control) in change in VA of the KE of +7%, but this change also was not significant.

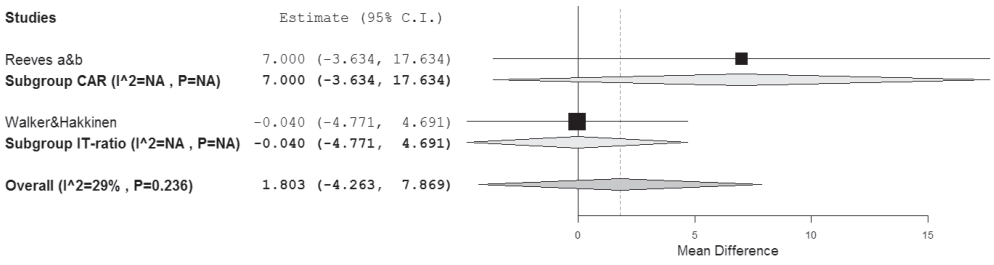

Fig. 1. Forest plot of one RCT and one non-randomized study investigating the effect of strength training on voluntary activation of knee extensor muscles measured by either IT-ratio or CAR. No significant overall effect of resistance training on voluntary activation of knee extensors was found (WMD) of +1.8%, (p=0.560). I^2 = % heterogeneity and corresponding p-value.

Data concerning the co-activation of the KF were obtained from the authors. Muscle co-activation of the M. Biceps femoris during isometric KE after the 10 weeks training decreased in the training group (-9%) and increased in the control group (+9%). The data were pooled with the results in five RCT's included in the previous meta-analysis, see figure 2. No significant overall effect of resistance training on antagonist co-activation was found (WMD = -4%, p=0.317), which was equal to our previous meta-analysis (overall effect was -1.1%, p=0.699).

The authors explain their results related to VA of the KE referring to the early (10 weeks) neural adaptation mechanism (increased VA and EMG-amplitude) in the older training group contributing to the strength gain. It remains unclear why equal increase (+2.2%) in VA in the non-trained control group was found.

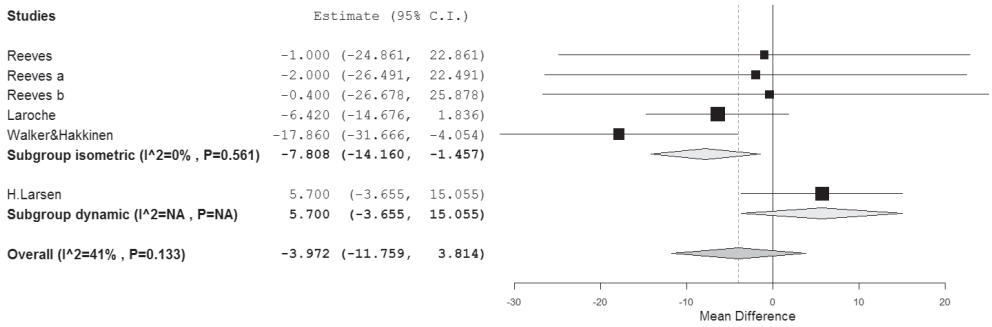

Fig. 2. Forest plot of five RCT's and one non-randomized study investigating the effect of strength training on antagonist co-activation (of knee flexor muscle) during knee extension, as measured by either isometric or dynamic contraction. No significant overall effect of resistance training on antagonist co-activation was found (overall effect (WMD) = -4%, (p=0.317). I^2 = % heterogeneity and corresponding p-value.

Stragier et al. (Stragier and others 2016) also performed a NRCT, with unknown risk of bias. The aim of this study was to answer the question if protein supplementation enriched in leucine might potentiate muscle hypertrophy and strength gain in response to a 24-week strength training programme in older adults. This study met the inclusion criteria. No statistical difference was observed between the two training groups after training, meaning that the specific protein supplementation did not potentiate the neural adaptations after 24 weeks of training. VA of plantar flexor muscles of the ankle (PF) and co-activation of dorsal flexor muscles (DF) during plantar flexor MVC's, were assessed respectively by twitch interpolation technique and sEMG. The mean data of the two training groups (N=25, age 63.3±3.1, 14 females) were compared to the non-training group (N=10, age 68.8±4.5, 7 females). VA of the PF in the training group showed an increase of 17% (p<0.001) and in the non-training group an increase of 0.4% was seen. The data of Stragier et al. could be pooled with the three

RCT's in our previous meta-anlysis. A significant overall effect of strength training on VA of PF was found (WMD = +9.5% [5.4, 13.5], p<0.001), see figure 3. No significant statistical heterogeneity was found (I^2= 0%, see figure 3). In our previously published meta-analysis the overall change in VA of the PF was of +8.8% (p<0.001).

Data for the co-activation of the dorsal flexors (DF) during PF MVC of the ankle could not be obtained from the authors.

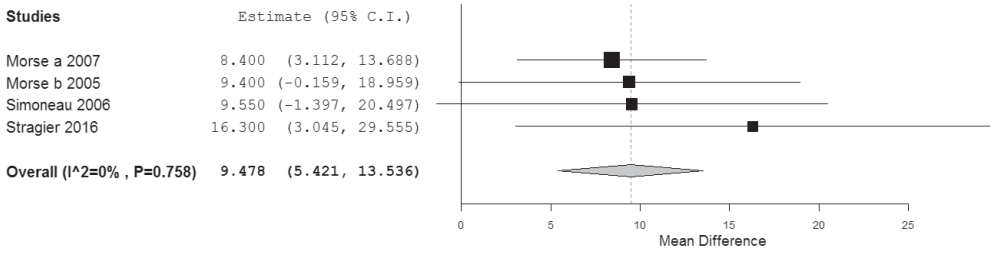

Fig. 3. Forest plot of three RCT's and one non-randomized controlled trial investigating the effect of strength training on voluntary activation of plantar flexor muscles measured by IT-ratio. Voluntary activation increased significantly following resistance training with an overall effect (WMD) of +9.5%, (p<0.001). I^2 = % heterogeneity and corresponding p-value.

Conclusion after update:

An exercise induced increase of VA and a decrease in antagonist co-activation might contribute to an increase in muscle strength. The new results show that we can maintain our previous conclusion, see table 1. The update of the meta-analysis resulted in non significant overall effects, except for VA of the PF.

	design	2014	design	2017
voluntary activation ankle plantar flexors	3 RCT	+ 9%, p<0.001	3 RCT + 1 NRCT	+ 9.5%, p<0.001
voluntary activation knee extensors	1 RCT	+ 7%, NS	1 RCT + 1 NRCT	+ 2%, NS
	3 NCET	+ 2%, p<0.001		
antagonist coactivation ankle dorsal flexors, during plantar flexion	4 RCT + 1 NRCT	+ 1%, NS	-	-
antagonist coactivation knee flexors, during knee extension	5 RCT	- 1%, NS	5 RCT + 1 NRCT	- 4%, NS
	3 NCET	- 2%, NS		

Table 1: RCT=randomized clinical trial; NRCT=non-randomized clinical trial; NCET=non-controlled experimental trial; NS=not significant

Clinical implication

The results show evidence for exercise-induced increase in VA related to strength gains in the lower extremities in elderly persons. Resistance training does adress the potential of neural activation which is preserved in the elderly. This should support all clinicians in their decision to prescribe resistance training as a countermeasure for elderly with sarcopenia.

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CHAPTER 5

Summary, general discussion and future perspectives

In this final chapter first the main findings and conclusions of this thesis are discussed, based on the research questions. In the second part, the clinical implications of our findings are outlined, followed by recommendations for future research.

Chapter 1 introduces the major concepts in our research and describes our general aim of this thesis: (1) to provide insight in underlying mechanisms, i.e. age-related changes in voluntary muscle activation related to inflammation, hypothesized to contribute to muscle weakness and slowness of movement in elderly persons and (2) to review systematically the literature for studies regarding the influence of resistance training on muscle activation in elderly persons.

Background

The progressive loss of muscle mass and muscle strength are consequences of biological ageing. This phenomenon, defined as sarcopenia, is associated with high risk of mobility-related outcomes leading to poor quality of life and premature death (Cruz-Jentoft and others 2010). The etiology of the sarcopenia syndrome is multifactorial and complex, with a multitude of internal and external processes that contribute to its development (Marzetti and others 2013; Muscaritoli and others 2010). Since the number of sarcopenic patients in Europe will increase dramatically in the next 30 years (Ethgen and others 2017), the relevance of answering questions concerning how the pathological pathways develop needs little argument. Improving our understanding of age-related decline in muscle functioning allows us to increase the effectiveness of our preventive and therapeutic interventions.

In explaining the mechanisms hypothesized to contribute to age-related decreasing muscle functioning we addressed two topics: muscle activation and muscle recruitment in relation to inflammation in elderly. These topics were based on the evidence for a much more rapid loss of muscle strength compared to loss of muscle mass (Clark and Manini 2008; Delmonico and others 2009; Frontera and others 2000; Visser and others 2005). Apparently not only muscle atrophy, i.e. mainly loss of type-II fibres (Lexell and others 1988), explains muscle weakness in elderly. Based on reported exercise-induced rapid strength gains (i.e. within 6 weeks), which cannot be explained by muscle hypertrophy, changes at the neuromuscular level must be involved. In this perspective muscle activation and antagonist coactivation as outcome muscle parameters have not been investigated before. Gaining insight in age-related changes in these muscle parameters will help clinicians and physiotherapists in justifying their decisions on prescribing exercise interventions. Sarcopenia can accelerate dramatically in older patients during inflammatory conditions, characterised by increased catabolic processes. The relation between the inflammatory profile and muscle activation has not been studied before, whereas the relation between inflammation and functional outcome measures has

(Calvani and others 2017). Two research questions in this thesis are based on previous studies of our research group investigating the association between inflammation and decline in muscle strength.

Summary of the research questions and main findings

Chapter 2

In chapter 2 the results of a cross-sectional experimental study (paper 1) investigating one hundred and twenty-four healthy adults, 60 young and 64 older subjects, are reported. *The aim of this study was to answer the question whether a difference in temporal agonist and antagonist muscle activation exists between young and older persons during a reaction time test.* This question builds on previous research showing that a longer reaction time, resulting in slowness of movement, was significantly related to an increase in muscle coactivation of the antagonist muscle before the start of the movement, i.e. during pre-movement time (PMT) (Bautmans and others 2011). According to this finding, we questioned if the *increased* muscle activity of the antagonist would be accompanied by an *early* activation of the antagonist muscle. Early activation of the antagonist muscle, before the agonist, would mean a different sequence of muscle activation, i.e. recruitment, in elderly persons compared to younger ones. In young people a triphasic muscle activation pattern is usually found, consisting of an initial burst of agonist muscle activity (AG1), followed by a burst in antagonist muscle activity (ANT) and a second agonist burst (AG2) (Berardelli and others 1996). From a mechanical point of view an early recruitment of the antagonist muscle might counteract and lower the net force exerted by the agonist muscle, attributing to muscle weakness. Based on our findings in this study we conclude that in our older healthy participants the muscle firing sequence is altered, characterized by delayed agonist muscle activation following stimulus onset, as well as a significantly earlier recruitment of the antagonist muscle before movement onset. This early antagonist muscle coactivation might contribute to weakness and slowness of movement in elderly persons.

Chapter 3

Here we present two experimental studies (paper 2 and 3) in two different cohorts.

In **Chapter 3a** the 64 older subjects in the study cohort described in chapter 2 were subject of investigation. The results of an explorative analysis are presented with focus on the influence of inflammation on muscle coactivation of the antagonist muscle during the fast dynamic extension movement of the upper limb in a reaction-time test. *The aim of this study was to answer the question*

whether inflammatory cytokines and Advanced Glycation End products (AGE's) in healthy elderly would relate to reaction time performance. Since muscle proteins in the collagen tissue are responsible for the transfer of muscle force, AGE accumulation (associated with muscle stiffness) and chronic inflammation (related to catabolism and muscle protein loss) might attribute to decreasing muscle function in elderly. Regression analysis showed a significant negative relationship between the pro-inflammatory cytokine MIP-1β and coactivation of the antagonist muscle during an isometric MVC (also described in paper 1). MIP-1β also correlated significantly with muscle activity of the antagonist muscle during pre-movement time (PMT) and movement time (MT) during the fast dynamic contraction (i.e. the reaction time test), again in a negative direction. This negative association most probably indicates an impairment mechanism, since the major function of antagonist muscle activation during dynamic movements in elderly is to add to joint stabilization, as a compensatory mechanism. In addition, Pentosidine (an AGE) seems to be predictive for a longer pre-movement time, probably contributing to the slowing of movement. A mechanical as well as an inflammatory mechanism may be underlying. Our overall findings support our hypothesis that chronic inflammation in healthy elderly, reflected by peripheral muscle processes, is involved in the impairment and slowing of muscle performance.

Chapter 3b continues with the focus on the mediating role of inflammation, in this study related to muscle fatigue, which is an often-neglected phenomenon in elderly. *The aim of this study was to answer the question what the involvement of central and peripheral contributions would be to the development of muscle fatigue during a fatiguing test in inflammatory hospitalized geriatric patients compared with community-dwelling older controls.* Both groups (10 hospitalized elderly and 19 community-dwelling controls) performed a maximal voluntary isometric contraction of the M. Adductor Pollicis until strength dropped to 50% of its maximum value. Voluntary muscle activation (VA) was assessed before and at the end of the fatigue protocol using the twitch interpolation method, and muscle activity was monitored using surface electromyography. Twenty-five circulating inflammatory biomarkers were determined. According to previous research findings (Beyer and others 2011) we assumed that muscle fatigability was mainly driven by a deficit in central activation rather than by local muscular impairments. However, contrary to our hypothesis, current results indicate that geriatric patients with acute infection showed a somewhat lower, but not statistically different, VA compared to older controls. Our results indicate that sustained isometric MVC induced similar central fatigue in both the geriatric patients and the healthy controls at the end of the fatigue protocol. No significant relation between VA and circulating markers of inflammation was found. Based on these findings it is unlikely that central fatigue was the main influencing factor for inflammation-related muscle fatigability in the geriatric patients. The geriatric patients showed a significant decrease in muscle activity during the fatigue protocol, which was not observed in the older controls. Likewise, the

decrease in muscle activity during the fatigue protocol in the geriatric patients was significantly related to higher levels of MCP-1 ($r = -0.72$, $p = 0.008$). In the community-dwelling controls post-fatigue twitch force, rate of force development and rate of force relaxation were significantly related with MCP-1 ($r = -0.61$, $p=0.003$, $r=-0.58$, $p=0.006$, $r=-0.54$, $p =0.012$ respectively). Overall, the results of this study indicate that geriatric patients with acute inflammation show substantially altered muscle activity and support the hypothesis that peripheral inflammatory processes at the level of the muscle itself are involved.

Chapter 4

Given the fact that inflammation and muscle activation are involved in muscle impairment in elderly, and that exercise is often prescribed to counter sarcopenia, this last chapter explores the evidence regarding the effects of resistance training on the improvement of muscle activation in elderly (paper 4). Evidence shows that neuromuscular adaptation is involved in rapid, i.e. 6-9 weeks, strength gains. While literature is consistent about the effect of resistance training to improve muscle strength in the aged, conflicting evidence consists on alterations in the central nervous system affecting the capacity to fully activate the muscle during maximal voluntary contraction at an older age (Clark and Manini 2012; Klass and others 2007). *The aim of the study was to answer the question what the influence of strength training would be on muscle activation in elderly.* We systematically reviewed the literature for studies reporting exercise-induced effects on voluntary muscle activation and antagonist muscle coactivation in elderly persons. Seventeen relevant studies were identified until November 2013 and included in the initial analysis. All were studies concerning the effect of resistance training on lower limb muscles. Meta-analysis showed an exercise-induced improvement in voluntary activation in plantar flexors and knee extensors, with greater gains in activation capacity obtained in subjects with lower voluntary activation level prior to the onset of training. No significant overall effect of strength training on antagonist coactivation during ankle plantar flexion or knee extension was found. An update was performed in March 2017, using the identical search strategy. Two additional relevant studies were included. Pooling resulted in significant overall effects for the voluntary activation of plantar flexors and a no effect for knee extensors, and no effect for antagonist coactivation during knee extension. Based on this update we can maintain our previous conclusion.

Discussion and clinical implications

Three general conclusions can be drawn based on our findings:

1. *Age-related changes in voluntary muscle activation, muscle recruitment and chronic inflammation are involved in muscle weakness and slowness of movement in healthy and cognitively intact older people;*
2. *Local peripheral inflammatory processes are involved in decreased muscle activity during a fatiguing contraction in hospitalized elderly with acute infection;*
3. *Exercise can be a countermeasure for muscle weakness by increasing voluntary muscle activation in healthy elderly.*

Although the exact mechanisms of the age-related differences in muscle (co)activation that we observed in our healthy participants in the first study (paper 1) remain unclear, our research has provided evidence for the presence of altered muscle recruitment patterns in elderly during a simple reaction-time test. Early antagonist muscle coactivation can counteract the net force production of the agonist muscle and might contribute to increased reaction time in elderly persons. It cannot be excluded that this earlier coactivation of the antagonist muscle is more pronounced in disabled older persons. Our participants had no functional disabilities in their daily activities. This needs further exploration. However, the relevance of our findings in the upper arm muscles with respect to function in older persons is supported by research of Pijnappels et al. (Pijnappels and others 2010). They showed that reaction time performance plays an important mediating role (explained variance 27%) in the association between choice-stepping reaction time and the occurrence of multiple falls within one year follow-up in elderly village residents. Inaccuracies in the scaling of flexion, extension and coactivation commands in elderly are also described by Hortobagyi et al. (Hortobagyi and others 2006; Hortobagyi and others 2009) and may underlie the altered muscle activation patterns with ageing. On the one hand, muscle antagonist coactivation in the lower limb in elderly leads to greater gait stabilization (Hortobagyi and others 2009), and on the other hand antagonist coactivation seems to be involved in increased reaction time performance, leading to increased risk of falling. It is suggested to pay attention to reaction time as outcome parameter in our therapeutic exercise interventions, the more so since evidence shows that resistance training in elderly can improve physical reaction time (Fragala and others 2014).

The relationship between the chronic low-grade inflammatory profile in healthy elderly and specific muscle parameters was analyzed and described in paper 2 (data were generated in the experimental

study presented in paper 1). To our best knowledge, this relationship has not been investigated before. An exploration of the possible relationships between the complex interrelated cytokines and AGEs and the relevant muscle parameters in the older healthy participants showed significant relationships contributing to age-related impairment of reaction time performance. The negative association between MIP-1β and antagonist coactivation in our participants most probably indicates impairment of the joint stabilization mechanism in elderly (Hortobagyi and Devita 2006; Klein and others 2001). Thus, the chronic inflammation is suggested to weaken this compensatory coactivation mechanism. In addition we also found that a higher level of pentosidine (AGE) seems to be predictive for a longer PMT. Slowness of movement seems to be influenced both in a mechanical and in an inflammatory way, whereas pentosidine is involved in the accumulation of crosslinks as well as in the activation of RAGE, resulting in increasing inflammation. We expected the relatively small regression coefficients representing the associations because of the complex mutual interrelationships of cytokines and AGEs. The complex pathways need further exploration. However, our findings confirm the relevance of chronic low-grade inflammation (CLIP) in studies of the musculoskeletal system in older persons. It indicates the importance of CLIP to be included in our clinical reasoning process. The relations we found should also motivate physical therapists to advise physical exercise as a countermeasure for decreasing muscle functioning in age-related sarcopenia. In a recent systematic review the beneficial effect of different types of exercise on the inflammatory profile in older adults has been established (Liberman and others 2017). In the study of Forti et al. (one of the studies included in the systematic review) the authors suggest that, based on the inflammation mediating effect of a twelve week resistance exercise program in community-dwelling older persons, exercising until volitional fatigue is the main trigger for the exercise-induced immune responses (Forti and others 2016).

The hospitalized geriatric patient population investigated in the study presented in paper 3 has not often been subject of electrophysiological testing. Studies mainly focus on muscle performance. The evaluation of muscle fatigability with simultaneous sEMG monitoring and the use of the twitch interpolation technique in frail, acutely ill and hospitalized geriatric patients provided unique data in these geriatric patients, on muscle weakness and fatigability, a condition that is often neglected in clinical decision-making. Since our experimental protocol was challenging for these patients with poor mobility, the sample size was relatively low, which might have influenced the statistical power of our analyses. However, despite the relatively low number of participants, and a correction for covariates in our statistical models, we were able to demonstrate significant differences between patients and healthy controls, as well as significant relationships with inflammatory markers. We studied the M. Adductor Pollicis, which is a small muscle of the hand, during isometric contraction. Caution is required when extrapolating our findings to other muscle groups such as muscles involved in locomotion. Our

results show that muscle activity is significantly altered in older patients with acute infection, which was the reason for their hospital admission, and that local processes are involved. It cannot be excluded that other factors such as chronic low-grade inflammation - already existing before admission of the hospitalized patients - might have influenced our results. Despite all this our findings contribute to the importance of muscle fatigability related to inflammation, acute and chronic, to be included in our clinical decision-making. Given the numerous contra-indications and side effects, standard non-steroidal anti-inflammatory treatment cannot systematically be recommended to counteract inflammation-induced weakness and muscle fatigue in geriatric patients with acute infection. Physical exercise for this population will be challenging. However, in the light of our findings it should motivate physical therapists to prescribe exercise in hospitalized or post-hospitalized geriatric patients, in order to rehabilitate muscle activity and force-generating capacity (Norheim and others 2017a; Norheim and others 2017b). Physical exercise has already been proven beneficial for acutely hospitalized elderly (Kosse and others 2013; Martinez-Velilla and others 2016). Patients who participated in an exercise program were less likely to be discharged to a nursing home, compared with patients receiving only the usual care. The introduction of an exercise program may not increase costs.

Literature is consistent about the effect of resistance training to improve muscle strength in elderly, and the involvement of neural adaptations. However, conflicting evidence consists on the alterations in the central nervous system affecting the capacity to fully activate the muscles during maximum voluntary contraction at an older age (Klass and others 2007). Our systematic review and meta-analysis (published in 2014 and updated in 2017) support the widely accepted hypothesis that neuromuscular adaptations are involved in the rapid (6-9 weeks) training-induced strength gains in the lower extremities seen in elderly people. We can conclude that there is evidence for an exercise-induced increase in voluntary activation related to strength gains in the lower extremities in elderly persons. Resistance training does address the existing potential in elderly people to voluntary activate the lower limb muscles. More research will be necessary to further unravel the neuromuscular pathways by which strength gains are obtained as a result of strength training in elderly persons, as well as the dose–response relationships. This will support the clinical decision-making in prescribing exercise interventions to counter muscle weakness and related physical dependency in elderly persons.

Future research recommendations

Our research provides background for new studies with the objective to get further insight in underlying mechanisms.

The study presented in paper one should be replicated including disabled elderly, to confirm changed recruitment patterns and early activation of the antagonist muscle during fast dynamic contraction in elderly. It should answer the question if the early activation is more pronounced in elderly with lower levels of daily activities. Applying a longitudinal design would allow to detect intraindividual changes in variables and draw inference on the time course of changing trajectories.

When designing a longitidinal study it will also be worthwile to investigate the changing chronic inflammatory profile over time and the influence on muscle activation, reflected by reaction time performance. Longitudinal analyses could identify which circulating markers of inflammation could best predict relevant muscle parameters, related to muscle weakness and slowness of movement. Insight in these predictive variables will allow more targeted interventions.

In order to confirm the influence of peripheral inflammatory muscle processes on muscle fatigue in acute inflammatory conditions in geratric patients, the study presented in paper three should be executed including a larger sample of geriatric hospitalized patients with acute infection. The relevance of this study is demonstrated by the fact that muscle fatigue is a well known complaint in elderly, and according to our findings an important, but often neglected factor in the assessment of elderly. The next step would be to explore whether these inflammation-related muscle impairments can be reversed by anti-inflammatory treatment. Resistance exercise might be a strategy, since the effect of resistance training on the improvement of fatigue-resistant muscle properties in healthy elderly has been shown (Walker and others 2014).

The effect of low- and high load external resistance training on muscle activation and antagonist coactivation, according to dose-response relationships, may show the effect of this regimens in healthy elderly, in line with the effect on muscle strength. The direct relationship between training-induced improvement in muscle activation and strength gain should be confirmed. Application of these patient-specific strategies in (post)hospitalized populations with inflammatory conditions could be a next step in studying the effect of resistance training on muscle activation and antagonist coactivation. In line

with the beneficial effect of resistance training on muscle strength and the inflammatory profile in older adults, a positive effect is to be expected.

Overall conclusion

The first aim of this thesis was to provide insight in the underlying mechanisms supposed to contribute to muscle weaknes and slowness of movement in elderly. Our results show for the first time that in healthy elderly chronic inflammation, reflected by higher levels of cytokines, is involved in the interplay between agonist and antagonist muscles. More research needs to be done to confirm the relationships. However, we can conclude that antagonist coactivation associated with chronic inflammation contributes to weakness and slowness of movement. In addition, we showed that muscle activity in our geriatric patients with acute inflammation, who performed a muscle fatigue protocol, decreased significantly. The decrease was associated with higher levels of inflammatory cytokines, suggesting that local muscle processes are involved. This result demonstrates the importance of assessing muscle fatigue in geriatric patients during acute inflammatory conditions. The second aim was to review the literature on studies regarding the influence of resistance training on muscle activation in elderly persons. We can conclude that resistance exercise can increase voluntary activation, showing that the neural activation potential in elderly is preserved. The increase is associated with clinically relevant strength gains in the lower extremities in healthy elderly persons. The results for exercise-induced effects on antagonist coactivation are inconsistent. These results should motivate clinicians to advise resistance training as a countermeasure for decreasing muscle functioning in age-related sarcopenia.

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CHAPTER 6

Samenvatting

In dit laatste hoofdstuk worden eerst de belangrijkste bevindingen en conclusies van deze thesis besproken, gebaseerd op de onderzoekvragen. In het tweede gedeelte, volgen de klinische implicaties van de bevindingen en aanbevelingen voor toekomstig onderzoek

Hoofdstuk 1 introduceert de belangrijkste concepten in onze onderzoeken en beschrijft het doel van de thesis: 1) inzicht verschaffen in onderliggende mechanismen, dat wil zeggen leeftijd gerelateerde veranderingen in vrijwillige spieractivatie gerelateerd aan inflammatie, verondersteld bij te dragen aan spierzwakte en traagheid van bewegen bij ouderen en 2) een systematische literatuur beoordeling te doen van studies over de invloed van weerstand training op spieractivatie bij ouderen.

Achtergrond

Het progressieve verlies van spiermassa en spierkracht zijn gevolgen van biologische veroudering. Dit fenomeen, gedefinieerd als sarcopenie, is geassocieerd met een hoog risico op ziekte gerelateerde uitkomsten, met een slechte kwaliteit van leven en vroegtijdig overlijden tot gevolg (Cruz-Jentoft and others 2010). De etiologie van sarcopenie is multifactorieel en complex, met een veelheid aan interne en externe processen (Marzetti and others 2013; Muscaritoli and others 2010). Aangezien het aantal patienten met sarcopenie de komende 30 jaar fors zal stijgen (Ethgen and others 2017), is de relevantie van vragen over ontwikkeling van de pathologische routes duidelijk. Verbetering van ons inzicht in de leeftijd gerelateerd afname in spierfunctie, maakt het mogelijk de effectiviteit van onze preventieve en therapeutische interventies te verhogen.

Bij het verklaren van mechanismen, verondersteld bij te dragen aan leeftijd gerelateerd afname van spierfunctie, hebben wij twee onderwerpen behandeld: spieractivatie en spierrekrutering in relatie tot inflammatie bij ouderen. De achtergrond voor deze keuze ligt in het bewijs dat spierkracht veel sneller afneemt dan spiermassa (Clark and Manini 2008; Delmonico and others 2009; Frontera and others 2000; Visser and others 2005). Blijkbaar verklaart niet alleen spier atrofie, d.w.z. vooral verlies van type II-vezels (Lexell and others 1988), de spier zwakte bij ouderen. Op basis van gerapporteerde snelle (d.w.z. binnen 6 weken) krachtwinst door fysieke training, die niet verklaard kan worden door spierhypertrofie, moeten neuromusculaire veranderingen betrokken zijn. Vanuit dit perspectief zijn vrijwillige spieractivatie en antagonistische coactivatie als uitkomstmaten niet eerder onderzocht. Het inzicht in leeftijd gerelateerde veranderingen in deze spierparameters zal clinici en fysiotherapeuten helpen om hun besluit te onderbouwen, bij het voorschrijven van oefen interventies. Sarcopenie kan fors toenemen bij oudere patienten met acute inflammatoire aandoeningen, gekarakteriseerd door toename van katabole processen. De relatie tussen het inflammatoire profiel en vrijwillige spieractivatie is niet eerder beschreven. Waar dit wel het geval is voor functionele

uitkomsten (Calvani and others 2017). Twee onderzoeksvragen in deze thesis, zijn gebaseerd op eerdere studies van de FRIA-onderzoeksgroep, waarin de associatie tussen inflammatie en spierkracht werd onderzocht

Samenvatting van de onderzoeksvragen en belangrijkste bevindingen

Hoofdstuk 2

In hoofdstuk 2 worden de resultaten van een cross-sectionele experimentele studie gerapporteerd (paper 1), waarin 124 gezonde volwassenen werden onderzocht, 60 jongeren en 64 ouderen. *Het doel van deze studie was om de vraag te beantwoorden of er een verschil is tussen jong volwassenen en ouderen, in het moment van agonistische-, en antagonistische spieractivatie, bij het uitvoeren van een reactie tijd test.* Deze vraag volgt op resultaten uit een eerdere studie waarin werd aangetoond dat een langere reactie tijd (resulterend in traagheid van bewegen) significant gerelateerd was aan een toename van antagonistische spier coactivatie, zelfs voordat de beweging startte, d.w.z. tijdens de pre-bewegingstijd (Bautmans and others 2011). Vervolgens vroegen wij ons af of deze *toename* van spieractivatie van de antagonist ook gepaard zou gaan met een *eerdere* activatie van de antagonist. Eerdere activatie van de antagonist, voordat de agonist activeert, zou een verschillende volgorde betekenen in spieractivatie, d.w.z. rekrutering, bij ouderen vergeleken met jongere personen. Bij jongeren en gezonde mensen wordt overwegend een trifasisch spieractivatie patroon gezien, bestaand uit een eerste uiting van agonistische activiteit (AG1), gevolgd door de antagonistische activiteit (ANT) en een tweede agonistische activiteit (AG2) (Berardelli and others 1996). Vanuit een mechanisch oogpunt kan een eerdere activatie van de antagonist, de kracht ontwikkeld door de agonist tegenwerken en daardoor verminderen, wat bijdraagt aan spier zwakte. Op basis van onze bevindingen concluderen wij dat bij ouderen de volgorde in spieractivatie patroon is veranderd, gekarakteriseerd door een uitgestelde spieractivatie van de agonist (als reactie op een visuele stimulus bij de test) en een significant eerdere rekrutering van de antagonist, voordat de beweging start. Deze eerdere antagonistische coactivatie kan bijdragen aan spierzwakte en traagheid van bewegen bij ouderen.

Hoofdstuk 3

Twee experimentele studies worden gepresenteerd (paper 2 en 3) in twee verschillende cohorten. In **hoofdstuk 3a** zijn de 64 ouderen, tevens besproken in hoofdstuk 2, weer onderzocht. De resultaten van een exploratieve analyse worden gepresenteerd, met als focus de invloed van inflammatie op spier coactivatie van de antagonist, tijdens de beweging van de arm bij een reactie tijd test. *Het doel van deze studie was om de vraag te beantwoorden of inflammatoire cytokines en 'Advanced Glycation End*

products' (AGEs) (versuikerde en gedegenereerde eiwitten) bij gezonde ouderen geassocieerd zijn met reactie tijd. Aangezien spier eiwitten in het spierweefsel verantwoordelijk zijn voor de overdracht van spierkracht, zouden AGE accumulatie (geassocieerd met spier stijfheid) en chronische inflammatie (geassocieerd met katabolisme en verlies van spier proteïne) kunnen bijdragen aan afnemende spierfunctie bij ouderen. Uit regressie analyse bleek een significante negatieve relatie tussen de pro-inflammatoire cytokine MIP-1β en coactivatie van de antagonistische spier tijdens een maximale isometrische contractie (zoals beschreven in paper 1). MIP-1β correleerde tevens significant in negatieve richting, met spier activiteit van de antagonist tijdens de pre-bewegingstijd en bewegingstijd, tijdens de dynamische contractie. Deze negatieve correlatie duidt mogelijk op een verstoring van gewricht stabilisatie (bij wijze van compensatie), aangezien dit een belangrijke functie is van antagonistische activatie tijdens dynamische contracties bij ouderen. Aanvullend lijkt Pentosidine (een AGE) voorspellend voor een langere pre-bewegingstijd, mogelijk bijdragend aan vertraging van beweging. Zowel een mechanisch als een inflammatoir mechanism ligt hier aan ten grondslag. De bevindingen ondersteunen onze hypothese dat chronische inflammatie, die tot uiting komt in perifere spierprocessen, bij gezonde ouderen betrokken is in afname en vertraging van spier functie. **Hoofdstuk 3b** gaat verder met de focus op de mediërende rol van inflammatie, in deze studie gerelateerd aan spiervermoeidheid, een fenomeen dat vaak genegeerd wordt bij ouderen. *Het doel van deze studie was het beantwoorden van de vraag, wat de centrale en periferere betrokkenheid is bij het ontstaan van spiervermoeidheid tijdens een vermoeidheids test bij geriatrische patienten in het ziekenhuis opgenomen, met een acute inflammatoire aandoening in vergelijking met thuis wonende ouderen.* Beide groepen (10 in het ziekenhuis opgenomen ouderen en 19 thuis wonende ouderen in de controle groep) voerden een maximale isometrische contractie uit van de M. Adductor Pollicis totdat de kracht tot 50% van de maximale waarde was afgenomen. Vrijwillige spieractivatie werd voor en na het vermoeidheids protocol gemeten met behulp van de 'twitch interpolation'-methode en de spieractiviteit werd gelijktijdig gemonitord met behulp van oppervlakte EMG. Vijfentwintig inflammatoire biomarkers in het bloed werden tevens onderzocht. Op basis van eerder onderzoek (Beyer and others 2011) hadden wij de hypothese dat spiervermoeidheid vooral het resultaat was van een deficiet in centrale activatie, meer dan het resultaat van verstoring van locale spier processen. In strijd met onze hypothese, laten de geriatrische patienten met een acute inflammatoire aandoening een niet significant verschillend, iets lagere vrijwillige spieractivatie zien, in vergelijking met de ouderen in de controle groep. Onze resultaten geven aan dat een aanhoudende maximale isometrische contractie een vergelijkbare vermoeidheid na het vermoeidheidsprotocol laat zien, in beide groepen. De vrijwillige spieractivatie vertoonde geen significante relatie met de inflammatoire markers in het bloed. Op basis van deze bevindingen is het onwaarschijnlijk dat centrale vermoeidheid de hoofdrol speelt in geval van inflammatoir gerelateerde spiervermoeidheid bij geriatrische

patienten. Zij vertoonden verder een significante afname in spier activiteit tijdens het vermoeidheidsprotocol, welke niet aanwezig was bij de ouderen in de controlegroep. Bovendien was deze afname in spier activiteit tijdens het vermoeidheidsprotocol, significant geassocieerd met hogere waarden van de cytokine MCP-1 (r=0.72, p=0.008). De contractiele eigenschappen ('twitch force' (samentrekkings kracht), 'rate of force development' (mate van kracht vorming) en 'rate of force relaxation' (mate van spierontspanning)) waren significant gecorreleerd met MCP-1 (resp. r=-0.61, p=0.003; r=-0.58, p=0.006; r=-0.54, p=0.012) bij de thuis wonende ouderen in de controle groep. De resultaten in deze studie wijzen op een substantiele afname van spier activiteit bij geriatrische patienten met een acute inflammatoire aandoening en ondersteunen de hypothese dat perifere inflammatoire spierprocessen daarbij betrokken zijn.

Hoofdstuk 4

Gezien het feit dat inflammatie en spieractivatie betrokken zijn bij vermindering van spierfunctie bij ouderen en dat fysieke oefeningen vaak geadviseerd wordt bij het tegen gaan van sarcopenie, wordt in dit laatste hoofdstuk het bewijs beschreven voor het verbeteren van spieractivatie bij ouderen als gevolg van krachttraining (paper 4). Bewijs laat zien dat bij snelle krachtwinst (d.w.z. binnen 6-9 weken) neuromusculaire adaptatie betrokken is. Terwijl de literatuur eenduidig is over het effect van krachttraining op verbetering van spierkracht, bestaat er tegenstrijdig bewijs voor veranderingen in het centrale zenuwstelsel, welke de capaciteit beïnvloedt, tot volledige spieractivatie bij maximale vrijwillige contractie bij ouderen (Clark and Manini 2012; Klass and others 2007). *Het doel van dit onderzoek was om de vraag te beantwoorden wat de invloed van krachttraining is op spieractivatie bij ouderen*. In een systematische litertuurstudie met meta-analyse beoordeelden wij studies over het effect van training bij ouderen op vrijwillige spieractivatie en antagonistische coactivatie. Zeventien relevante studies werden geïdentificeerd tot november 2013 en geïncludeerd in de analyse. Allen waren studies over het effect van krachttraining op de beenspieren. De meta-analyse liet een significante verbetering zien in vrijwillige activatie van plantair flexoren en knie extensoren door krachttraining, met grotere winst in activatie capaciteit bij personen met een lager aanvangsniveau. De antagonistische coactivatie van plantair flexoren en knie extensoren liet geen significante verandering zien door training. In maart 2017 is een update gedaan, gebruik makend van de identieke zoek strategie. Twee aanvullende relevante studies konden worden geïncludeerd. Pooling resulteerde in een significant effect voor de vrijwillige activatie van plantair flexoren, maar niet voor de knie extensoren. Eveneens geen significant overall effect voor de antagonistische coactivatie tijdens knie extensie. Op basis van deze update kunnen wij de eerdere conclusie handhaven.

Discussie en klinische implicaties

Drie algemene conclusies kunnen worden geformuleerd:

1. Leeftijd gerelateerde veranderingen in vrijwillige spieractivatie, spierrekrutering en chronische inflammatie zijn betrokken bij spierzwakte en traagheid van bewegen bij gezonde en cognitief goed functionerende ouderen;
2. Locale perifere inflammatoire processen zijn betrokken bij afgenomen spier activiteit tijdens een vermoeidheids protocol bij ouderen opgenomen in een ziekenhuis met een acute inflammatoire aandoening;
3. Training kan spierzwakte bij gezonde ouderen tegen gaan door toename van spieractivatie.

Ondanks dat de exacte mechanismen van leeftijd gerelateerde verschillen in spier (co)activatie, gerapporteerd in de eerste studie (paper 1), nog niet zijn opgehelderd heeft onze studie bewijs geleverd voor de aanwezigheid van veranderde spierrekruterings patronen bij ouderen tijdens een reactie tijd test. Eerdere antagonistische coactivatie kan de kracht genererende agonistische spier tegen werken en bijdragen aan toegenomen reactie tijd. Het is mogelijk dat deze eerdere coactivatie meer uitgesproken is bij minder goed functionerende ouderen. Onze deelnemers hadden geen functionele beperkingen in de ADL. Dit moet verder worden uitgezocht. De relevantie van onze bevindingen in de arm wordt ondersteund door onderzoek van Pijnappels et al. (Pijnappels and others 2010). Zij toonden aan dat reactie tijd een belangrijke mediërende rol speelt (verklaarde variantie 27%) in de associatie tussen reactie tijd, gemeten bij een reactie tijd test met 'keuze-stappen', en het optreden van meerdere valincidenten binnen een jaar bij thuis wonende ouderen. Onnauwkeurigheden in de centrale afstemming tussen flexie, extensie en coactivatie worden beschreven door Hortobagyi et al. (Hortobagyi and others 2006; Hortobagyi and others 2009) kunnen onderliggend zijn aan de veranderde spieractivatie patronen bij ouderen. Aan de ene kant leidt antagonistische coactivatie in het been tot grotere stabiliteit tijdens het lopen (Hortobagyi and others 2009) en aan de andere kant lijkt antagonistische coactivatie betrokken te zijn in toegenomen reactie tijd, resulterend in toenemend valrisico. Welk mechanisme prevaleert is onduidelijk. Het lijkt van belang om aandacht te besteden aan reactie tijd bij therapeutische interventies, zeker sinds bewijs aantoont dat krachttraining bij ouderen fysieke reactie tijd kan verbeteren (Fragala and others 2014).

In paper 2 werd een eerste verkenning van de relatie tussen chronische inflammatie bij gezonde ouderen en specifieke spier parameters beschreven. Voor zover bij ons bekend werd deze relatie niet eerder onderzocht. Het onderzoek toont verschillende significante relaties die bijdragen aan afname van reactie tijd. De negatieve associatie tussen MIP-1β en antagonistische coactivatie duidt

waarschijnlijk op een verzwakt mechanisme van gewricht stabilisatie (Hortobagyi and Devita 2006; Klein and others 2001). De chronische inflammatie kan dit compensatie mechanisme verzwakken. Aanvullend bleek een hoger niveau van Pentosidine voorspellend voor een langere reactie tijd. De invloed op traagheid van bewegen werkt dan zowel mechanisch als inflammatoir, gezien de betrokkenheid van Pentosidine bij de accumulatie van cross-links en bij de activatie via de receptor voor AGE (RAGE), waardoor inflammatie aanwakkert. Wij hadden de kleine regressie coëfficienten bij de associaties verwacht, vanwege de complexe wederzijdse relaties van cytokines en AGEs. Ondanks dat deze complexe routes verder onderzocht moeten worden, bevestigen de resultaten het belang van chronische inflammatie in studies van het musculoskeletale systeem bij ouderen. Bovendien is het van belang deze factor op te nemen in ons klinisch redeneren. De associaties die wij vonden zouden clinici en fysiotherapeuten moeten motiveren om, bij het tegen gaan van sarcopenie, fysieke oefeningen te adviseren. In een recente systematische literatuur studie werden de gunstige effecten van verschillende typen training op het inflammatoir profiel bij ouderen vastgesteld (Liberman and others 2017). In de studie van Forti et al. (één van de studies geincludeerd in de review) geven de auteurs aan dat, gebaseerd op het inflammatie remmend effect van een krachttraining programma gedurende 12 weken, bereiken van momentane vermoeidheid de belangrijkste prikkel is voor de immuun respons, door training (Forti and others 2016).

De populatie geriatrische patienten opgenomen in het ziekenhuis beschreven in paper 3 is tot nu toe niet vaak onderzocht met behulp van electrofysiologische metingen. De evaluatie van spiervermoeidheid, met gelijktijdige EMG monitoring en de 'twitch-interpolation'-methode bij kwetsbare, acuut zieke geriatrische patienten, leveren unieke data betreffende spierzwakte en spiervermoeidheid, een conditie die vaak wordt genegeerd in klinische besluitvorming. Aangezien ons protocol uitdagend was voor deze patienten, bleef het aantal proefpersonen relatief laag, wat mogelijk de statistische power van de analyses heeft beïnvloed. Ondanks dat konden wij significante verschillen aantonen tussen patienten en de gezonde controlegroep, evenals significante relaties met de inflammatoire markers. Wij bestudeerden de M. Adductor Pollicis, een kleine handspier, tijdens isometrische contracties. Daarom moeten wij voorzichtig zijn, bij extrapolatie van onze bevindingen naar andere spiergroepen zoals spieren betrokken bij het lopen. Onze resultaten tonen aan dat spieractivitiet bij de geriatrische patienten significant is veranderd en dat locale spierprocessen daarbij betrokken zijn. Het kan niet worden uitgesloten dat andere factoren, zoals chronische inflammatie, reeds aanwezig voor de opname in het ziekenhuis, van invloed zijn geweest op de resultaten. Ondanks dit dragen de bevindingen bij aan de relevantie om spiervermoeidheid, gerelateerd aan acute en chronische inflammatie, op te nemen in onze klinische besluitvorming. Vanwege de vele contra-indicaties en bijwerkingen, kan behandeling met NSAID's om spierzwakte en spiervermoeidheid door

inflammatie tegen te gaan, niet standaard worden toegepast bij geriatrische patienten met acute inflammatoire aandoeninge. Voor deze populatie zal een oefenprogramma uitdagend zijn, maar gemotiveerd door onze bevindingen zouden fysiotherapeuten oefeningen voor moeten schrijven, om spieractiviteit en het kracht genererende vermogen te herstellen (Norheim and others 2017a; Norheim and others 2017b). Training is al bewezen gunstig gebleken in deze populatie (Kosse and others 2013; Martinez-Velilla and others 2016). Patienten die deelnamen aan een trainings programma werden minder vaak verwezen naar een verpleegtehuis, in vergelijking met patienten die de standaard zorg ontvingen. Het toevoegen van een trainingsprogramma verhoogde de kosten niet.

De literatuur is éénduidig over het effect van krachttraining op verbetering van spierkracht en de betrokkenheid daarbij van aanpassingen van het centraal zenuwstelsel. Tegenstrijdig bewijs bestaat echter over aanpassingen in het centrale zenuwstelsel, die de capaciteit beinvloeden van de spieractivatie bij maximale vrijwillige contractie (Klass and others 2007). Onze systematische review en meta-analyse (gepubliceerd in 2014 en ge-update in 2017) ondersteunt de geaccepteerde hypothese dat neuromusculaire aanpassingen betrokken zijn bij de snelle krachtwinst door training in de benen. Wij kunnen concluderen dat er bewijs is voor een toename van de vrijwillige activatie, door training en gerelateerd aan krachtwinst. Krachttraining spreekt het nog aanwezige potentieel aan spieractivatie, aan bij ouderen. Meer onderzoek is nodig om te ontrafelen via welke neuromusculaire routes de krachtwinst verkregen wordt. Evenals de dosis-respons relaties. Inzicht hierin zal het adviseren van krachttraining, bij het tegen gaan van spierzwakte en daaraan gerelateerde fysieke afhankelijkheid bij ouderen, onderbouwen.

Aanbevelingen voor toekomstig onderzoek

Ons onderzoek geeft aanleiding voor nieuwe studies met als doel verder inzicht te krijgen in onderliggende mechanismen.

De studie in paper 1 zou herhaald moeten worden met inclusie van minder goed functionerende proefpersonen. Het zou veranderde rekruterings patronen en eerdere activatie van de antagonist moeten bevestigen. Het zou de vraag moeten beantwoorden of eerdere antagonistische activatie meer uitgesproken is bij ouderen met een lager ADL-niveau, wat indien bevestigd, het belang van dit mechanisme aangeeft. Een longitudinaal design maakt het mogelijk intraindividuele veranderingen te meten en conclusies te trekken over het tijdsaspect van veranderingen.

Een longitudinale studie maakt het tevens mogelijk veranderingen in het inflammatoir profiel te onderzoeken en de invloed daarvan op spieractivatie, tot uiting komend in reactie tijd. Longitudinale analyse kan verder identificeren welke inflammatoire markers de beste voorspeller zijn voor spier parameters, gerelateerd aan spierzwakte en traagheid van bewegen.

Om de invloed te bevestigen van perifere inflammatoire spierprocessen op spiervermoeidheid bij geriatrische patienten met acute inflammatoire aandoeningen, zou de studie beschreven in paper 3 uitgevoerd moeten worden met een groter aantal proefpersonen. Spiervermoeidheid is een vaak gehoorde klacht bij ouderen en wordt veelal genegeerd. De volgende stap zou kunnen zijn om te onderzoeken of de spier dysfunctie door de inflammatie, behandeld kan worden met een anti-inflammatoire behandeling. Dit zou krachttraining kunnen zijn, aangezien het effect van krachttraining op verbetering van de weerstand tegen spiervermoeidheid is aangetoond (Walker and others 2014).

Het effect van lage- en hoge belasting externe krachttraining op spieractivatie en antagonistische coactivatie moet het effect van deze strategieën aantonen, vergelijkbaar met het effect op krachtwinst. De associatie tussen verbetering in spieractivatie en krachtwinst moet verder bevestigd worden. Een volgende stap zou kunnen zijn om de stratgieën toe te passen bij patienten na ziekenhuisopname, zodat het effect ervan kan worden onderzocht op spieractivatie en antagonistische coactivatie. Vergelijkbaar met het gunstige effect van krachttraining op krachtwinst en het inflammatoire profiel, is een positief effect te verwachten.

Afsluitende conclusie

Het eerste doel van deze thesis was om inzicht te verschaffen in onderliggende mechanismen die bijdragen aan spierzwakte en traaghied van bewegen bij ouderen. Onze resultaten laten voor het eerst zien dat bij gezonde ouderen het chronisch inflammatie profiel, met aanwezigheid van cytokines, betrokken is in het samenspel tussen agonist en antagonist. Meer onderzoek is nodig om de associaties te bevestigen, maar wij kunnen concluderen dat antagonistische coactivatie, onder invloed van chronische inflammatie, bijdraagt aan spierzwakte en traagheid van bewegen. Aanvullend laten wij zien dat spieractiviteit fors afneemt, bij geriatrische patienten met een acute inflammatoire aandoening, die een spiervermoeidheids protocol uitvoeren. Dit resultaat geeft het belang aan, om spiervermoeidheid te onderzoeken bij deze patienten. Het tweede doel was om middels een systematisch litertuur onderzoek, studies te beoordelen over het effect van krachttraining op spieractivatie. Wij concluderen dat door krachttraining de vrijwillige activatie kan toenemen, wat aantoont dat het centrale activatie vermogen is bewaard. De toename bij gezonde ouderen is

geassocieerd met klinisch relevante krachtwinst in de benen. Het bewijs voor de effecten op antagonistische coactivatie is tegenstrijdig. Deze resultaten zouden clinici en fysiotherapeuten moeten motiveren om krachttraining te adviseren, bij het tegen gaan van afnemende spierfunctie bij aan leeftijd gerelateerde sarcopenie.

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Curriculum Vitae

Publications and communications

Curriculum Vitae

Pauline Arnold was born in Hilversum, The Netherlands, on the 3th of January 1958. She finished secondary school (VWOb) in 1977 and studied physiotherapy from 1977-1981 in Amsterdam, at Stichting Academie Fysiotherapie Amsterdam (S.A.F.A.). After graduation she started working in a physiotherapy practice in Baarn and started her own practice in 1986 in Blaricum. She worked as a physiotherapist on her own until 2008. From 1993 she studied 'Manual therapy' at SOMT in Amersfoort and graduated in 1997. In 2002 she started her Master of Science Education at Utrecht University, where she graduated in 2006 (cum laude) as Clinical Health Scientist, specialized in Physiotherapy research. She started to work parttime at SOMT, as a teacher in manual therapy, combining this with working in her own practice. Since 2008 she works fulltime at SOMT, at first in the Master Manual Therapy department, combining teaching with coordinating functions. Since April 2013 she is fulltime head of the Master Physiotherapy in geriatrics department at SOMT University of Physiotherapy, with organizing, teaching, developing and supervising (Mastertheses) responsibility. In January 2013 she started as a PhD-student at the FRIA-research group, led by professor dr. Ivan Bautmans. Pauline is married to Roland van Loenen and they have one daughter, Leonie, born in 1989.

Publications and communications

Publications in Peer-reviewed Journals:

Arnold P, Bautmans I. The influence of strength training on muscle activation in elderly persons: a systematic review and meta-analysis. Exp Gerontol. 2014; 58: 58-68. SCI IF 2014: 3.485

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Oral presentations on international conferences:

Arnold P (2017) - Florence (IT): World Congres WCO-IOF-ESCEO. Title: Can exercise counter muscle activation deficits?

Arnold P (2016) - Oostende (BE): Wintermeeting BVVG. Title: Age-related differences in muscle recruitment and reaction-time performance.

Arnold P (2014) - Gent (BE): Geriatrie Kinesitherapie Congres. Title: Age-related changes in muscle activation pattern and the influence of strength training in elderly.

Oral presentations on national conferences:

Arnold P (2015) - Amersfoort (NL): Tweede Nationaal Symposium musculoskeletale therapie en geneeskunde. Title: Leeftijd gerelateerde veranderingen in spieractivatie en de invloed van krachttraining bij ouderen.

Poster presentations:

Arnold P (2017) – Den Bosch (HOL): Nationaal Gerontologie Congres "Geriatriedagen". Title: Is muscle fatigue in hospitalised geriatric patients associated with circulating markers of inflammation?

Arnold P (2017) – Oostende (BE): Wintermeeting BVVG. Title: Is muscle fatigue in hospitalised geriatric patients associated with circulating markers of inflammation?

Arnold P (2015) - Manchester (UK): University of Manchester, PhD-day. Title: Age-related changes in muscle activation and muscle recruitment and the influence of resistance training in elderly.

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