Functional and Metabolic Consequences of Sarcopenia

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Catalog Data

Keywords: aging, muscle, strength, contraction, atrophy
Mots clés: vieillissement, muscle, force, contraction, atrophie

Abstract/Résumé
Sarcopenia associated with the normal aging process is often combined with the detrimental effects of a sedentary lifestyle in older adults, leading to a significant reduction in reserve capacity of the neuromuscular system. A clear example of the aging effect is the pattern of reduction in muscle strength after the sixth decade for both isometric and concentric contractions. However, older adults are relatively stronger for movements in which muscles lengthen, due to the inherent advantage of eccentric contractions, plus their stiffer muscle structures and prolonged myosin cross-bridge cycles. Also, the capacity for physiological adaptations in the motor pathways remains into very old age when an appropriate exercise stimulus is given, and older adults can obtain adaptations in both enhanced neural control of motor units and increased protein synthesis leading to moderate muscle hypertrophy. Since periods of sedentary lifestyle or bed rest due to illness can have severe detraimental consequences on the neuromuscular function of an older person, long-term prevention strategies are advocated to avoid excessive physical impairments and activity restrictions in this age group.

La sarcopénie, associée au processus normal du vieillissement, est souvent accompagnée des effets nuisibles d'un style de vie sédentaire avec comme résultat la diminution significa-

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tive de la capacité de réserve du système neuromusculaire. Voici un exemple type : la réduction de la force musculaire au cours d'actions isométriques et miométriques après la sixième décennie. À cause des caractéristiques inhérentes aux actions pliométriques, de la raideur musculaire plus importante et des cycles prolongés des ponts de myosine, les personnes âgées sont relativement plus fortes au cours de mouvement entraînant l’étirement des muscles. En outre, les capacités d’adaptation physiologique des voies motrices sont possibles même à un âge avancé en autant que les bons exercices soient pratiqués : les personnes âgées sont donc capables d’un meilleur contrôle des unités motrices et leurs muscles peuvent augmenter la synthèse de protéines qui se manifester par une hypertrophie modérée. Comme les périodes de sédentarité liées aux habitudes de vie et le repos au lit par cause de maladie peuvent avoir des conséquences néfastes sur la fonction neuromusculaire d’une personne âgée, il faut développer des stratégies de prévention à long terme pour éviter une trop grande détérioration physique et une réduction des activités chez ces individus.

Introduction

Effects of aging on the neuromuscular system can be readily demonstrated by measuring loss of lean body mass and muscular strength in older adults. While the age-related phenomenon of muscle wasting or sarcopenia is currently viewed as part of the normal changes associated with the final third of the human lifespan (see Doherty, Vandervoort, and Brown, 1993; Fiatarone Singh et al., 1999; Lexell, 2000), it must also be recognized that other factors such as a sedentary lifestyle, inadequate nutrition, and disease in the later years of life will have deleterious influences on muscular capacity (ACSM, 1998; Health Canada, 1999). Given that muscle tissue is an important contributor for many other body functions as well as force development (e.g., resting metabolic rate; maintenance of core temperature; regulation of blood glucose; protection of internal structures such as bones, organs, nerves and blood vessels), it is fortunate that sarcopenia is partly reversible with appropriate exercise interventions. This review will first provide an overview of these age-related changes in structure and physiology, which affect neuromuscular function and metabolic capacity. Potential bases and theories of biological aging are also briefly described and then a discussion is provided of the cellular mechanisms for potential hypertrophic adaptation of muscle in older adults who undertake strength training exercise programs.

Basis of Sarcopenia: The Loss of Functional Cells
From the Motor System

To begin, it should be noted that human nerve and muscle cells are generally considered to be in a post-mitotic state for most of the lifespan, after the early development phase (McComas, 1996). Thus, the longevity of some of these cells is quite amazing; for example, in centenarians some of their excitable cell complement will have been signaling action potentials and manufacturing a wide array of proteins for over 100 years. However, other nerve and muscle cells that were present at maturation will have since disappeared, leaving a reduced reserve; the extent of this reduction depending on the location in the body, age, and presence of disease
(Brody and Vijayashanker, 1977; Janssen et al., in press). Indeed, the existence of neuronal loss can be subtle and generally well-compensated in even the oldest individuals, while others who are less fortunate as they age may succumb to the dramatic effects of such diseases as Amyotrophic Lateral Sclerosis and Post-Polio Syndrome. It should also be noted that nerve cells can still remain anatomically present in aged people, yet be dysfunctional because of accumulated biochemical changes such as the presence of lipofuscin (McComas, 1996).

Skeletal muscles are the end-target of motor planning by the central nervous system, and the final movement signal goes through the motor unit (MU), consisting of a single motoneuron and its family of innervated muscle cells. There is considerable flexibility built into the peripheral motor pathways due to the variability in muscle contractile properties. With aging, the complement of motor units undergoes a process of reduction and adaptation, which in turn affects the capacity to produce forces on the joints. Using the electrophysiological technique of motor unit (MU) estimation, a striking decline in excitable MUs was found beginning in the seventh decade of life (Doherty et al., 1993b; McComas, 1996). Not surprising then are the cadaveric and radiological observations that the thigh and leg muscles have significant reductions in size during comparisons between older adults versus young (e.g., Hakkinen, Alen, et al., 1998; Hakkinen, Kallinen, et al., 1998; Janssen et al., in press; Lexell, 1993; Vandervoort and McComas, 1986; and see other articles in this issue based on presentations by Heymsfield and Roubenoff). Muscles of the upper limb do not seem to show quite as much atrophy, however, and this intriguing regional difference reflects the variability inherent in biological aging (Janssen et al., in press; Porter et al., 1995). What does seem consistent in human muscles with aging is an overall loss in the total number of muscle fibres for both the Type I and Type II components, along with a significant reduction in the average size of the latter. These observations have been demonstrated using either the in-vivo biopsy technique, or analysis of cadaveric specimens, usually in studies of the human quadriceps muscle (Table 1).

Histochemical evidence of fibre type grouping, along with preferential atrophy of the Type II fibres have been interpreted as evidence of an ongoing denervation and reinnervation process, in which some of the motoneurons have enlarged their own motor unit territory by capturing neighbouring fibres of failing ones (apparently failing in vitality because they have simply reached a predetermined, genetically programmed lifespan, cf. Lexell, 1993; McComas, 1996). In support of this theory of motor unit adaptation is the observation of extra large motor unit potentials during electromyographical recordings of older adults (Doherty, Vandervoort, Taylor, et al., 1993; Rice, 2000). Reduction in sarcoplasmic reticulum activity also appears to occur with aging (Delbono et al., 1997; Hunter et al., 1999), and this effect combines with the Type II fibre atrophy to produce a slowing of lower limb muscle contractile properties (Table 2). In turn, it has been observed that muscles of older adults will demonstrate tetanic fusion at lower frequencies of stimulation, thereby creating the possibility for the aged nervous system to use reduced firing frequencies to achieve a full contraction (Connelly et al., 1999; Kamen et al., 1995; Rice et al., 2000; Roos et al., 1999). Thus, aging can be viewed as an inevitable, genetically programmed process that causes both decline and physiological adaptation.
Table 1  Age-Related Reductions in Quadriceps Muscle Fibre Sizes

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Reduction of fibre size type 1</th>
<th>Reduction of fibre size type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larsson et al. (1978)</td>
<td>M</td>
<td>22-65</td>
<td>1%</td>
<td>25%</td>
</tr>
<tr>
<td>Essén-Gustavsson &amp; Borges (1986)</td>
<td>F</td>
<td>20-70</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Lexell et al. (1988)</td>
<td>M</td>
<td>15-83</td>
<td>25%</td>
<td>45%</td>
</tr>
<tr>
<td>Hakkinen et al. (1998)</td>
<td>M</td>
<td>29-61</td>
<td>1%</td>
<td>29%</td>
</tr>
<tr>
<td>Fiatarone Singh et al. (1999)</td>
<td>M &amp; F</td>
<td>72-98</td>
<td>+7%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Table 2  Muscle Twitch Contraction Durations in Young Versus Older Adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Muscle</th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yr)</td>
<td>CD (ms)</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>Vandervoort &amp; McComas (1986)</td>
<td>DF 20-32 183</td>
<td>80-100 255</td>
<td></td>
</tr>
<tr>
<td>Connelly et al. (1999)</td>
<td>EF 22-38 198</td>
<td>60-81 203</td>
<td></td>
</tr>
<tr>
<td>Roos et al. (1999)</td>
<td>DF 20-22 185</td>
<td>80-85 232</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VM 19-35 161</td>
<td>73-91 177</td>
<td></td>
</tr>
</tbody>
</table>

CD = contraction duration (time-to peak tension + half-relaxation time); ms = milliseconds; EDB = extensor digitorum brevis; EF = elbow flexors; VM = vastus medialis; DF = dorsiflexors of ankle; PF = plantarflexors of the ankle.

Aging and Muscle Strength

Given the age-related loss of muscle mass, it is not surprising that there is an associated loss of muscle strength when comparisons are made across the adult age span. This loss has been clearly demonstrated in simple isometric tests, and in such comparisons among people of different ages, decreases in voluntary strength do not become apparent until after the age of about 60 (see Figure 1). Healthy people in the seventh and eighth decades score on average about 20 to 40% less during tests of isometric strength than young adults, and the very old show even greater (50% or more) reduction. Muscles in both the upper and lower limbs, including proximal and distal locations, have been examined, and the size of the age effect shows some minor variation from muscle to muscle (see Doherty,
Vandervoort and Brown, 1993). Males and females appear to show similar age-related trends when their values are compared on a relative basis.

Concentric muscle actions (tests in which the muscle is allowed to shorten) will also produce lower values in older people than young adults (Porter et al., 1995; Poulin et al., 1992; Vandervoort et al., 1990). At higher velocities of movement, the age-related deficit is quite marked, and others have demonstrated that power output is also considerably reduced in older people when they’re tested for maximal rate of doing work (Bassey, 1997), maximal rate of evoked or voluntary isometric force development (Hakkinen, Newton, et al., 1998; Vandervoort and Hayes, 1989), or ability to use the stretch-shortening cycle effectively in jumping (Bosco and Komi, 1980). Since many activities of daily living involve dynamic movements where power is generated by the muscles (e.g., walking, stair-climbing, sports), the functional impairments associated with low power capacity are of much current interest. It may be, for example, that very old adults no longer have adequate propulsive power in their plantar flexor muscles for achieving the same gait pattern as young adults, thereby slowing them considerably, creating excessive muscle fatigue (Faulkner and Brooks, 1995) and also putting more requirements on other leg muscles (DeVita et al., 1998).

There is, however, one important exception to the pattern of strength loss with aging described above. In several studies of various muscles, it has been observed that strength decreases with aging have been found to be consistently less for the eccentric type of muscle action (lengthening) than during either isometric or concentric contractions (see Figure 1), and in some situations there may be no difference at all (e.g., Porter et al., 1997; Poulin et al., 1992). Apparently the
changes with aging in muscle mass, contraction speed, and connective tissue (cf. Brooks and Faulkner, 1994; Souminen, 1997) that reduce strength when muscle shortens enhance its performance while being lengthened. Although the explanation for why aged muscle has this relative advantage to lengthen against resistance still remains to be fully clarified, it is a phenomenon worth noting. For example, one possible functional advantage is that for a given absolute load (e.g., body weight), the intensity of muscular effort and related cardiovascular response is less for exercise involving the eccentric condition versus concentric (Figure 2, Thompson et al., 1999), thereby suggesting older people might find some relative advantage in learning to use their muscles under lengthening situations (Krishnathasan and Vandervoort, 2000). In turn, their fatigue-resistance at a given intensity of work can be enhanced during eccentric loading, as compared to concentric (i.e., because the muscle can work at a lower relative intensity of maximum capacity for a given task requirement, see Faulkner and Brooks, 1995).

**Eccentric Resistance Exercise and Capacity for Protein Synthesis in Older Adults**

Learning to utilize the apparent strength advantage of muscle for lengthening types of activation appears to be quite useful for older adults. Initially, they may experience difficulty with the coordinative aspect of switching movement patterns from one type of pattern to another (Enoka, 1997; Greene and Williams, 1996). We studied this phenomenon in our laboratory within the context of concentric/eccentric strength training exercises themselves. Via use of an isokinetic, motor-driven
dynamometer, subjects’ ankle joints were rotated into plantar flexion while they resisted with their dorsiflexor muscles as much as possible, a form of training that proved to be an effective way to increase strength of the ankle dorsiflexors (Porter and Vandervoort, 1997).

Older adults underwent considerable learning with this task, going from an initial pattern of eccentric movements that were quite uncoordinated to a more smooth and effective torque generation pattern (Connelly et al., 2000). We noted that this learning effect was most pronounced at a rapid velocity, and also that young adults had better initial performances for baseline measurements prior to training. Maximal voluntary torque levels also improved, along with EMG evidence that the older adult’s nervous system adapted by learning to activate the dorsiflexor muscles at a higher intensity (Connelly and Vandervoort, 2000). Thus, in our studies and those of others (e.g., Hakkinen, Newton, et al., 1998), evidence of improved intensity and coordination of muscle activation levels in older adults has been found, as well as moderate amounts of muscle hypertrophy (e.g., McCartney et al., 1996).

Since age-related changes in muscle mass reflect a decreased synthesis rate of mixed muscle proteins, myosin heavy chains and mitochondrial proteins rather than excessive catabolism (Balagopal et al., 1997; Short & Nair, 1999), there has been recent interest in how to stimulate increased anabolic processes in older people (see Table 3). Research to date has been encouraging; resistance training at both moderate and heavy intensities has increased protein synthesis in the young and older subjects. Yarasheski and colleagues (1993) observed increases from the acute effects of progressive daily resistance training over 2 weeks on muscle protein synthesis in a group of men and women aged greater than 60 years. Yarasheski and colleagues (1995) then found further evidence of increased mixed muscle protein synthesis (~50%) after 16 weeks of progressive resistance exercise training in older men 65 to 75 years old, along with improved muscle strength. However, Welle and colleagues (1995) reported in their study that 3 months of progressive resistance training in older men and women (62–72 years old) resulted in no significant increase in myofibrillar protein synthesis, and Yarasheski and colleagues (1999) suggested that a possible reason for the varying results was a different exercise intensity in Welle and colleagues’ (1995) study. In their most recent study, Yarasheski and colleagues (1999) examined the effects of resistance training on the rate of mixed protein synthesis in frail elderly (72–92 years old) women and men, and confirmed that 3 months of supervised progressive resistance training stimulated the rate of mixed protein synthesis in the vastus lateralis muscle. Therefore, the skeletal muscle contractile proteins in even the very old, frail population still retain the ability to synthesize new protein at an increased rate in response to an adequate exercise stimulus.

As stated previously, eccentric training may be the optimal way to provide a strong stimulus for muscle tissue adaptation in the elderly population, since it appears that the age-related changes in muscle mass, contraction speed, and connective tissue enhance the muscles’ ability to achieve relatively high forces under eccentric loading (Brooks and Faulkner, 1994; Porter et al., 1995; Suominen, 1997; Vandervoort et al., 2000). Therefore, older individuals are capable of generating relatively high eccentric force compared to concentric force, which in turn indicates that the potential stimulus for muscle tissue adaptation could be greater via
### Table 3  The Effects of Resistance Training Exercise on Skeletal Muscle Protein Synthesis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>n</th>
<th>Duration</th>
<th>Frequency</th>
<th>Sets</th>
<th>Repetitions</th>
<th>Results</th>
</tr>
</thead>
</table>
| Yarasheski et al.       | M/F | 63 ± 1| 6  | 2 weeks    | 5 days/week| 2-4  | 4-10        | • initial fractional rate of muscle protein synthesis was lower in the elderly, but increased at a comparable rate to the young  
• whole body protein breakdown rate did not change after training in both the young and old                                                                                                  |
| (1993)                  |     | 24 ± 1| 6  |            |            |      |             |                                                                                                                                                                                                       |
| Yarasheski et al.       | M   | 64-75 | 23 | 16 weeks   | 4 days/week| 4    | 5-10        | • muscle mass was unchanged in the elderly after training   
• vastus lateralis muscle protein synthesis increased ~50%   
• muscle strength and anabolism were not enhanced by exercise plus daily growth hormone supplementation                                                                                     |
| (1995)                  |     |       |    |            |            |      |             |                                                                                                                                                                                                       |
| Welle et al. (1995)     | M/F | 62-72 | 9  | 3 months   | 3 days/week| 3    | 8           | • fractional myofibrillar protein synthesis was 33% slower in the older group and remained 27% slower after training   
• training did not significantly increase myofibrillar protein synthesis in either the young or old  
• whole body protein turnover increased only in the young                                                                                                                                         |
|                         |     | 23-21 | 9  |            |            |      |             |                                                                                                                                                                                                       |
| Yarasheski et al.       | M/F | 76-92 | 12 | 3 months   | 3 days/week| 1-3  | 6-12        | • fractional and absolute rates of vastus lateralis muscle protein synthesis increased in the trained group and remained unchanged in the control group   
• whole body protein synthesis increased only after resistance training   
• training increased total body mass   
• insulin-like growth factor I significantly increased (~5 fold) in both of the exercise groups  
• suggesting it may be a mechanism of increased protein synthesis required for new or hypertrophied myofibril formation                                                                                  |
| (1999)                  |     | 5     |    |            |            |      |             |                                                                                                                                                                                                       |
| Fiararone Singh et al.  | M/F | 72-98 | 26 | 10 weeks   | 3 days/week| 3    | 8           |                                                                                                                                                                                                       |

*Note.* Resistance training exercise includes both upper and lower body exercises.
eccentric resistance exercises. Fiatarone Singh and colleagues (1999) explored the possible benefit of eccentric muscle training in their extensive investigations of weight-lifting exercise in frail elders. They concluded that the long-term adaptation to their high-intensity resistance training, which included an eccentric component, was characterized by muscle damage and repair cycles that were associated with large gains in strength. Their muscle biopsy results suggested that the early adaptation to the progressive resistance training includes such muscle damage as a step in a remodeling process that ultimately leads to regeneration of skeletal muscle. Further, the appearance of insulin-like growth factor I in the skeletal muscle of their frail elderly subjects following standard resistance training indicates that it may be a mechanism of increased protein synthesis required for new or hypertrophied myofibril formation.

In summary, it can be concluded from considerable gerontology research on the human neuromuscular system that, following the growth and maturation phase, maximal muscle strength levels of healthy men and women are well-maintained through middle age until after the sixth decade of life. However, older adults experience an age-related sarcopenia that reduces muscle mass and strength, especially in the lower limb, which in turn leads to potential health problems such as impairments in mobility and activities of daily living, obesity, metabolic disorders, and reduced aerobic capacity. The pattern of strength reduction varies according to the type of muscle contraction B greatest for concentric contractions and least for eccentric actions. Thus, older adults appear to have a relative advantage for movements in which muscles lengthen rather than shorten, attributable to their stiffer muscle structures and prolonged cross-bridge cycle of the aging myosin. The knowledge about how to attenuate or prevent the effects of age-related sarcopenia will be advanced in the future with further investigation of protein synthesis following exercise, especially with improved methodology to specifically investigate rates of synthesis of individual muscle proteins as opposed to mixed muscle proteins (Proctor et al., 1998). The topics of the most appropriate strength training programs for older adults and future research directions in this area are dealt with more fully in the accompanying paper by Porter in this issue.

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**Acknowledgments**

This paper is based on gerontology research conducted with many colleagues, students, and older people whose contributions are much appreciated, and was funded by the Canadian Fitness and Lifestyle Research Institute and the Natural Sciences and Engineering Research Council of Canada.

*Received April 4, 2000; accepted in final form April 11, 2000*. 
