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Impact of Aging on Endurance and Neuromuscular Physical Performance: The Role of Vascular Senescence

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Abstract The portion of society aged ≥60 years is the fastest growing population in the Western hemisphere. Aging is associated with numerous changes to systemic physiology that affect physical function and performance. We present a narrative review of the literature aimed at discussing the age-related changes in various metrics of physical performance (exercise economy, anaerobic threshold, peak oxygen uptake, muscle strength, and power). It also explores aging exercise physiology as it relates to global physical performance. Finally, this review examines the vascular contributions to aging exercise physiology. Numerous studies have shown that older adults exhibit substantial reductions in physical performance. The process of decline in endurance capacity is particularly insidious over the age of 60 years and varies considerably as a function of sex, task specificity, and individual training status. Starting at the age of 50 years, aging also implicates an impressive deterioration of neuromuscular function, affecting muscle strength and power. Muscle atrophy, together with minor deficits in the structure and function of the nervous system and/or impairments in intrinsic muscle quality, plays an important role in the development of neuromotor senescence. Large artery stiffness increases as a function of age, thus triggering subsequent changes in pulsatile hemodynamics and systemic endothelial dysfunction. For this reason, we propose that vascular senescence has a negative impact on cerebral, cardiac, and neuromuscular structure and function, detrimentally affecting physical performance.

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> **Key Points**
>
> Above the age of 60 years, aging is associated with a substantial decline in global physical performance (endurance exercise capacity and neuromuscular strength and power).
>
> Vascular senescence may represent a common link between declines in cardiac function, neuromuscular function, brain function, and physical function with aging.

1 Introduction

Aging is a natural and complex process influenced by many factors that can be classified as intrinsic (primary aging, e.g., genetic factors), extrinsic (secondary aging, e.g., psychosocial and environmental factors) and related to the effects of disease [1, 2]. The biological nature of this phenomenon and the physiological mechanisms underlying its progression remain largely unknown. Despite that the United Nations has indicated that age ≥60 years may be denoted as old age, the developing world often delimits old age not by years but by new roles, loss of previous roles, or the inability to make an active contribution to society [3]. Thus, the definition of old age continues to change, especially as life expectancy in developed countries has risen to

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beyond 80 years. Gerontologists distinguish between three subgroups: younger older adults (60–74 years), older adults (75–85 years), and very old adults (>85 years) [4]. Since a considerable decrease in physical and cognitive function typically occurs beyond the age of 80 years, clinicians often distinguish between two additional subgroups of older adults: those aged <85 years (old) and those aged >85 years (old-old) [4], with some classifications considering adults aged ≥100 years as oldest-old.

The number of individuals aged >60 years worldwide is expected to nearly triple from 760 million in 2010 to 2 billion in 2050 [5]. The oldest group (≥80 years, including centenarians) is the most rapidly expanding among Westerners and is expected to increase by 387 % until the year 2030 [6–8]. However, longevity comes at a price that includes a higher rate of morbidity, functional, and mental disability and the eventual loss of independence [9], all of which may play an important role in an increasing use of healthcare services and a reduction in quality of life in the elderly [10, 11]. Human aging involves a progressive decline in cognitive function, cardiovascular (CV) function, skeletal muscle mass (sarcopenia), and neuromotor performance (dynapenia) (Fig. 1). In the elderly, loss of independence is therefore associated with neurodegeneration, reduced muscle strength/power, and increased physiological fatigue [12]. For this reason, one purpose of this narrative review of the literature was to discuss the age-related physiologic changes in global physical performance operationally defined as encompassing exercise endurance, exercise economy, anaerobic threshold, peak oxygen uptake (VO_{2peak}), and neuromuscular strength and power. In addition, we intended to characterize the influence of aging on cerebrovascular, cardiorespiratory, and systemic vascular function. Finally, we argued that vascular changes with aging are important effectors of CV, cerebrovascular, and neuromuscular functional decline, impacting physical performance.

2 Changes in Physical Performance with Aging

2.1 Exercise Endurance and Aging

Within the general population, exercise endurance is objectively measured as the amount of work done during a standardized exercise protocol using large muscle mass (e.g., Bruce treadmill test or 6-min walking test). While a great deal of variation exists, an average decline of 20 % in endurance capacity has been reported between the ages of 40 and 60 years due to a deterioration in both aerobic and musculoskeletal function [13]. From then on, up until the age of 94 years, a linear age-related decline can be observed in both men and women for total duration of exercise in response to the Bruce treadmill test (~0.3 min/ year) [14].
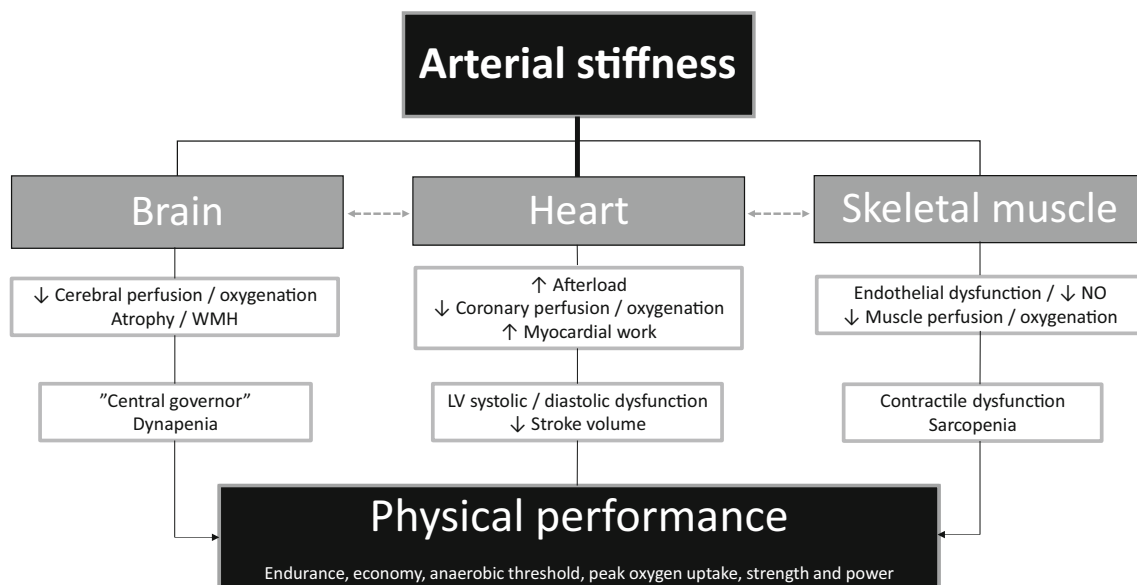

Fig. 1 Schematic representation of the impact of vascular senescence on physical performance. Aging interacts with human physiology at the vascular level and this has a negative impact on cerebral, cardiac and neuromuscular structure and function, detrimentally affecting exercise performance. *WMH* white matter hyperintensities, *LV* left ventricle, *NO* nitric oxide

Aged athletes represent a human niche for which exercise endurance is more closely linked to their personal bests achieved during a training season [15]. For this reason, in these individuals, exercise endurance is typically quantified as the time to complete long-distance events (e.g., 10-km running time or 1500-m swimming time) [16]. Its values decline modestly after ∼35 to 40 years of age and are well maintained until ∼60 to 70 years [16–18]. From a physiological point of view, this suggests that most trained adults should be able to sustain functional capacity until this age [16]. In contrast, after 60–70 years of age, endurance exercise performance declines exponentially [16–18]. Research also indicates that this decrease follows a sexually dimorphic pattern and depends on task specificity. This is supported by data demonstrating that the deterioration in running endurance is up to threefold greater in women than in men, with the largest differences occurring at an age >60 years [16]. It is additionally corroborated by findings indicating that the overall magnitude of reduction in swimming endurance with advancing age is ∼30 % smaller than that observed in running endurance. Moreover, it is interesting to note that sex differences in age-related declines in swimming endurance are limited to short-duration events [18]. These differences are no longer observed in response to longer-duration events (i.e. 1-h swimming distance) [19].

Cardiopulmonary exercise testing is a methodology that assesses physical function by linking individual endurance capacity to physiological parameters and the underlying metabolic substratum. In humans, VO_{2peak}, together with exercise economy and the anaerobic threshold (AT), is an important physiological factor related to exercise endurance [15, 20, 21]. There is considerable evidence to support the clinical significance of all these factors as they are commonly reduced in several pathological conditions (e.g., coronary artery disease, myopathic heart disease, valvular heart disease, congenital heart disease, peripheral arterial disease; diabetes, anemia, obesity, obstructive lung disease, and restrictive lung disease) [20, 22]. Interestingly, the decline in endurance capacity with advancing age can be attributed to collective reductions in most of these physiological determinants of physical functioning [15, 23].

2.1.1 Exercise Economy and Aging

Exercise economy is an important factor that contributes to endurance capacity. Economy refers to how much speed or power can be generated for a given level of VO_2 (ml kg^{-1} min^{-1}) during activities such as walking and running. Exercise economy depends on the interaction of numerous factors, including muscle morphology, elastic elements, and joint mechanics in the efficient conversion of chemical energy to mechanical speed. Good exercise economy is manifested by lower fractional utilization of VO_{2peak} at a given speed [24]. Even though VO_{2peak} is an important determinant of health and physical function in the elderly, exercise endurance depends on a complex interplay between VO_{2peak} and exercise economy (Fig. 2) [25].

The influence of exercise economy on age-related decreases in endurance capacity is poorly understood. However, it is evident that, while running economy remains relatively well preserved with aging, this is not sustained for walking economy. Walking has a 15–20 % greater metabolic cost in the elderly than in younger adults [21, 26]. Importantly, past research has shown that this is paralleled by deterioration in walking performance (a key predictor of morbidity among older adults) with advanced age [27, 28]. Over the past few years, there has been some interest in unraveling the factors underlying disturbed walking economy in this specific population. Data from these studies indicate that older adults exhibit a similar cost of balance and perform external mechanical work to a similar or lower level during walking than younger individuals [21, 29]. Yet, both a decrease in muscular efficiency and an increase in antagonist leg muscle coactivation have also been shown to contribute to the greater oxygen cost of walking in both sedentary and active older adults [21, 26, 29–31]. Nevertheless, to our knowledge, no study has found a single mechanical factor accounting for
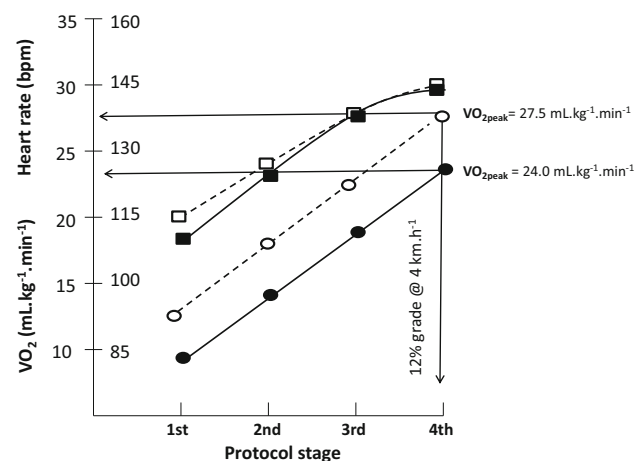

Fig. 2 Representative example of the aerobic profile of two older adults (age 75 years) obtained in response to a modified Bruce graded exercise protocol. The figure includes both submaximal and maximal data for VO_2 (oxygen uptake) (*circles*) and heart rate (*squares*). *Open symbols*: lower exercise economy, but higher VO_{2peak}; *closed symbols*: higher exercise economy, but lower VO_{2max}. Protocol stages: *1st* 2.7 km h^{-1}, 0 % grade; *2nd* 2.7 km h^{-1}, 5 %; *3rd* 2.7 km h^{-1}, 10 %; *4th* 4.0 km h^{-1}, 12 %. Importantly, exercise is terminated at exactly the same stage of the Bruce protocol in both individuals. VO_{2peak} peak oxygen uptake, *bpm* beats per minute

the 15–20 % greater metabolic cost of walking in this population.

2.1.2 Anaerobic Threshold and Aging

The ability to exercise for long periods at high fractions of the VO_{2peak} is an important determinant of endurance capacity and physical performance. The self-selected fractional utilization of the VO_{2peak} during prolonged sub-maximal exercise is linked to the AT [15]. It has long been determined that, when measured in absolute terms (i.e., absolute VO_2 or speed), the AT declines with the aging process [32]. In line with previous reports, exercise endurance is closely associated with not only VO_{2peak} but also velocity at the AT in both male and female runners aged 21–69 years [11, 33]. Thus, there is some evidence to support that the age-related reduction in endurance capacity may partially rely on a progressive decrease in the AT absolute values. This notwithstanding, it is generally believed that, while a reduction in the AT appears to play a primary role in limiting exercise endurance from young adulthood to middle age, this is not the case from early to later middle age. Under these circumstances, additional losses in endurance are mediated more strongly by the reduction in VO_{2peak} [16].

When expressed as the percentage of VO_{2peak} (relative terms), the AT values do not follow a linear decrease with aging. In fact, under these conditions, a U-shaped relationship has been described between the AT and VO_{2peak} [34]. That is, it appears that the AT in individuals with low and high fitness levels is higher than that seen in those with normal fitness levels [34, 35]. Ultimately, this means that the physiological reserve for engaging in heavy exercise intensities is substantially reduced at both extremes of the physical fitness spectrum in the elderly.

2.1.3 Peak Oxygen Uptake and Aging

The upper limit of aerobic metabolism that can be achieved during exercise is termed VO_{2peak}. This usually occurs during exercise using relatively large muscle mass (e.g., running, swimming, and cycling) and represents the integrative ability of the heart to generate a high cardiac output, total body hemoglobin, high muscle blood flow, and muscle O_2 extraction, and, in some cases, the ability of the lungs to oxygenate the blood [36]. Despite being the most important determinant of age-related changes in large-muscle endurance in athletes, the fall in VO_{2peak} with age is steeper than the reductions seen in long-distance exercise performance [16]. This is likely explained by a smaller decline in other determinants of exercise performance over the years (e.g., exercise economy and AT) [11, 35]. Conversely, in sedentary adults, the age-associated decline in

VO_{2peak} is similar to that seen in endurance work capacity from the age of 55 to 94 years [14].

In a longitudinal study (initial median age of 70 years), VO_{2peak} was estimated to decline 6.9 and 3.9 ml kg^{-1}-min^{-1} per decade in men and women, respectively [37]. In another report, the losses per decade in a group of participants aged 55–85 years were 4.3 and 1.9 ml kg^{-1} min^{-1} in men and women, respectively [38]. More recently, it has been reported that VO_{2peak} remains constant to a large extent up to the age of 30–35 years and then declines 5–8 % per decade until the age of 60 years. From then on, individuals aged 60–69 years as well as those aged >70-years experience a more pronounced deterioration (20 % per decade) in the ability to transport oxygen from the air for consumption in the working muscles [39]. Thus, despite the differences in the existing literature, it seems that the decline in VO_{2peak} is $\geq$4–5 ml kg^{-1} min^{-1} per decade and continues into later life [40].

2.2 Neuromuscular Performance: Muscular Strength and Power with Aging

In addition to changes in muscular endurance and VO_{2peak}, aging may also be accompanied by decreases in muscle strength and power. These changes affect the ability of older people to perform functional tasks [41, 42]. Just as importantly, they also predispose to osteopenia, osteoporosis, reduced physical activity, decreased daily energy expenditure, and adverse changes in body composition (e.g., increased adiposity and visceral fat deposition) [43–45]. Low skeletal muscle strength has clinical consequences. For instance, strength is inversely and independently associated with death from all causes and from cancer from the age of 20 to 80 years, even after adjusting for VO_{2peak} and other potential confounders [46, 47].

Muscle strength is usually measured by quantifying the maximal value of force that a muscle group produces during a single voluntary contraction. Strength levels usually peak between 25 and 35 years of age and then remain relatively stable until the age of 50 [12, 48–51]. Even though muscle strength decreases after the fifth decade of life, the higher rate of decline has been shown to occur after 60 years [52, 53]. Data from longitudinal studies indicate that, from then on, the age-related decline in muscle strength occurs at a rate of 2–5 % per year [54–57]. The magnitude of loss in muscle strength is more impressive in the lower than in the upper limb [58]. Strength loss is also more evident in concentric and isometric muscle actions than in those involving eccentric contractions [49, 59–62]. It is therefore evident that poor levels of muscle strength affect the ability of the elderly to perform motor actions involving the lower limbs (e.g.,

walking, stair ascent and/or descent), thus increasing the risk of falling in this specific population [63].

The vertical jump allows for determination of the instantaneous muscle power—an indirect index of the maximal rate of energy released from the hydrolysis of adenosine triphosphate stored in the muscles [64]. As described for muscle strength, instantaneous muscle power is substantially reduced at an older age [65, 66]. However, during the aging process, muscle power declines at an even faster rate than maximal strength [67–73]. The existing data suggest that, at 75 years of age, instantaneous muscle power decreases to about 50 % of the value measured at 20 years (both in absolute and relative terms—per unit of body mass) [65]. More recent research has shown that, in well-trained masters athletes, peak anaerobic power declines at a rate of ∼8 % per decade from 35 to 64 years [66]. As described for muscle strength, the age-related reduction in muscle power is also more prominent in the lower limb [70, 74]. Because of its positive correlation with everyday task performance (i.e., rising from a chair, stair climbing, fast walking, dynamic balance, and postural sway), muscle power is believed to be more strongly associated with functional independence than maximal strength [10, 69, 75–77]. In fact, poor muscle power is associated with a threefold greater risk for mobility impairment than reduced muscle strength, and improving muscle power leads to improvements in physical function independent of changes in strength [76, 78]. Further corroborating this notion, previous findings also indicate that muscle power is a better predictor of falls among the community-dwelling elderly than is muscle strength [79]. Thus, its deterioration with aging can lead to a dramatic decrease in independence and quality of life.

3 Physiological Correlates of Age-Associated Changes in Physical Performance

3.1 Muscle Structure and Function

Physiological factors that contribute to age-related decrements in muscle strength, power, and endurance are multifactorial but may be partially mediated by changes in skeletal muscle structure and function. The gradual loss of muscle mass has been identified as a primary cause of age-related decrease in muscle strength (generally explaining >90 % of its variation) [56]. Loss of muscle mass, together with concomitant changes in metabolic machinery and vascular capillarization, have also been implicated in age-associated reductions in VO_{2peak} via effects on peripheral oxygen delivery and extraction [80–83]. Thus, past studies support that muscle mass, strength, and power are all associated with exercise endurance and physical

performance in older adults [80, 82, 84]. The reduction in muscle mass is particularly impressive after the age of 50 years. Evidence is compelling that total muscle mass declines by ∼30 % from the fifth to the eighth decade of life [85]. Data from other reports suggest this process reaches a rate of decline of ∼1.4 % per year after the age of 50 years [56]. The loss of muscle mass with aging is followed by an increase in the intramuscular content of non-muscle tissue (adipose and connective tissue), which may also independently affect muscle contractile properties and exercise endurance [86, 87].

Satellite cells are stem cells that have a primary role in the regulation of muscle growth and control of muscle mass [88]. Activation, proliferation, and differentiation of these cells represent important elements participating in the increase of myonuclei number, protein turnover, and muscle hypertrophy [89, 90]. Older adults exhibit a decreased number of satellite cells per muscle fiber than younger adults [91, 92] and, thus, a reduced myogenic potential. The activation of satellite cells, as well as the metabolic balance between muscle tissue anabolism and catabolism, is dependent on several chemical regulators. Insulin-like growth factor (IGF)-1 is one of the main factors that influences the activation of satellite cells positively. Conversely, myostatin has been demonstrated to exert a negative influence on muscle growth [90]. Interestingly, several studies have shown that serum myostatin levels are substantially increased in the elderly. This implicates greater inhibition of satellite cell activation (primarily in type II fibers), leading to age-related sarcopenia [93–95].

The progressive loss of muscle fibers is largely responsible for the decline in muscle mass with aging [85]. The vastus lateralis muscle undergoes extensive changes in the number of muscle fibers (loss of ∼35 %) between the ages of 50 and 80 years [96]. Importantly, this affects all fiber types with similar magnitude [54, 85, 96–100]. Thus, in human aging, muscle deterioration is not characterized by substantial changes in muscle fiber type relative distribution. Further evidence has suggested that mitochondrial-mediated apoptosis may play an important role in the progression of muscle fiber loss in aging [101]. To date, the loss of muscle fibers past the age of 50 years has not been shown to be reversible by any form of training, which suggests that the progressive aging of skeletal muscle mass is not completely preventable [102].

Despite not being the primary cause for muscle atrophy, decreased muscle fiber size also contributes to sarcopenia [54, 59, 85, 98, 99, 103]. The age-related muscle atrophy seems to be particularly impressive in type II fibers (∼10 to 40 % smaller in muscle tissue collected from elderly than from young controls) [56]. In contrast, the size of type I fibers (i.e., slow twitch) does not change considerably

with age [104–106]. Moreover, it has been shown that type IIB muscle fibers tend to be more affected than type IIA [54, 97]; this suggests the different subtypes of fast-twitch fibers are differently affected by senescence. This is relevant because this pattern of selective atrophy in type II muscle fibers likely underlies the etiology of reduced muscle strength and power in elderly. As importantly, since individuals who lack strength for upright locomotion may not reach the true limits of their VO_2 reserve, muscle weakness may also contribute to decreases in aerobic capacity by limiting the ability of the elderly to reach higher levels of work [82, 84].

Muscle quality, also known as specific muscle tension, is defined as the maximum force normalized to muscle cross-sectional area [107]. The interaction between aging and specific muscle tension has generated some controversy in the literature. While some studies found that aging does not influence specific tension [107–110], others reported decreased muscle tension in the elderly [49, 74, 99, 111–114]. It has been argued that such contradictory results might reflect the following methodological differences between studies [115]: (1) muscles studied (upper or lower limb muscles) [49, 99], (2) participants' sex [49, 114, 116], (3) contraction type [117], (4) velocity chosen for isokinetic testing [109], (5) experimental design (i.e., cross-sectional or longitudinal) [107], and (6) methods used to quantify specific tension (i.e., whole muscle or single fiber testing) [56]. For instance, Frontera et al. [56] found similar values for specific tension between younger and older individuals when testing the whole muscle cross-sectional area. In contrast, it has been shown that older skeletal muscle exhibits a 34 % reduction in intrinsic force-generating capacity [118]. Hypothetically, this might be caused by age-related alterations in cellular and molecular processes, such as changes in satellite cell population, excitation-contraction coupling, myofilament interaction, mitochondrial function, and adipocyte infiltration [119, 120]. However, another experimental design showed that differences in single muscle fiber peak force were virtually dissipated when normalized to cell size [103]. These findings do not support the notion that the intrinsic properties related to myofilament interaction are affected with age. Conversely, they indicate that the reduction in whole muscle strength and function with aging is more closely regulated by quantitative than by qualitative parameters of single muscle fiber contractile function [103].

Aging also influences other factors involved in the ability of individual muscle fibers to perform powerful contractions. Among these, the increase in the duration of twitch contraction together with prolonged half-relaxation time is particularly important [113]. Maximal muscle fiber shortening velocity has also been shown to be reduced with aging in some [121] but not all studies [103], and there is some evidence pointing towards changes in the excitation–contraction coupling process (i.e., decreased amount of Ca^{2+} release from the sarcoplasmic reticulum of fast-twitch fibers) [118, 122]. Finally, there is compelling evidence that glycation-related cross-linking of intramuscular connective tissue may contribute to altered muscle force transmission and function with healthy aging [123].

From a metabolic standpoint, while glycolytic enzymes seem to be slightly affected, aerobic enzymes have consistently been shown to decline throughout the aging process [97, 124, 125]. Cross-sectional experimental designs exploring the effects of aging on intramuscular capillarization have also reported some contradictory findings. Some indicate that the number of muscle capillaries tends to be reduced in older individuals [97, 126], whereas others were not able to replicate these findings [127, 128]. Nonetheless, with aging, there appears to be redistribution of muscle blood flow from highly oxidative to highly glycolytic muscle fibers [129]. Greater flow to type II muscle fibers may be a compensatory adaptation aimed at preserving contractile function concomitant with reduced fiber volume. Indeed, it has been shown that, despite age-associated changes in muscle mass, single fiber contractile properties of type II fibers are largely preserved [130].

3.2 Neural Structure and Function

The age-related decrements in strength, power, and muscular endurance may be partially explained by a decrease in voluntary neural drive [70, 115, 131]. Senescence leads to a decomposition of the α-motor neurons within the spinal cord [96, 132–136], with a consequent denervation and re-innervation of muscle fibers [134, 137]. This degeneration process occurs mostly after 60 years of age [100]. In fact, the number of motor neurons in the spinal ventral horn may be reduced by a margin of 50 % at the age of 60 years [132]. While some muscle fibers simply necrotize shortly after denervation, others are re-innervated by collateral branches arising from the remaining spinal motor neurons [134, 138]. The process of re-innervation typically means that the affected muscle fiber becomes innervated by a motor axon displaying a different pattern of synaptic discharge. This accounts for the phenotypic changes in muscle fibers and leads to a more homogeneous motor unit distribution within the muscle. Thus, in the aging muscle, each motor unit integrates a greater number of muscle fibers [115]. The reduction in the number of motor units, combined with the strengthening of the remaining units, affects motor unit recruitment and decreases the ability to discriminate force accurately. Thus, aged people experience decreased performance in most tasks involving fine motor control.

Aging also affects other mechanisms of intramuscular coordination, such as the rate coding (i.e., action potential firing rates at which motor neurons discharge), which has a fundamental role in power production and contraction speed [139]. The duration of twitch contraction of the tibialis anterior during maximal voluntary contraction is 23 % longer [140] and the maximal rate of torque during ballistic contractions is lower in older adults than in younger controls [141]. Both these studies also found lower motor neuron firing rates in the elderly. Importantly, this is similar to that described for voluntary isometric contractions of the first dorsal interosseous muscle performed at 20 and 50 % of maximal voluntary contraction [142]. The age-related prolongation of motor neuron after hyperpolarization [143] and the nervous fiber degeneration in the remaining motor neurons are possible explanations for the reduced maximal rate of motor unit discharge in the elderly. Electrophysiological studies within humans and animals found lower nerve conduction velocities in the peripheral nervous system of older than in younger adults [144]. These findings may well be secondary to alterations in myelinated fibers occurring with aging (i.e., size and intrinsic properties of myelin sheaths) [144].

An increase in agonist/antagonist co-activation during maximal voluntary contraction might further contribute to decreasing maximal strength in older individuals [70, 145, 146]; however, this is not a universal finding [147]. The agonist/antagonist co-contraction level is an important variable because part of daily life movement is ballistic in nature. Successful performance in ballistic movement depends on proper coordination between agonist and antagonist muscles, which relies on the integrity of the structures underlying the mechanism of reciprocal inhibition. During a visual step-tracking elbow movement, the elderly had higher levels of agonist/antagonist co-activation because they exhibited longer periods of forearm acceleration while performing slowly than young subjects [148, 149]. Despite slowing the expression of voluntary body movement, increased agonist/antagonist co-activation increases joint stiffness [150]. In the elderly, this may represent a strategy to minimize the age-related tendency for increased movement variability in ballistic movements [148, 151].

3.3 Brain Structure and Function

Aging is associated with profound structural changes to the brain, including many key regions necessary for motor performance, sensorimotor integration, perceived exertion, and volitional drive. Structural changes extend beyond the primary motor cortex and may also include the prefrontal cortex, cerebellum, and hippocampus [152]. These areas have been implicated in endurance exercise performance via their inter-connectivity to the motor cortex and central command ('central governor'). They may also affect exercise performance via reception of afferent feedback regarding autonomic arousal, cardiac perfusion, thermoregulation, thirst/fluid loss, muscle damage, and perceived exertion [153–157].

Recent evidence indicates that age-related muscle weakness is not entirely explained by the classical concept of muscle atrophy. Overall, these findings suggest that the communication between the brain and skeletal muscle is impaired with advancing age, which raises the hypothesis that many neurologic changes associated with senescence are mechanistically linked to impaired skeletal muscle performance in the elderly [158]. Aging does not lead to a widespread loss of cortical neurons (i.e., pyramidal or stellate cells). In contrast, neuronal atrophy, together with a disruption in white matter integrity and an impressive reduction in myelinated nerve fiber length ($\sim$45 % from 18 to 93 years), is particularly incident among the elderly [159, 160]. Aging of the cerebral cortex may therefore be compatible with axon degeneration [161], thus affecting the connectivity of the cortex with itself and the spinal cord. Ultimately, from a functional standpoint, this might underlie impaired muscle strength in older adults [158].

As the structures of the brain age, the ability of the brain to transmit signals is progressively impaired. The loss of dopaminergic neurons in the striatum results in an age-associated inability to attenuate neural noise [162]. Neural noise disturbs the fine-tuning of central motor command, and this introduces a considerable level of unpredictability in motor unit discharge, likely affecting force production [158]. There is partial evidence that dopaminergic degeneration is secondary to the cytotoxic effects of high levels of extracellular glutamate around the striatal neurons [163, 164]. From a different perspective, it has also been reported that older adults exhibit more intra-cortical inhibition and less intra-cortical facilitation than younger controls [165]. Importantly, this is consistent with the notion of disuse-muscle weakness being associated with increases in intra-cortical inhibition [166, 167]. Taken together, these findings suggest that aging results in decreased motor cortical excitability and plasticity, which may affect voluntary activation capacity in older adults.

Voluntary activation is commonly assessed using the interpolated twitch method, which measures the electrical stimulation of the nerve or muscle itself during maximal voluntary contraction. It represents the proportion of maximal possible muscle strength produced during a voluntary contraction. Any increment in force evoked by the electrical stimulus indicates that voluntary activation is <100 % [168]. Despite the lack of consensus on this topic, several studies indicate that voluntary activation is substantially impaired in the elderly (by $\sim$15 % or more)

and that this is particularly evident in motor tasks involving knee extension and elbow flexion [169–171]. In fact, one previous report demonstrated that incomplete voluntary activation (ranging from 69 to 93 %) is found in virtually all people aged ≥87 years. Thus, deficits in voluntary activation likely contribute to a significant proportion of muscle weakness observed in the old and very old [169].

3.4 Cerebrovascular Function

With the aforementioned reductions in brain white/grey matter come commensurate reductions in cerebral vascularization. Aging is associated with reductions in regional and global cerebral blood flow [172]. Moreover, given limited energetic substrate storage in the brain, increases in metabolic demand upon neuronal activation during exercise necessitate increased delivery via increases in regional blood flow [173]. Reductions in cerebral oxygenation and disruptions in metabolic homeostasis during exercise have been directly linked to physical performance and fatigue [172]. It has been suggested that reduced oxygenation may impact on cortical activation, affecting skeletal muscle recruitment patterns. Indeed, older adults have reduced cerebral conductance during exercise, which may lead to impaired cerebral oxygen provision and central fatigue, although this is not an undisputed finding [174].

3.5 Cardiorespiratory Structure and Function

In aging individuals, respiratory function progressively deteriorates along with functional changes, and this might theoretically suggest that the respiratory system would become limiting to VO_{2peak}. Increasing rigidity of the chest wall, decline in respiratory muscle strength and endurance, loss of elastic recoil, decrease in the alveolar surface area, and reduction in the number of capillaries perfusing the lung are among the prime candidates for affecting the VO_2 response at peak exercise intensities [175]. However, it has been shown that the physiological response to peak exercise is characterized by a breathing reserve of 41 % independently of age and sex [176]. Moreover, in the elderly, maximal voluntary ventilation and lung diffusion capacity for carbon monoxide both decline at a slower rate than VO_{2peak} (~5 to 6 % per decade). Finally, there is also evidence that exercise-induced arterial hypoxemia is very uncommon in this population [36, 175]. For all these reasons, the data from the existing literature do not support the hypothesis that VO_{2peak} is limited by inadequate ventilation and/or pulmonary gas exchange in the healthy elderly. In contrast, the blood oxygen-carrying capacity decreases by ~10 % from 30 to 80 years of age, at least in men [36]. The oxygen-carrying capacity depends on blood hemoglobin levels, and reductions in the serum levels of this

metalloprotein are well known to impact VO_{2peak} (e.g., anemia) [177]. Thus, a progressive decrease in blood-carrying capacity along the aging process might hypothetically limit the VO_{2peak} in the elderly to a small extent.

Even in the absence of disease and other risk factors, aging per se instigates pervasive changes in the CV system [178, 179]. The aging heart is marred by numerous structural and functional changes. While traditional views held that left ventricular (LV) mass increased with age, autopsy studies and findings from magnetic resonance imaging suggest that, in the absence of hypertension, cardiac mass does not change in women and may actually decrease in men [180, 181]. Structural changes to the heart are more complex than captured by conventional echocardiography, with newer 3D imaging modalities noting heterogeneous and asymmetric wall thickening to occur such that mass is redistributed from the free wall to the interventricular septum [181]. In addition, reduced autophagy, myocyte apoptosis, scarring, fibrosis, and collagen cross-linking ultimately reduces LV compliance, impacting cardiac function [182–185].

There is general agreement that reduced maximal cardiac output is the principal cause for the decrease in VO_{2peak} and endurance exercise capacity in older people. It is believed that 70–85 % of the limitation in VO_{2peak} is linked to cardiac output irrespective of age and sex [186]. Therefore, it is not surprising that any decline in cardiac output with aging will result in a secondary decrease in VO_{2peak}. The main cause for such relevant reduction in cardiac output is the decline in the maximum achievable heart rate. Maximal heart rate decreases by ~3 % per decade, and the relative contribution of this drop to reduced maximal cardiac output with aging ranges from 40 to 100 % [187, 188]. Despite the etiological basis, an age-related decrease in maximal heart rate remains open to debate, and previous findings suggest it is largely caused by a progressive reduction in intrinsic heart rate and limited chronotropic responsiveness to β-adrenergic stimulation, with the reduction in intrinsic heart rate playing by far the greatest role [189].

LV systolic function remains largely unperturbed by age [190]. In aging, stroke volume is also mildly altered during intense aerobic exercise, while the ejection fraction is considerably influenced, as illustrated by the double increase in end-systolic volume compared with young adults [6]. During peak exercise, the ejection fraction normally decreases from 85 % in the third decade to 70 % in the ninth [191]. Therefore, in the elderly, the maintenance of stroke volume during exercise is primarily attained via the Frank–Starling mechanism (cardiac preload). Importantly, this is different from that seen in younger adults in whom stroke volume is adjusted to the metabolic demands of work rate by means of enhanced

cardiac preload, positive inotropism, and decreased after-load. Aforementioned age-associated changes in LV cardiac structure and compliance most notably reduce diastolic function (e.g., diastolic filling and relaxation kinetics), an important determinant of exercise capacity. Interestingly, recent studies exploring cardiac twist mechanics note that cardiac twist may increase with age [192]. When viewed from the apex, the healthy LV maintains a 'wringing' systolic displacement, with an initial counterclockwise rotation followed by a clockwise rotation in the LV basal plane and a counterclockwise rotation in the LV apical plane [193]. In general, the apical and basal twist increases during the aging process, leading to an increased LV twist value at rest [193]. This accentuated twist may be an important compensatory adaptation with aging, as subsequent untwisting of the LV produces a suction effect that may enhance LV filling during diastole, particularly during exercise [194]. Loss of LV twist reserve with aging during exercise may thus affect stroke volume and be an important arbiter of reduced physical performance.

3.6 Systemic Vascular Structure and Function

Vascular senescence is a phenotypic expression of human aging. With advancing age, there is pervasive macro and microvascular dysfunction. Two key vascular changes that have recently received considerable attention are stiffening of central elastic arteries (i.e., aorta and carotid) and systemic endothelial dysfunction stemming largely from loss of nitric oxide (NO) bioavailability. Recent literature highlights increased large artery stiffness and endothelial dysfunction as novel correlates of reduced physical performance [195]. The aging arterial system may directly impair cardiac function with age by detrimentally altering ventricular–vascular coupling. Arterial compliance (the inverse of stiffness) reflects the ability of large central elastic arteries, such as the aorta and carotid, to expand and recoil during systole and diastole. Appropriate coupling between the LV and the compliant aorta results in an optimal transfer of blood from the LV to the periphery (optimal cardiometabolic efficiency) without excessive changes in hemodynamic pulsatility. Loss of arterial compliance, or an increase in stiffness, alters ventricular–vascular coupling such that arterial load is increased, as is pulsatility of pressure and flow [196]. With respect to cardiac function, increased aortic stiffness with age contributes to increased afterload, reduced coronary perfusion, altered LV twist mechanics, reduced LV synchronicity, increased myocardial work, myocardial deformation, and left atrium enlargement [197–199]. Increased arterial stiffness may thus detrimentally impact both systolic and diastolic function during exercise, contributing to reductions in exercise stroke volume. Increased stiffness of the aorta and carotid also reduces the sensitivity of baroreceptors housed within these vascular regions. Resultant autonomic dysregulation affects exercise heart rate, fostering chronotropic incompetence. Thus, arterial stiffness may be a key factor contributing to the aforementioned reductions in exercise cardiac output [200, 201].

It has been suggested that a decrease in the maximal difference between the arterial and venous oxygen content (a-vO$_2$) with aging ($\sim 3\%$ per decade) contributes, in a small proportion, to the age reduction seen in the VO$_{2peak}$ [186, 202, 203]. There is a bi-directional association between arterial stiffness and endothelial dysfunction [204, 205]: loss of NO and subsequent endothelial dysfunction contributes to increases in arterial stiffness, and loss of the inherent buffering capacity of the central conduits owing to increased arterial stiffness begets further endothelial dysfunction via promulgation of pulsatile pressure and flow into the peripheral microcirculation [196]. Increases in arterial stiffness, with subsequent changes in blood flow pulsatility, affect blood flow delivery to working skeletal muscle [206–208]. Blood flow in the periphery is tri-phasic in nature with a large antegrade peak during systole owing to LV ejection, retrograde flow occurring during late systole/early diastole, and additional antegrade flow occurring during late diastole owing to the reservoir capacity of the elastic vessels [209]. Increased arterial stiffness results in more oscillatory flow (larger retrograde flow component), which increases with age [208] and may further damage the endothelium [210, 211] and impair oxygen extraction at the tissue level.

With aging, limitations in oxygen and nutrient delivery limit contractile work, and age-associated impairment in endothelial-dependent vasodilation contributes to lower exercise hyperemia [212]. During exercise, vasodilation occurs via an increase in several vasoactive agents, including but not limited to NO. Resultant increases in blood flow ensure that oxygen delivery is closely matched to metabolic demand. Endothelium-dependent vasodilation increases circulatory time in the capillaries and allows for more effective oxygen extraction in the tissues [213]. Conversely, endothelial dysfunction will result in a state of heightened vasoconstriction, reducing blood flow into the capillary bed and preventing efficient oxygen extraction by muscle mitochondria (lower a-vO$_2$), ultimately reducing exercise endurance [214]. A reduction in blood flow to working skeletal muscle (i.e., reduced perfusion) may limit the ability to perform functional tasks [206, 215]. With aging, the relative contribution of NO to exercise hyperemia is reduced by approximately 45% [212]. Indeed, with aging there is a generalized reduction in limb blood flow and vascular conductance both at rest [216] and during exercise, contributing to reduced endurance capacity [217, 218].

Recent studies also support links between large artery stiffness, endothelial dysfunction (and loss of NO), and muscular strength/power in older adults [219]. NO is obligatory for optimal contractile function and has been shown to enhance velocity of muscle fiber shortening, reduce twitch time-to-peak contraction, and increase rate of force development [220–222]. Such effects are mediated by the NO-dependent activation of soluble guanylate cyclase and have been implicated in numerous aspects of excitation–contraction uncoupling with aging (e.g., reduced sarcoplasmic reticulum calcium–ATPase activity, reduced ryanodine receptor-mediated calcium release, and reduced calcium sensitivity) [221]. NO is also crucial for satellite cell activation and hypertrophy of fast-twitch muscle fibers [223]. Both arterial stiffness and endothelial dysfunction with aging have been causally linked to reduced muscle mass and sarcopenia via effects on reduced skeletal muscle perfusion [224–226]. Moreover, reduced muscle mass has been implicated in increased central hemodynamic load at rest and during exercise, which, as alluded to previously, impacts cardiac function [227–229]. Thus, vascular function may be an important effector of neuromuscular function in older adults.

Arterial stiffness has also been shown to be an important determinant of cerebral perfusion with advancing age. Similar to skeletal muscle during exercise, the brain is a high-flow target organ particularly susceptible to hemodynamic pulsatility [230]. Because the skull is a rigid structure, entry of excessive extracranial hemodynamic pulsatility into this non-expandable space may pervade the deep microcirculation of the brain [231, 232]. Indeed, hemodynamic pulsatility can be detected even in the venous efflux [232–235]. Excessive hemodynamic pulsatility may cause cerebral microbleeds, microvascular hypoperfusion, and focal lacunar infarcts, contributing to detrimental rarefaction and remodeling [236–238]. Pulsatility may also negatively affect the neurovascular unit by contributing to neuronal demyelination and parenchymal damage, ultimately manifesting as white matter hyperintensities [235, 239–243]. Thus, reduced oxygenation and cerebrovascular damage secondary to age-associated increases in arterial stiffness may detrimentally impact key regions of the brain necessary for regulating optimal physical performance. Indeed, older adults with increased arterial stiffness and blunted peripheral vasodilation report higher ratings of perceived exertion during exercise [206, 215].

4 Conclusions

Older adults aged 60–80 years exhibit substantial reductions in endurance capacity. The aging process is also characterized by an impressive deterioration of neuromuscular function affecting both muscle strength and power. Muscle atrophy has been viewed has one of the primary causes of dynapenia. However, more recent findings have clearly demonstrated that minor deficits in the structure and function of the nervous system and/or impairments in intrinsic muscle quality also play an important role in the development of dynapenia. Large artery stiffness increases as a function of age, thus triggering subsequent changes in pulsatile hemodynamics and systemic endothelial dysfunction. Ultimately, since target organs such as the brain, heart, and skeletal muscle are sensitive to hemodynamic pulsatility, this may represent a common link between declines in cardiac function, neuromuscular function, brain function, and physical function with aging. No single drug stands out as the optimal approach for improving and extending quality of life in the aging population. For this reason, the search for alternative strategies for management of human senescence must continue.

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