ARTICLE

Inflammaging and the Age-Specific Responsiveness to Stretch-Shortening Contractions

Erik P. Rader and Brent A. Baker

Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV

RADER, E.P. and B.A. BAKER. Inflammaging and the age-specific responsiveness to stretch-shortening contractions. *Exerc. Sport Sci. Rev.*, Vol. 45, No. 4, pp. 195–200, 2017. *With aging, muscle injury from rapid, continuous stretch-shortening contractions (SSC) is prolonged, and maladaptation to moderate-velocity, intermittent SSC is more common. We hypothesize that high baseline levels of inflammatory signaling and oxidative stress may underlie these outcomes, whereas careful modulation of high-intensity SSC training design resets basal conditions and permits muscle adaptation to SSC.* **Key Words:** stretch-shortening contraction training, dynamometer, cytokines, lipid peroxidation, resistance training

Key Points

- With aging, chronic levels of inflammatory signaling and oxidative stress increase.
- Accompanying this environment is a muted inflammatory response and slow recovery after an acute exposure to rapid, continuous SSC (comparable to sprint training) and exacerbated weakness from frequent exposure to moderate-velocity, intermittent SSC (comparable to resistance training).
- Decreasing exposure frequency (*e.g.,* 3 to 2 d per wk) of moderate velocity intermittent SSC improves lipid peroxidation levels and muscle performance.
- High-activation SSC training with restrained training frequency is a potential intervention to restore muscle to a younger phenotype.

INTRODUCTION

In daily activity and exercise, ranging from such undertakings as walking, sprinting, jumping, resistance training, and plyometric exercise, muscles are commonly exposed to stretch-shortening contractions (SSC), contractions consisting of successive lengthening and shortening contractions (18,42). In exercise training, many of these activities are performed at high intensity in terms of muscle activation with intent to maximize the stimulus for adaptation (1,17,41). However, concerns about inappropriate exposure to such high-intensity SSC, especially at old age, have prompted investigators to explore training at lower intensities (26,43). Reports regarding dynamometer-based experimental rodent models have been essential for characterizing the potential for detrimental outcomes from high-intensity SSC (10,30,31). Two distinct negative outcomes have been well documented from these studies — acute injury versus chronic maladaptation. SSC-induced injury in young rats has been observed in the form of an acute decrease in force output concomitant with overt muscle edema, cellular infiltration of inflammatory cells, and muscle fiber degeneration after exposure to a single SSC protocol consisting of rapid (500 degrees per second), continuous SSC comparable with sprint training (5,6,31). SSC-induced maladaptation has been characterized in detail in rodent studies as a long-term decrease in force generation that develops over time (*e.g.*, weeks to months) with only acute and long-term marginal muscle edema, cell infiltrates, and muscle fiber degeneration — a phenotype after chronic SSC exposure consisting of slower (60 degrees per second), intermittent SSC analogous to contractions during resistance training (4,10,32). Training-induced decrements in strength also have been well established in human studies regarding athletes after overintensive resistance training, training largely consisting of SSC (23,27). Studies regarding rats suggest that with aging, injury from rapid SSC becomes more prolonged, and susceptibility to maladaptation from chronic SSC is heightened (10,19,30). In this review, we summarize evidence that is consistent with the hypothesis that high basal levels of inflammatory signaling and oxidative stress may underlie age-related impairment in muscle injury recovery and maladaptation after inappropriate SSC exposure and that selective SSC training improves basal conditions and prevents maladaptation.

Address for correspondence: Brent A. Baker, Ph.D., ATC., CDC/NIOSH/HELD/TMBB/SMART, MS 3027, 1095 Willowdale Rd, Morgantown, WV 26505 (E-mail: BWB3@cdc.gov).

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ACUTE INJURY

Contraction-induced skeletal muscle injuries in the form of muscle strains are among the most common injuries incurred during demanding work and sport (12,13). Such injury is especially prevalent during the lengthening phase of contractions, a phase in which force output is highest (22). The primary initial injury consists of focal mechanical damage to sarcomeres and excitation-contraction–coupling disruption (7,20). A secondary response follows in the hours to days after an extreme primary injury characterized by edema, cellular infiltration, and muscle fiber degeneration (5,6,45). In a recent study, we characterized the secondary response to different degrees of injury (mild to severe) dependent on SSC repetition number and investigated the influence of age (31). In this study, muscles of young and old rats were exposed to 0, 30, 80, or 150 SSC. For young rats, 30 SSC induced an initial force deficit of 27%, and, 3 d afterwards, an indication of edema was evident. This observation of edema was consistent with other reports regarding 30-SSC training demonstrating increased interstitial space in muscle cross section and magnetic resonance imaging signal intensity (5,11). Interestingly, overt cellular infiltration and muscle degeneration did not accompany this apparent edema. Such infiltration and degeneration was only evident after 80 and 150 SSC, protocols with initial force deficits exceeding 30%. This is consistent with the notion that for mild SSC-induced injuries (*i.e.*, those with less than 30% initial force deficits), edema is independent of inflammation and muscle degeneration, whereas for more severe injuries, edema accompanies inflammation/degeneration (31). The implications of these findings confirm that edema alone is not a reliable indicator of whether anti-inflammatory drugs should be used for strain injury treatment.

Despite comparable initial force deficits between the groups, age-related differences emerged in our study in the days after the 80- and 150-SSC protocols in particular (31). At 3 d, muscles of young rats responded with a robust secondary response that included an increase in interstitial space, cellular interstitium (indicative of interstitial inflammatory cells), muscle fiber degeneration, gene expression, and cytokine/chemokine protein levels, whereas muscles of old rats had no such response (Fig. 1 A-D, Table). By 10 d, for young rats, indicators of inflammation/degeneration had subsided, and muscle mass was diminished predominately because of decreased muscle fiber size consistent with regenerating/remodeling muscle fibers (Table) (31). Interestingly, the muscle fiber remodeling was sufficiently advanced by 10 d to recover performance to control values (19,31). In contrast, muscles of old rats did not undergo overt degeneration/regeneration by 10 d as indicated by the lack of degenerative and centrally nucleated muscle fibers, an indicator of previous degeneration/regeneration, at that time point (31). Accompanying this lack of degenerative/regenerative response was a sustained force deficit at 10 d (19,31). Furthermore, additional analysis of gene expression data from our recent study indicate that for old rats, oxidative stress–relevant pathways such as glutathione-mediated detoxification, GADD45 signaling, and nuclear factor (erythroid-derived 2)–like mediated oxidative stress are high at baseline and remain unchanged with SSC-injury exposure, whereas for young rats, the redox environment is heightened by SSC-injury exposure, and at 10 d, the redox environment begins to return to physiological levels (31). The implication is that a secondary response and concomitant inflammatory signaling is possibly required for recovery from muscle injury in general (19,31). For instance, cytokines interleukin-1β (IL-1β) and interleukin 10 (IL10) promote proper satellite cell function, and the chemokine (C-C motif) ligand 2 (CCL2) is required for functional recovery from muscle damage (2,21). Yet,

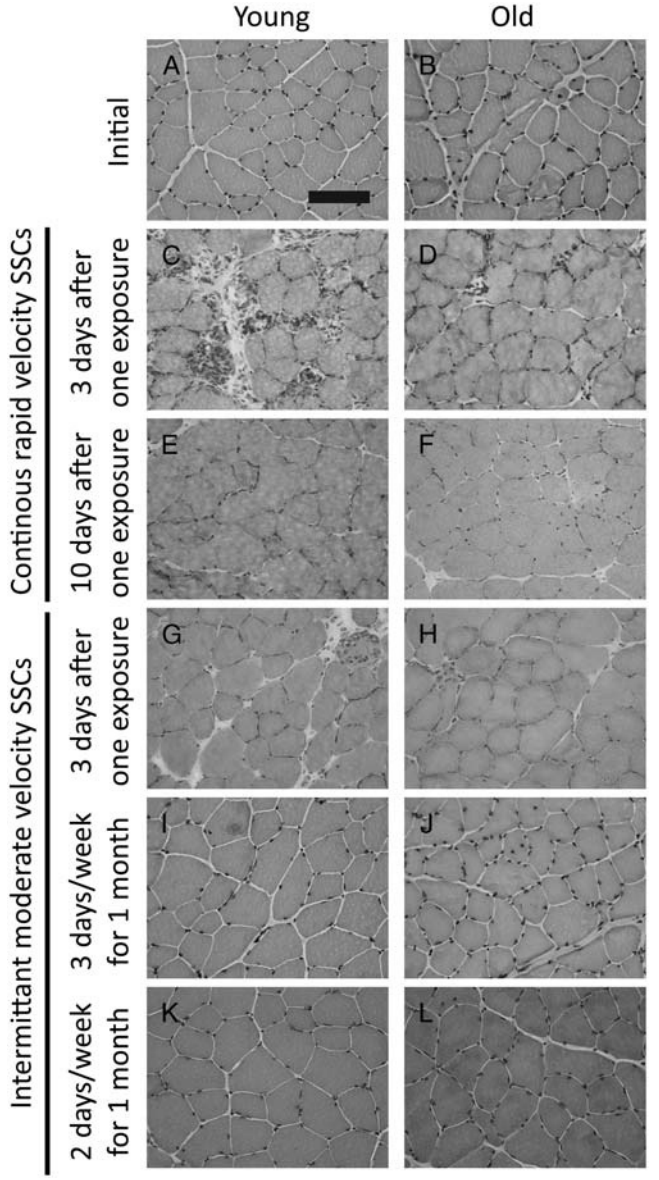

Figure 1. Age-dependent responses to distinct stretch-shortening contractions (SSC) exposures are observable in transverse sections of muscles. Images depicted are for tibialis anterior muscles of young (3 months old) and old (30 months old) male Fischer Brown Norway hybrid rats sectioned and stained with hematoxylin and eosin. At baseline conditions, the presence of degenerative muscle fibers and cellular interstitium increases with age (A, B). At 3 d after 80 (*i.e.,* 8 sets of 10 repetitions) rapid (500 per second), continuous SSC, muscles of young rats display robust muscle fiber degeneration, cellular infiltration, and an increase in interstitial space (C). At 10 d, accompanying the restoration of muscle performance is a muscle morphology that returns to the initial state (indicative of healing) (E). For muscles of old rats exposed to the same protocol, the degenerative response is muted and muscle recovery is compromised (D, F). In the days to weeks after 80 (*i.e.,* 8 sets of 10 repetitions) moderate-velocity (60 per second), intermittent SSC, only minor muscle fiber degeneration is observed for both young and old rats (G-L). Scale bar = 100 μm.

TABLE. Age-dependent morphological and functional responses to distinct stretch-shortening contractions exposures

Age	SSC Type	Exposure	Non-Cellular Interstitium (% of tissue)	Cellular interstitium (% of tissue)	Degenerative muscle fibers (% of tissue)	Muscle mass (% change)	Performance (% change)	References
Young	Nonexposed	None	4	1	0	0	0	4, 10, 31, 32
	Continuous rapid-velocity SSC	3 d after a single exposure	11	7	6	0	−20	31
		10 d after a single exposure	4	1	0	−20	0	31
	Intermittent moderate-velocity SSC	1–5 d after a single exposure	6	1	1	10	0	4, 10, 35
		1 month of 3-days-per-week exposure	5	1	1	20	30	10, 32, 35
		1 month of 2-days-per-week exposure	4	1	0	20	30	32
Old	Nonexposed	None	5	2	1	0	0	4, 10, 31, 32
	Continuous rapid-velocity SSC	3 d after a single exposure	6	1	0	0	−20	31
		10 d after a single exposure	6	1	0	0	−20	31
	Intermittent moderate-velocity SSC	1–5 d after a single exposure	5	1	0	10	0	4, 10, 35
		1 month of 3-days-per-week exposure	5	2	0	0	−30	10, 32, 35
		1 month of 2-days-per-week exposure	5	1	0	20	0	32

Values are approximations based on listed references regarding dorsiflexor muscles of young (3 months) and old (30 months) Fischer Brown Norway hybrid rats. For the continuous rapid-velocity stretch-shortening contractions (SSC) exposure, data are from reports using 80 (*i.e.*, 8 sets of 10 repetitions) continuous SSC at a velocity of 500 per second with the exception of the performance data, which are based on 150 SSC (*i.e.*, 15 sets of 10 repetitions). Such functional data are not available for 80 SSC, and therefore, data regarding 150 SSC are used for an approximation based on comparable quantitative morphology responses between 80 and 150 SSC exposures (31). For the intermittent moderate-velocity SSC, all data are from reports regarding 80 (*i.e.*, 8 sets of 10 repetitions) intermittent SSC at a velocity of 60 per second. Performance values denote available peak force or work capacity values from the listed references.

diminished SSC injury-induced levels of these cytokines/chemokines were present in muscles of old rats (31). The possibility exists that overt inflammatory signaling may arise after 10 d following such an injury at old age because such time points were not investigated (31). However, such signaling would be too late to prevent the prolonged performance deficits already sustained by 10 d postinjury (19,31). The notion that a timely secondary response is necessary for clearing sites of damage and attracting functional satellite cells for recovery is supported by studies of multiple-injury paradigms (*e.g.*, lengthening contractions and cardiotoxin-induced injury) and research in which whole muscle grafts are transplanted between young and old hosts (16,25,38,44).

The age-related muted secondary response of muscle to injurious SSC occurs at old age, an age associated with low-level chronic inflammatory signaling (31). In our study, basal protein levels of cytokines — interferon gamma (IFNγ) and IL10 — and chemokines — chemokine (C-C motif) ligand 3 (CCL3), chemokine (C-X-C motif) ligand 1 (CXCL1), and chemokine (C-X-C motif) ligand 2 (CXCL2) — were twofold to fourfold elevated in serum of old rats relative to that of young rats (31). Age-related increases in basal levels of cytokines also have been observed in elderly populations as well (24,29,39). Chronic subclinical inflammation and inflammatory signaling associated with aging has been referred to as *inflammaging*, and this has been proposed to limit immune cell response to new challenges (28,31,39). Supporting this notion are findings of age-related reductions in cytokine release to stimuli ranging from muscle activity and lipopolysaccharide and toll-like receptor stimulation, especially for frail elderly populations (8,9,29,39). Therefore, inflammaging provides a compelling mechanism for the reduction in the secondary response to SSC-induced muscle injury and compromised recovery.

ADAPTATION VERSUS MALADAPTATION

Chronic exposure to moderate-velocity, intermittent SSC more typical of resistance training and repetitive occupational tasks results in adaptation or maladaptation in terms of performance gain or loss, respectively (3,41). A distinctive feature of moderate-velocity, intermittent SSC is the absence of overt muscle fiber degeneration induced acutely or chronically (Fig. 1 G-H, Table) (4,10,30). Exposure of muscles of young rats to 1 month of SSC training (80 SSC: 8 sets, 10 repetitions per set, 3 d per wk) at maximal intensity induces an increase of ~30% in work capacity accompanied by increased muscle mass (Table). Consistent with research regarding resistance training of fast-contracting muscle, SSC-induced adaptation also includes type IIb to IIx fiber-type shifting (30,33). This shift is accompanied by an enhanced capacity to recover from fatiguing contractions (30).

The response to resistance-type training is sensitive to aging and has been well documented for extreme-age groups. The capacity to increase muscle mass and performance is present but diminished for the elderly (40,41). In a report regarding women older than 75 y, resistance exercise induced muscle volume and strength gains, which were half of those for young women (14). This notion has been supported by animal studies and demonstrated to occur relatively early in adulthood. Whereas 3-day-per-week 80-SSC training at early adulthood (6 months) in muscles of rats induces a fiber type IIb to IIx shift and increased capacity to recover from fatiguing contractions, maximum force output is unaltered and positive work capacity decreases by 27% (30). At more advanced age, such training is ineffective at inducing substantial muscle hypertrophy and exacerbates age-related deficits in performance (Table) (10,30,32). Similar to the response at young age, overt muscle fiber degeneration was absent days to weeks throughout

the response to this moderate-velocity SSC training (Fig. 1 G-J, Table) (4,10). Therefore, the maladaptive response of exacerbated age-related deficits in performance after such training could not be attributed to a blatant increase in degenerative muscle fibers.

Age-related differences in responsiveness to general SSC training are concomitant with differences in oxidative stress levels within muscle. Compared with the SSC-induced response in muscles of young rats, the response for old rats exhibits increased oxidant levels (*e.g.*, hydrogen peroxide) without increased antioxidant activity (*e.g.*, catalase and copper-zinc superoxide dismutase activity) and, consequently, an overall heightened oxidative stress (as measured by glutathione to oxidized glutathione ratio) (34,35). This heightened SSC-induced oxidative stress occurs in the context of increased basal levels of oxidants (*e.g.*, hydrogen peroxide), oxidative stress (*e.g.*, diminished glutathione-to-oxidized glutathione ratio), and oxidative damage (*e.g.*, lipid peroxidation and oxidized DNA) with aging (32,34,35). The link of age-related oxidative stress and reduced adaptation is consistent with findings regarding vitamins E and C supplementation and SSC training. Such supplementation for old rats decreased both the basal and SSC-induced levels of oxidative stress while enabling gains in positive work capacity after 3-day-per-week 80-SSC training (35).

Age-related maladaptation and muscle injury (although distinct in their outcomes) both have commonality in the basal state in which these phenomena occur — chronic oxidative stress and cytokine/chemokine signaling (*e.g.*, inflammatory) (31,34). Oxidative stress and inflammatory signaling are closely linked. Activator protein-1 and nuclear factor κb (NF-kB) are redox-sensitive transcription factors that induce proinflammatory cytokine production (37). Conversely, this result, in the form of inflammaging, can generate additional oxidative stress, thereby furthering a cycle of inflammation and oxidative stress. The findings regarding SSC suggest that such a microenvironment impairs recovery from injury and increases susceptibility to maladaptation.

The observations that oxidative stress levels increase during muscle contractions and that, at old age, antioxidant buffering capacity is compromised has motivated investigators to explore antioxidant-based supplementation in conjunction with resistance-type training at advanced age (35,36). However, modulation of training design (*e.g.*, exercise prescription) itself also may be effective at improving the response with age without requiring supplementation. We investigated this possibility for high-intensity SSC training in rats (32). Young and old rats were exposed to 80-SSC training differing only in frequency of training — 2 versus 3 d per wk. Whereas oxidative stress, as

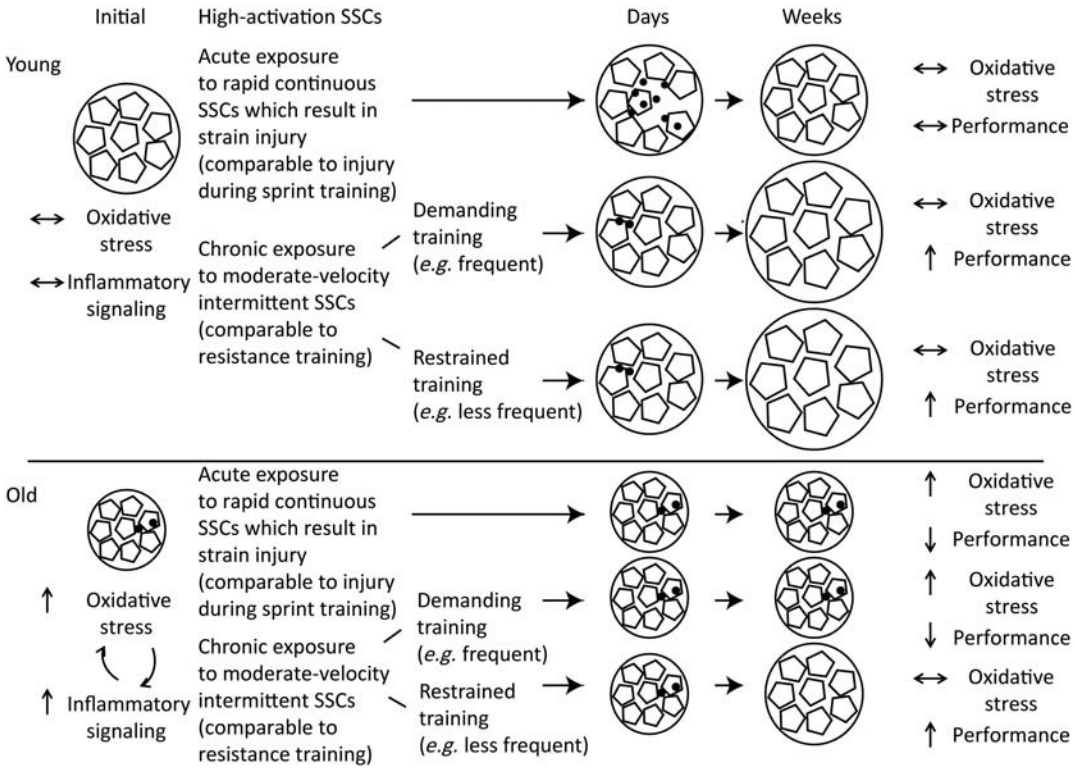

Figure 2. Schematic illustrating hypothesis regarding the interaction of age, oxidative stress, inflammatory signaling, and response to distinct stretch-shortening contractions (SSC) exposures. At young age, baseline levels of oxidative stress and inflammatory signaling are at physiological levels (↔). At old age, these outcomes are high (↑) and perpetuate each other while muscle fiber atrophy and cellular infiltrates (·) are present. Different exposures to high-intensity SSC (in regards to muscle activation) result in distinctive responses. Muscles are prone to strain injury especially during rapid, continuous SSC, contractions inherent in such activities such as sprint training. In the days after this type of injury, an overt inflammatory response, increase in interstitial space, muscle fiber degeneration, and centrally nucleated fibers; outcomes consistent with degeneration/regeneration, occur at young age. The muscle recovers oxidative stress levels, morphology, and performance in the following weeks. With aging, the inflammatory/degenerative phase is blunted, and recovery of oxidative stress and muscle function is compromised. For activities consisting of chronic, moderate-velocity, intermittent SSC such as resistance training, the inflammatory/degenerative response is marginal regardless of age. At young age, muscle can adapt to a wide range of training regimes. At advanced age, the range of adaptive training protocols narrows. Demanding training, especially in terms of training frequency, induces muscle maladaptation and low (↓) force output in the context of high oxidative stress. Less demanding training (*e.g.,* less frequent training) is capable of improving the basal state (*e.g.,* oxidative stress levels) to more youthful levels, preserving muscle performance and inducing muscle fiber hypertrophy at old age.

indicated by lipid peroxidation levels, remained high and low muscle quality (force normalized to muscle mass) persisted for old rats with 3-days-per-week training, oxidative stress and muscle quality were restored to young levels with 2-days-per-week training. Furthermore, 2-days-per-week training induced muscle mass increases regardless of age (Table). Therefore, the results indicate that providing additional recovery time between exposures allowed for the development of a favorable redox environment and, subsequently, muscle adaptation. Given the link between age-related oxidative stress and inflammation, the implication would be that such a modulation in training frequency may have the potential to promote muscle adaptation and counter the effects of inflammaging in skeletal muscle.

CONCLUSIONS

Overall, we have summarized evidence based on rodent studies consistent with the notion that the response to high-activation SSC depends on age and exposure parameters (*e.g.*, repetition number and training frequency) (Fig. 2). Rapid, continuous SSC rather than slower, intermittent SSC tend to induce acute muscle injury, and the extent of this injury depends on repetition number (5,11,31). Such a finding highlights the importance of recognizing that the degree of SSC-induced strain injury is highly sensitive to repetition number when considering recommendations at work and in daily activity. At young age, exposure to high-repetition injurious SSC is followed by overt inflammation, edema, muscle fiber degeneration, and eventual recovery (31,32). This is consistent with inflammation and degeneration as necessary components of muscle regeneration and healing (15,25). No such overt inflammation/degeneration response is observed in old animals, and recovery from rapid, continuous SSC is compromised (19,31). This outcome is consistent with inflammaging and the desensitization of the immune response. The implication is that interventions targeting inflammation should be directed toward the chronic low-level inflammation associated with inflammaging rather than after SSC-induced muscle strain injury because extensive SSC-induced inflammation is lacking at advanced age.

The presented evidence also supports the view that muscle becomes more discriminatory with age in regards to the SSC training regimens that induce adaptation. At young age, muscle hypertrophy and increased performance occur regardless of whether the training was demanding or restrained in terms of training frequency (32). At old age, however, maladaptation follows demanding SSC training and is accompanied by oxidative stress levels that remain high throughout exposure. Adaptation only results after more restrained SSC training, training that reduces lipid peroxidation levels and restores muscle quality to young levels, thereby indicating some degree of restoration of the microenvironment (32). Because this has been demonstrated for maximally activated contractions, the implication is that muscles can adapt to high-intensity SSC exposure well into old age. Therefore, challenging exercise or occupational tasks may very well be tolerated and even promoted at advanced age as long as such activity is modulated appropriately.

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