Physical activity and oxidative stress in the elderly

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K.R. Westerterp, E.P. Meijer, Physical activity and oxidative stress in the elderly, Gerontechnology 2002; 2(2): 189-197. Aging is associated with a decline in the daily physical activity level. Regular physical activity is thought to be an important determinant of health and an active lifestyle might delay the age-associated decline in body function and thus enhance the quality of life of older adults. On the other hand, a high physical activity level might be associated with an increased production of reactive oxygen species (ROS). A state of increased levels of intracellular ROS production is referred to as oxidative stress. The relationship between oxidative stress and physical activity, however, is still poorly understood, particularly in advanced age, which could be attributed to methodological problems concerning the assessment of oxidative stress and the assessment of the physical activity level. Results are presented on the effects of imposed exercise training on physical activity and exercise-induced oxidative stress. It is concluded that (i) a training program of moderate intensity results in a decline of non-training physical activity; (ii) spending relatively more time on low-intensity activities negatively affects the mean physical activity level. Despite this, it is not necessary for elderly to participate in high-intensity, sporting activities in order to increase their physical activity level; (iii) oxidative stress occurs during cycling at sub-maximal intensity as measured by free radical mediated products of antipyrine; (iv) a training or antioxidant supplementation intervention has no effect on exercise-induced oxidative stress; (v) physically active elderly subjects have a reduced exercise-induced oxidative stress compared to elderly with a lower level of physical activity. Thus, regular physical activity improves the antioxidant defense capacity.

Key words: energy expenditure, body composition, exercise training, fitness, aging

In western societies aging of the population occurs rapidly. In 1999, 10%, 7%, and 6% of the Dutch population consisted of people in the age categories 55-64 y, 65-75 y, and 75+ y, respectively. It has been estimated that in 2030, the percentages for those age categories will increase to 13%, 11% and 10%, respectively. Thus, in 2030, 34% of the Dutch population will be older than 55 y, which is equivalent to approximately 6.100.000 people[1].

An increase in the age of the population also means an increase in the prevalence of age-related chronic diseases such as obesity, type 2 diabetes, and coronary heart disease. Aging is associated with several changes including an increase in body

weight and central adipose tissue, a decrease in muscle mass, bone density, and strength. Additionally, aging is generally known to be associated with a decline in the daily physical activity level[2]. Regular physical activity is thought to be an important determinant of health and an active lifestyle might delay the age-associated decline in body function and thus enhance the quality of life of older adults[3]. Additionally, most prevalent chronic diseases, such as coronary heart disease, type 2 diabetes, and obesity, have an association with physical inactivity. Higher levels of physical activity have been related with a lower cardiovascular disease profile and lower overall mortality[3].

An important modulator of the physical activity level might be the level of physical fitness (maximal oxygen uptake: VO_{2max})[4]. Maximal oxygen uptake, an index of functional capacity of the cardiovascular system, decreases with advancing age. The rate of decline in VO_{2max} ranges from 10 to 13% per decade in males and from 7 to 11% per decade in females[5]. This reduction results in a decrease in physiological functional capacity that would contribute to a loss of independence, increased incidence of disability, and reduced quality of life with increasing age. Exercise training, however, improves VO_{2max} in elderly to the same relative extent as in younger adults[6]. The degree to which VO_{2max} improves in older people with training is quite variable, with average improvements, depending on training intensity, ranging from 5 to 28%. Although training cannot completely prevent the age-related reduction in VO_{2max}, it might modulate the age-associated change in VO_{2max}[5]. In addition, even small improvements in VO_{2max} are associated with a significantly lowered mortality[7-8]. Therefore, exercise programs for the elderly are promoted to improve or maintain maximal oxygen uptake.

On the other hand, however, there is increasing evidence that exercise, especially when performed strenuously, is associated with an increased production of reactive oxygen species (ROS) such as superoxide, hydroxyl radical, and singlet O_2[9]. In skeletal muscle, mitochondria consume most of the oxygen and serve as the primary source of metabolic energy. This process, mitochondrial oxidative phosphorylation, couples respiration with generation of high-energy ATP. About 2-5% of the oxygen consumed in the respiratory chain at rest has been estimated to escape as superoxide[10-11]. ROS generation may increase during exercise as a result of a higher mitochondrial oxygen consumption and electron transport flux[9]. A state of increased levels of intracellular ROS production is referred to as oxidative stress. It has been shown that aging is associated with an increased susceptibility to oxidative stress[12]. The relationship between oxidative stress and physical activity, however, is still poorly understood, particularly in advanced age, since there is a substantial lack of data regarding the effects of exercise and training on oxidative stress in the elderly. One of the reasons for the lack of data is the methodological aspect concerning the assessment of oxidative stress and the physical activity level.

The present paper provides further insight in physical activity and oxidative stress in the elderly. The following objectives are addressed: energy expenditure and physical activity; assessment of oxidative stress; exercise training and oxidative stress; and antioxidant supplementation and oxidative stress.

ENERGY EXPENDITURE AND PHYSICAL ACTIVITY

Aging is associated with a decline in physical activity level (PAL). Therefore, exercise programs for the elderly are promoted to improve or maintain physical fitness and health. Goran and Poehlman[13], however, did not observe an enhancement of average daily metabolic rate (ADMR) after an 8-wk training program in elderly sub-

jects as measured with the doubly labeled water method. It was suggested that the intensity of the training program (3 h·wk^{-1} at 85% VO_{2max}) was too high, and thus fatigued the subjects during the remainder of the day, which resulted in a decline in non-training physical activity. Therefore, it was examined if a training program of moderate intensity could affect the daily physical activity level. Physical activity was measured with a tri-axial accelerometer, an objective method for movement registration. Subjects trained twice a week, for one hour, on non-consecutive days for 12-wk. All training sessions were performed at a fitness center and supervised by a fitness instructor. The intensity of the training program was approximately 50% of heart rate reserve.

The results clearly showed that also a training program of moderate intensity did not increase ADMR[14-15]. On the contrary, after subtracting the physical activity of the session of exercise training, subjects showed a significant decrease in non-training physical activity on training days. Because the exercise training sessions were performed during the late afternoon, the decline in non-training physical activity likely preceded the training sessions. The results, therefore, suggest that the compensation in physical activity as a consequence of participation in an exercise training program, as suggested by Goran and Poehlman[13], seems to be an anticipatory mechanism, i.e. the elderly participants anticipated the advent of exercise training by lowering their physical activity even before the training sessions. Interestingly, the subjects were not aware of the fact that they compensated for the imposed exercise by a corresponding decrease in non-training physical activity. Unfortunately, it is unknown at what time the training sessions were performed in the study of Goran and Poehlman[13]. Recently, Hunter et al.[16] reported that a 26-wk resistance training program significantly increased ADMR (963 kJ·d^{-1}) in elderly subjects (61-77 y). It has to be mentioned, however, that the increase in activity associated energy expenditure (AEE = ADMR minus maintenance metabolism and the thermic reponse to meals; 503 kJ·d^{-1}) failed to reach significance (p=0.18) after adjusting for the estimated energy cost of the resistance training (215 kJ·d^{-1}). Furthermore, Hunter et al.[16] did not use a non-training control group and it could be questioned whether appropriate statistical analyses were used. Therefore, it can be concluded that exercise training in an elderly population, independent of intensity, frequency, or type of training, does not affect the daily physical activity level. Conversely, the results indicate that in elderly humans an exercise intervention reduces non-training physical activity.

To obtain a higher level of physical activity, elderly should spend relatively less time on low-intensity activities[17]. Spending relatively more time on low-intensity affects the mean PAL negatively, whereas high-intensity activities do not have much impact on PAL. Low-intensity activity, associated with an accelerometer output ≤200 counts·min^{-1}, includes activities such as lying, sitting, and standing (<3 METs [work metabolic rate/resting metabolic rate]). Moderate-intensity activity, associated with an accelerometer output between 200-500 counts·min^{-1}, includes activities like walking (3-6 METs), whereas high-intensity activity, associated with an accelerometer output ≥500 counts·min^{-1}, includes household activities, exercise, and sports (>6 METs). Recently, we observed that the decline of 37% and 35% in ADMR for women and men, respectively, between the age groups 20-34 y and 75+ y was mainly a consequence of a substantial reduction in AEE[18]. The reduction in AEE could be explained by a shift from spending more time on low-intensity activities instead of moderate- and high-intensity activities[17]. Elderly spent approximately 17% more of their time on low-intensity activities than younger adults. Therefore, elderly wanting

to increase their activity level should be recommended to exchange low-intensity activities for moderate-intensity activities. Additionally, it has been shown that regular moderate-intensity physical activity provides substantial health benefits[19]. Thus, reduction of physical inactivity does not necessarily imply high-intensity sports (exercise training).

Intuitively, one might hypothesize that elderly individuals with a high physical fitness (VO_{2max}) might be more physically active compared to elderly humans with a lower physical fitness. Recently, Brochu et al.[20] reported a positive association between VO_{2max} and AEE. Additionally, we observed a strong positive relationship between VO_{2max}, adjusted for differences in fat-free mass (rVO_{2max}-FFM) and the physical activity level, as assessed directly by using tri-axial accelerometers, in elderly females ($r=0.31$; $P=0.014$) and males ($r=0.41$; $P<0.001$; Fig. 1)[21]. Because of the strong association between AEE and VO_{2max}, it remains speculative why exercise training does not result in an increased level of free-living physical activity. The imposed 12-wk training intervention resulted in a significant increase in VO_{2max} of about 8%[15,22]. It could be argued that although a strong positive correlation exists between AEE and VO_{2max}, this relationship is not straightforward. To address this point, Dvorak et al.[23] reported that in an elderly population (n=117), high levels of VO_{2max}, independent of physical activity levels, were associated with a more favorable cardiovascular disease risk profile. Additionally, Erikssen et al.[24] showed that even small improvements in VO_{2max} were associated with a lowered risk of death, whereas, Pate et al.[3] showed that higher levels of PAL were associated with a lower cardiovascular disease profile and overall mortality. These studies support the idea that VO_{2max} and the daily level of physical activity may act in a unique and independent manner to improve cardiovascular and metabolic health in the elderly. Cause and effect, however, remain unclear: VO_{2max} can be modulated by physical activity and VO_{2max} might modulate physical activity.

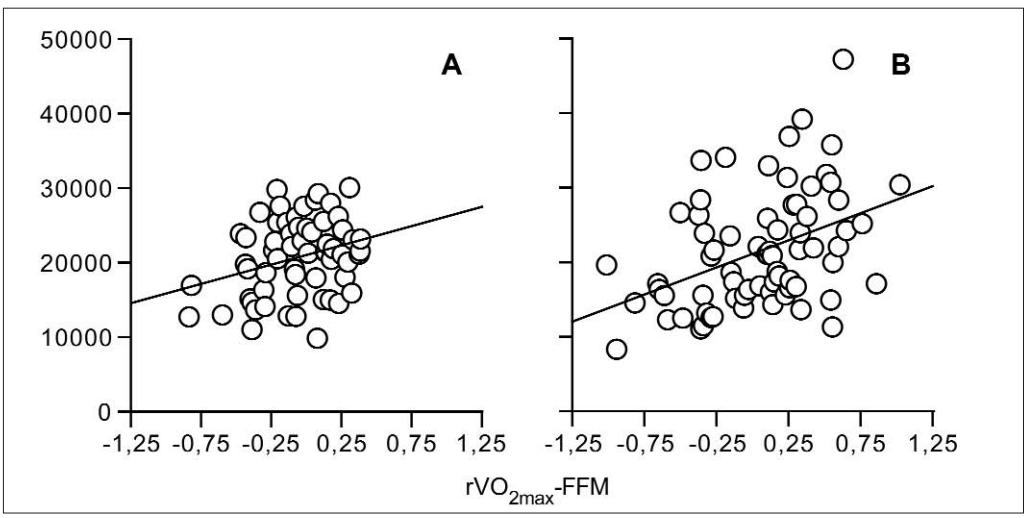

Figure 1. Average accelerometer output for 14-d (counts·day^{-1}) as a function of VO_{2max}, adjusted for fat-free mass (rVO_{2max}-FFM, in l·min^{-1}). A, in elderly females (n=62). Regression line: accelerometer output = 21107 + 5532 x rVO_{2max}-FFM (r=0.31; P=0.014). B, in elderly males (n=71). Regression line: accelerometer output = 21116 + 7263 x rVO_{2max}-FFM (r=0.41; P=0.0004).

ASSESSMENT OF OXIDATIVE STRESS

Regular physical activity and exercise are thought to be important determinants in the maintainance of optimal health and prevention of chronic disease. On the other hand, physical exercise markedly increases oxygen consumption, particularly in skeletal muscle. Increased oxygen consumption further increases the leaking of reactive oxygen species (ROS), such as superoxide and hydroxyl radicals, as products of oxidative phosphorylation, from the electron transport chain. The imbalance, in favor of the free radicals, between the increased ROS generation and the scavenging capacity is termed oxidative stress. Studies performed in humans have shown that exercise results in an increased oxidative stress [25-26]. It has to be mentioned, however, that these studies have relied on the use of endogenous markers for assessing oxidative stress. Because endogenous markers have several methodological disadvantages[27], we attempted to measure exercise-induced oxidative stress in vivo by using a newly developed technique of aromatic hydroxylation. The principle of aromatic hydroxylation is that an aromatic compound undergoes addition reactions with hydroxyl radicals, producing characteristics of hydroxylation[11]. Due to its high reactivity, the hydroxyl radical has a very short half-life and is therefore transiently present at extremely low concentrations. Therefore, to assess oxidative stress in vivo, it is at least necessary that (i) the aromatic probe has a sufficient high concentration (in relation to its rate constant for hydroxyl radicals) to be able to compete with other scavenger molecules; (ii) the hydroxylated product(s) cannot be further metabolized; (iii) the product(s) hydroxylated by hydroxyl radicals is (are) different from possible enzyme-produced hydroxylated metabolites[28]. An appropriate candidate for use in man is antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one). Exposure of an antipyrine solution in water to $^{60}Co\gamma$-radiation leads to the formation of three phenolic antipyrine derivatives: para-hydroxyantipyrine (p-APOH), ortho-hydroxyantipyrine (o-APOH) and meta-hydroxyantipyrine (m-APOH). The last two metabolites are not endogenously formed[29]. Recently, it was reported that 5-min walking exercise in patients with claudicatio intermittens resulted in a significant increase in the plasma concentration of p-APOH and o-APOH30. Thus, the ratio of the hydroxylated products of antipyrine to the plasma concentration of antipyrine reflects the oxidative stress in vivo.

However, it could be argued that the ingested antipyrine affects the intracellular antioxidant balance. In spite of that, subjects orally ingested only 10 mg antipyrine per kg body mass. Assuming that a subject has a body mass of 70 kg and a body fat percentage of 25%, then the amount of FFM is 52.5 kg. Antipyrine is uniformly distributed on the total body water (approximately 70% of FFM). Thus, 700 mg antipyrine is distributed over 36.8 l total body water, resulting in a concentration (molecular weight: 188.2) of 100 $mmol \cdot l^{-1}$. One might expect that this concentration is too low to affect the intracellular antioxidant balance. Additionally, one might argue that the available concentration of antipyrine could be the limiting factor in the formation of the free radical reaction productions during exercise. However, it was observed that the concentration of antipyrine was not different between pre- and post-exercise conditions (158.5±9.8 μM and 155.6±9.4 μM, respectively)[31]. Therefore, the exercise-induced increase in both ratios was due to an increased concentration of p-APOH and o-APOH and not to changes in antipyrine concentration. Moreover, the results clearly show that submaximal endurance exercise in elderly subjects significantly increased oxidative stress.

EXERCISE TRAINING AND OXIDATIVE STRESS

In view of the age related increase in the susceptibility to oxidative stress and

because of the significant increase in oxidative stress during exercise one might question if untrained elderly would benefit from following an exercise-training program. Therefore, we examined the effects of an exercise-training program of twelve weeks in older adults. Subjects trained, twice a week for 1 h, at a fitness centre. It was hypothesized that a training program would result in an upregulation of the antioxidant system to cope with an increased oxidative stress, i.e. a reduced oxidative stress during exercise. Oxidative stress was measured during a 45 min cycling test by using the antipyrine method as described previously[22]. The results clearly showed that exercise training had no effect on exercise-induced oxidative stress. Despite the fact that training in elderly humans improves functional capacity, it appears not to compromise antioxidant defense mechanisms. It could be argued that the intensity of the training program (~50% heart rate reserve) was too low to pose a challenge for adaptive responses to the antioxidant defense system. In addition, it may be possible that greater elevations of VO_{2max} (~9% increase in this study) or a longer training period may be necessary before any significant changes in oxidative stress during exercise would occur.

Interestingly, the habitual activity level as assessed with the doubly labeled water method was inversely correlated with the exercise-induced increase in oxidative stress[32]. Additionally, it has been reported in twelve younger adults (17-19 y) that the superoxide dismutase activity in skeletal muscle was significantly related to the physical fitness level ($r=0.70$; $P<0.05$)[33]. Furthermore, Shern-Brewer et al.[34] showed a decreased in vitro oxidizability of isolated LDL in physically active young adults when compared to sedentary young adults. Although it is difficult to compare the results of these studies with our findings, because they used only moderately to highly trained young adults, it seems that the antioxidant defense capacity is improved in physically active older adults. It could be discussed whether genetic or environmental factors mediate the antioxidant defense capacity. However, no muscle biopsies were taken in our study to measure gene expression of antioxidant enzymes; thus it can only be speculated that in elderly humans, a physically active lifestyle is a more important factor to improve the antioxidant defense capacity than an exercise training program. Further studies are needed on this topic. Additionally, more research is needed to examine whether the mitochondrial oxidant production is affected by advancing age and if physical activity and exercise can alter it.

ANTIOXIDANT SUPPLEMENTATION AND OXIDATIVE STRESS

In elderly subjects, submaximal exercise resulted in a significantly increased oxidative stress[29] and training did not affect this increase in oxidative stress[22]. Because aging is associated with an increased susceptibility to free radical damage, it was hypothesized that supplementation with antioxidants could possibly reduce the exercise-induced oxidative stress in elderly subjects. In the human body, the effects of ROS are scavenged by antioxidant enzymes, as well as with low molecular-weight non-enzymatic antioxidant vitamins. In cell membranes the most important is a-tocopherol, the major member of the vitamin E family. Other lipid-soluble compounds that can act as antioxidant are the carotenoids like ß-carotene. The major water-soluble free radical scavenger is vitamin C that also plays a role in sparing vitamin E. In our study, supplementation with antioxidant vitamins (100 mg dl-a-tocopheryl-acetate, 200 mg ascorbic acid and 2 mg ß-carotene) had no effect on the exercise-induced oxidative stress. Although subjects were supplemented for 12 weeks with relatively low doses, supplementation significantly increased the plasma levels of a-tocopherol (Δ 14.4±3.2

μmol·l^{-1}, P<0.001) and ß-carotene (Δ 0.4±0.1 μmol·l^{-1}, P<0.01)[35]. Therefore, the doses of antioxidant supplementation used should have been sufficient to increase the antioxidant status and capacity of exercising elderly. It could be argued, however, that humans only benefit from antioxidant supplements if they are deficient or exposed to exceptionally heavy workloads like maximal exercise tests or eccentric exercise protocols. The subjects, however, were not deficient concerning antioxidant intake. Measured vitamin C intake was higher than the Dutch recommended dietary allowance of 70 mg·d^{-1}. In addition, plasma concentrations of a-tocopherol and ß-carotene were similar to findings of previous studies in elderly populations[36-37]. It has been hypothesized that antioxidant supplementation is warranted in elderly subjects having a high daily physical activity level[38-39]. Although the subjects in this study were characterized as sedentary active, further research on this topic is needed.

It has to be mentioned that during the last decades the emphasis in free radical research has relied on the negative side effects of free radical damage. However, ROS might play an important role in the cellular stress signaling pathway cell, to protect against severe stress and to adapt or resist the stress[40]. There is increasing evidence that ROS are used as signal, messenger and trigger molecules. For example, nuclear factor (NF)-ℜB signaling system, AP-1 and thioredoxin effect gene expression[41-42]. This might explain why the evidence that dietary antioxidants can cure life-threatening diseases in humans is still lacking. If ROS are involved in the oxidation-reduction (redox) regulation of cell functions, then it is perhaps easier to understand why attempts to advantageously change antioxidant balance in disease and aging experiments have largely failed. Cells normally function in a reducing environment but, as this is changed to a more oxidizing (or less reducing) state, cell functions and gene expressions also change[43]. Antioxidants can inhibit the oxidant triggered signaling mechanisms that the cell uses to adapt to a free radical insult. Additionally, most free-radical scavengers act in oxidant-reduction reactions that are reversible, and some, such as ascorbate, can act both as antioxidants and pro-oxidants, depending on the conditions[40]. Thus, administration of a powerful antioxidant (i.e. powerful reducing agent) after oxidative damage has started could promote damage[44]. Moreover, one should realize that the best mechanism for boosting the antioxidant defense system seems to be the oxidative stress itself. In humans, physical activity is believed to have many anti-aging benefits. It is therefore likely that some of its benefits are derived through the imposed oxidative stress on the antioxidant defense system. The fact that the exercise-induced oxidative stress in an elderly population is inversely related to the habitual activity level[32], supports this hypothesis.

CONCLUSION

In conclusion, in elderly subjects, a training program of moderate intensity results in a decline of non-training physical activity. Spending relatively more time on low-intensity activities negatively affects the mean physical activity level. Despite this, it is not necessary for elderly to participate in high-intensity sporting activities in order to increase their physical activity level. Submaximal exercise induces oxidative stress as measured by free radical mediated products of antipyrine. A training or antioxidant supplementation intervention has no effect on exercise-induced oxidative stress. Physically active elderly subjects have a reduced exercise-induced oxidative stress compared to elderly with a lower level of physical activity. Thus, regular physical activity improves the antioxidant defence capacity.

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