Exercise Limitations by the Oxygen Delivery and Utilization Systems in Aging and Disease: Coordinated Adaptation and Deadaptation of the Lung-Heart Muscle Axis – A Mini-Review

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Key Words
Oxygen delivery · Oxygen utilization · Heart · Lung · Muscle · Aging · Disease · Exercise training · Adaptation · Deadaptation

Abstract
Cardiorespiratory fitness (aerobic exercise capacity) is one of the most important prerequisites for successful aging in human beings and depends on adequate oxygen transport by the respiratory and circulatory systems from environmental air to the working muscles and the efficient utilization of oxygen by the mitochondria. A linear dose-response relation between aerobic exercise capacity, morbidity, mortality, and quality of life is well documented. The process of normal aging is associated with a variable reduction in functional capacity of the main organs involved in oxygen delivery and utilization. Integrated changes of the heart-lung muscle axis are termed here ‘coordinated deadaptation’, e.g. due to aging and disease, in contrast to the beneficial effects of ‘coordinated adaptation’, e.g. resulting from exercise training. Physical inactivity in aging persons initiates a circulus vitiosus resulting in coordinated deadaptation of the oxygen delivery and utilization systems mainly affecting the heart-muscle axis. Whereas in the healthy elderly the deadaptation process starts from inactive locomotor muscles, the lung or the heart represent the origin in patients suffering from respiratory or cardiovascular diseases. Specific exercise training programs, considering the state of cardiorespiratory health and physical activity, are the most important and almost the only effective intervention to avoid or to break the circulus vitiosus, thereby promoting quality and expectancy of life in aging humans.

Introduction

To maintain cardiorespiratory fitness is one of the most important prerequisites for successful aging in human beings. Cardiorespiratory fitness depends on adequate oxygen transport by the respiratory and circulatory systems from environmental air to the working muscles and the efficient utilization of oxygen by the mitochondria (fig. 1). Many studies have assessed individual fitness level as an objective measure of physical activity, consistently showing a strong dose-response relation between aerobic exercise capacity, morbidity, mortality, and quality of life [1]. Generally, the reduction of the mortality risk of sedentary subjects ranges between 10 and 25% for each
metabolic equivalent (1 MET = approx. 3.5 ml O₂·min⁻¹·kg⁻¹) increase in aerobic exercise capacity up to approximately 13 METs [1]. Although aerobic exercise capacity inevitably decreases with aging, oxygen uptake at the anaerobic threshold remains about 3.5-fold higher in elite endurance athletes up to 70+ years when compared to their untrained peers [2]. On the other hand, physical inactivity and disease may accelerate the decline of oxygen delivery and utilization capacities and the related exercise performance below the level necessary for performing daily activities. The process of normal aging is associated with a variable reduction in functional capacity of the main organs (lung, heart, skeletal muscles) involved in oxygen delivery and utilization. Several studies, including the Baltimore Longitudinal Study of Aging, have demonstrated that modifications occur in both structure and function of organs. For instance, skeletal muscles not regularly used will undergo hypotrophy and lose oxidative capacity. According to the concept of symmorphosis, functional capacities (and structure) of the cardiovascular and respiratory systems, responsible for oxygen delivery, will also decline when mitochondrial volume decreases [3]. Integrated changes of the heart-lung muscle axis are termed here ‘coordinated deadaptation,’ e.g. due to aging and disease, in contrast to the beneficial effects of ‘coordinated adaptation,’ e.g. resulting from exercise training. Although there is a plethora of studies demonstrating the loss of aerobic exercise capacity with aging in health or disease and its improvement by exercise training, only little information is available on stimulus-spe-

specific mechanisms of coordinated deadaptation and adaptation of the oxygen delivery and utilization systems. However, the understanding of such mechanisms may be of utmost importance to avoid detrimental effects of deadaptation and optimize the application of exercise training.

The Oxygen Transport System

Like other tissues, skeletal muscles rely on a continuous supply of oxygen at a rate which is precisely matched to changing metabolic requirements. These requirements increase steeply with increasing intensity of muscle work. If oxygen supply is inadequate, anaerobic metabolism compensates transiently for the lack of oxygen, resulting in the production of lactate. The transport of the environmental oxygen to the mitochondria of the skeletal muscles occurs as a series of steps: oxygen uptake in the lungs and oxygen delivery from the lungs to the mitochondria driven by the pumping heart. Even in a healthy aging organism, this system works energy efficiently by properly matching oxygen delivery with the metabolic demand. Adequate ventilation of the alveoli is necessary to maintain alveolar oxygen pressure (PAO₂) and to remove carbon dioxide (CO₂). PAO₂ constitutes the driving pressure for the diffusion of oxygen into the pulmonary capillary blood. Oxygen is then transported from the lung to the tissues by the central circulation (fig. 1). Since oxygen is predominantly carried by the hemoglobin, the amount of oxygen that can be transported by the blood depends on the hemoglobin concentration of the blood. Oxygen delivery (DO₂) is determined by the cardiac output (Q), the hemoglobin concentration (Hb) and the level of its saturation with oxygen (SaO₂); DO₂ = Q × Hb × SaO₂ × K, with K representing the coefficient for hemoglobin-oxygen binding capacity: 1.33 ml/g. The amount of oxygen used by the mitochondria is given by the difference between the arterial and venous oxygen content (CaO₂ – CvO₂; a-VO₂ difference) indicating the amount of oxygen extraction (fig. 1). As the demand for oxygen increases during intense exercise or supply is diminished, oxygen extraction increases. According to the Fick principle, VO₂ = Q × a-VO₂ difference. VO₂max or aerobic capacity is defined as the highest achievable rate at which oxygen can be transported from air to tissues and utilized by the mitochondria during high-intensity exercise. The term ‘maximum oxygen uptake’ was introduced by Hill and Lupton [4] in 1923, who stated that there is an upper limit to oxygen uptake depending on the ability of the car-

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**Fig. 1.** Oxygen delivery and utilization systems. VE = minute ventilation; BF = breathing frequency; TV = tidal volume; PAO₂ = alveolar oxygen partial pressure; PACO₂ = alveolar partial pressure of carbon dioxide; Q = cardiac output; SV = stroke volume; HR = heart rate; DO₂ = oxygen delivery; CaO₂ = arterial oxygen content; SaO₂ = arterial oxygen saturation; Hb = haemoglobin; CvO₂ = mixed venous oxygen content; SvO₂ = mixed venous oxygen saturation; a-vO₂ difference = arterio-venous oxygen difference; La⁺ = lactate.
dirorespiratory system to transport oxygen to the exercising muscles. Their VO₂ max paradigm was mainly based on the observation that there is an upper limit (plateau) of oxygen uptake which cannot be forced to increase despite increasing the exercise intensity. This view has been questioned by some exercise physiologists because a large proportion of subjects (approx. 50%) do not demonstrate a VO₂ plateau despite exercising at maximal effort. The failure to reach a plateau has been interpreted as skeletal muscles being the limiting factor to VO₂ max than the maximal DO₂. However, many persons, especially the elderly, likely fatigue just when reaching VO₂ max and consequently a plateau will not be apparent. At any rate, VO₂ max is considered as the result of integrated functioning of the lung-heart muscle axis at maximal exercise and ranges from below 20 ml/min/kg in the very elderly subjects and in those with cardiovascular and/or lung diseases up to values of 90 ml/min/kg in elite endurance athletes [5]. As proposed by the concept of coordinated (de)adaptation, a single disturbance in this multistep pathway is assumed to trigger adaptation or deadaptation in the remaining steps [6]. Aging, disease, and physical activity mostly affect various steps (organs) differently and the resulting adaptations or deadaptations will largely depend on the type, duration, intensity, and interaction of primary and secondary stimuli.

Determinants of VO₂ max Related to Aging and Training

The Respiratory System

At the exercise intensity equivalent to VO₂ of 1 l/min, pulmonary ventilation (VE) of about 25 l/min is necessary to adequately remove CO₂ and to maintain PAO₂ in healthy subjects. Thus, at a VO₂ of 4 l/min, VE must increase to 100 l/min. If VE has additionally to compensate for lactate acidosis, it will increase to or above 120 l/min. Despite this high VE demand, the individual maximal voluntary ventilation (MVV) usually far exceeds VE max in healthy young individuals. In some highly trained young and older endurance athletes, however, the respiratory system may in fact become limiting. Exercise-induced arterial oxygen desaturation (>5% from resting levels of 98%) in athletes may occur due to a shortened pulmonary capillary transit time at an extraordinarily high Q or due to an insufficient hyperventilatory response to exercise resulting in reduced PAO₂ and consequently SaO₂, or because of the rightward shift of the oxyhemoglobin dissociation curve due to lactic acidosis and hyperthermia [7]. In aging individuals, respiratory function progressively declines along with structural and functional changes, e.g. increasing rigidity of the chest wall, decline in respiratory muscle strength and endurance, loss of elastic recoil, decrease in the alveolar surface area, and a reduction in the number of capillaries perfusing the lung [8]. These age-related changes might theoretically suggest that the respiratory system would progressively become limiting to VO₂ max. However, the findings of Habedank et al. [9] do not support this assumption. The authors demonstrated a breathing reserve [BR = (MVV – VE/MVV) ×100] of 41% independent of age and gender in a relatively large sample of young and older healthy subjects. In addition, exercise-induced arterial hypoxemia is rare in the elderly population, but seems to be somewhat more prevalent in highly fit older subjects [10], similar to what is reported for highly trained young athletes [7]. The alveolar-to-arterial oxygen difference starts to widen at about 50% of VO₂ max and is about threefold higher at maximal exercise compared to rest, but is very similar in young and elderly subjects with average fitness [8]. The VO₂ max declines at a rate of approximately 10% per decade, but MVV (calculated from normal values of forced expiratory volumes in 1 s; FEV₁) decreases at a rate of approximately 6% and lung diffusion capacity for carbon monoxide only at a rate of approximately 5% per decade, indicating no significant limit to VO₂ max [8]. Whereas lung function has been shown not to be different between young trained and sedentary subjects, the age-related decline may be attenuated in well-trained elders compared to their sedentary peers. In conclusion, VO₂ max is usually not limited by insufficient ventilation and pulmonary gas exchange in the healthy elderly, likely due to the fact that age-related reduction in the maximal metabolic demand of exercise occurs at a rate equal to or greater than the changes in the respiratory system. Effects of coordinated adaptation or deadaptation due to physical activity or inactivity will not largely affect the healthy respiratory system.

The Heart, Q max and VO₂ max

The limiting role of the maximal DO₂, particularly of the Q max, is supported by the fact that VO₂ max is typically achieved by exercise involving only about half of the total body muscles. Since the 1990s, it has been widely accepted that although there is no single limiting factor, VO₂ max in healthy subjects performing maximal exercise testing at low altitude is predominantly limited by Q max. When a large proportion of blood flow is directed to a rather
small group of muscles exercising maximally, VO₂ is 2–3 times higher as compared to the same muscles during whole body exercise [11]. These results convincingly demonstrate the significance of Qₘₐₓ (and maximal DO₂) for VO₂ₘₐₓ. It has been suggested that 70–85% of the limitation in VO₂ₘₐₓ is linked to Qₘₐₓ. Ogawa et al. [12] demonstrated an approximate 72% contribution of Qₘₐₓ to VO₂ₘₐₓ changes in sedentary young and older subjects of both sexes, and an 81–89% Qₘₐₓ contribution in trained young and older subjects of both sexes. Thus, it is not surprising that a decline of Qₘₐₓ with aging or in patients suffering from cardiac diseases will result in a dramatic decrease of VO₂ₘₐₓ which, however, may be partly compensated by increasing oxygen extraction [13]. Whereas the reduction in Qₘₐₓ is associated with a decline in maximal heart rate, the higher Qₘₐₓ in trained older subjects is explained by larger stroke volumes (SV) [12, 14]. Heart rate decreases (beats per minute) can be predicted according to the formula: 208 – 0.7 × age, and the underlying mechanisms seem to be related to the decrease in intrinsic heart rate [15]. VO₂ₘₐₓ gradually declines with aging in sedentary as well as in highly trained athletes. In sedentary adults of both sexes it decreases by approximately 10% per decade after the age of 30 years [14]. Trained individuals show a somewhat steeper decline in VO₂ₘₐₓ especially after the age of 50 years, but they have much higher mean levels at any age compared to sedentary persons [2, 14]. Pronounced improvements in aerobic capacity are observed after endurance training in healthy young and older subjects (approx. 70 years). VO₂ₘₐₓ increases after 12 weeks of training were mainly achieved (2/3) through changes in Qₘₐₓ in the young and elderly [16]. Improved left ventricular function accompanied by increases in VO₂ₘₐₓ Qₘₐₓ and submaximal exercise performance has been shown to occur already after short-term (6 days) exercise training [17]. The authors suggest that these short-term effects are due to the exercise-induced rapid expansion of plasma volume producing enhanced SV and ventricular filling secondary to a Frank-Starling effect. These changes might support cardiac structural adaptations during subsequent long-term training provided training stimuli are sufficiently intense. Conversely, when trained and untrained subjects were exposed to physical inactivity (12 week), SVₘₐₓ and Qₘₐₓ declined in both groups to a similar extent in the early period of inactivity followed by a later decline in maximal a-VO₂ difference [18]. Muscle capillarization and oxidative enzyme activity in the trained, however, remained above sedentary levels explaining why the a-VO₂ difference and VO₂ₘₐₓ after 12 weeks of inactivity were still higher in trained than in untrained subjects. Qₘₐₓ and maximal DO₂ rapidly decline as a consequence of coordinated deadaptation to physical inactivity and will markedly improve with regular physical activity, but increases may be especially pronounced when stimuli to the cardiovascular system are sufficiently intense (fig. 2a). Also important for the elderly, prior endurance training helps maintain oxidative capacity of locomotor muscles during a subsequent prolonged period of physical inactivity, which enables the individual to start at higher training intensities resulting in more rapid improvements of Qₘₐₓ and VO₂ₘₐₓ.

**Oxygen Carrying Capacity**

The oxygen carrying capacity depends on the amount of Hb of the blood. Most of the oxygen (>98%) is transported attached to Hb and changes in Hb are accompanied by changes in VO₂ₘₐₓ. Well-designed studies evaluating the effects of blood doping or those elevating Hb mass by erythropoietin administration have convincingly demonstrated increases in VO₂ₘₐₓ by 4–9% [19]. On the other hand, low Hb values in anemia are associated with reduced aerobic capacity. Blood-carrying capacity is generally lower in females than males and there is a small decrease with age (approx. 10% from 30–80 years) at least in males, which may also contribute to the age-related decline in VO₂ₘₐₓ.
The Vascular System

Advancing age is typically associated with macrovascular and microvascular dysfunction resulting in stiffening of central elastic arteries, elevation of pressure from wave reflections, and peripheral endothelial dysfunction. These changes also negatively affect blood flow and oxygen delivery to exercising muscles. Nitric oxide (NO), released by endothelial cells, is largely involved in regulating vascular tonus. NO-bioavailability is reduced with aging and might therefore contribute to endothelial dysfunction. On the other hand, regular exercise increases NO-bioavailability and has been suggested as the single most important modulatory influence on vascular aging [20].

Mitochondrial Respiration Capacity of Skeletal Muscles

The oxidative capacity of the mitochondria of skeletal muscles has been estimated to be at least two times higher than that used during whole body exercise [11], and is unlikely to be a limiting factor to VO2 max in humans. Training-induced large elevations of mitochondrial density and enzymes resulted in only modest VO2 max improvements, indicating that these adaptations are not of limiting importance [21]. The same is true for training-related increases in capillary density which elongate mean transit time, thereby maintaining or improving oxygen extraction [21]. During heavy exercise, almost all of the available oxygen (approx. 200 ml O2/l) is extracted out of the arterial blood, with only about 20 ml O2/l in the venous blood draining the exercising muscles. At least in trained males and females, the a-VO2 difference only contributed a little to VO2 max reductions with aging [12]. It declines by about 12% in the untrained elderly and only by 3–5% in trained old men and women compared to the untrained. A recent study demonstrated that relative VO2 max (ml/min/kg) was 46% higher in long-term endurance-trained older subjects (approx. 71 years) compared to untrained (approx. 71 years) [22]. Time to exhaustion was 35% longer and capillarization (number of capillaries per fiber) was 27% higher in the trained subjects compared to the untrained. The authors concluded that metabolic and angiogenic adaptability of skeletal muscle is maintained in elderly subjects at least up to the age of 75 years [22]. Mitochondrial respiration capacity of skeletal muscles varies, dependent on exercise training, over a wide range and is unlikely to be a limiting factor to VO2 max even in the untrained elder, but is considered to be of utmost importance to perform sustained exercise.

Capability to Perform Sustained Exercise

Whereas VO2 max can be maintained for no longer than a few minutes, endurance sports are typically performed for a prolonged duration up to several hours. This is also true regarding daily physical activities and leisure time activities of the elderly. Depending on the training state and the exercise duration, only a certain percentage of VO2 max can be used. The highest percentage of VO2 max that can be maintained, e.g. for an hour, is a measure of the capability to perform sustained exercise or of the anaerobic threshold of an individual. Åstrand and Rhodal [23] reported that well-trained subjects could maintain VO2 at 87 and 83% of VO2 max for 1 and 2 h compared to 50 and 35% in their untrained peers. Thus, VO2 max does not determine the ability to perform sustained exercise, but represents an upper limit. The ability to use a high percentage of the individual VO2 max results predominantly from chronic adaptations in skeletal muscle due to cumulative effects of repeated bouts of exercise. These adaptations include the increase of key enzyme activities of the mitochondrial electron transport chain and an associated increase in mitochondrial protein accumulation and an increased capillary supply. The resulting improvements in endurance capacity are mainly due to a higher rate of fat oxidation and a concomitant reduction in glycolytic flux, and a tighter control of the acid-base status. Thus, exercise at the same work rate elicits smaller disturbances in homeostasis in the trained muscles, lesser use of muscle glycogen, and decreased lactate production. Consequently, muscle-metaboreceptor activation is reduced, eliciting lower cardiovascular and ventilatory responses and improved exercise tolerance not necessarily associated with VO2 max increase. A longitudinal study (10 years) including 441 older men and women aged 55–85 years found no significant decrease in the anaerobic threshold as a percentage of VO2 max in men and women, confirming that the anaerobic threshold declines with aging at a slower rate than VO2 max [24]. This may well be related to the observation that the muscle oxidative capacity is affected to a lesser degree by physical activity and inactivity than Qmax or in other words, changes in maximal DO2 are more rapid and more pronounced compared to those in the a-VO2 difference (oxygen utilization). These observations also indicate that coordinated
adaptation and deadaptation occur stimuli-dependent differently at the various levels of the lung-heart muscle axis.

**Determinants of \( V_{O_{2}} \text{max} \) In Elderly with Cardiopulmonary Diseases**

The prevalence of cardiorespiratory diseases is steeply increasing with age. In patients suffering from lung and/or cardiovascular diseases, ventilatory restriction and/or the pumping function of the heart may become predominantly limiting factors. Mechanisms of coordinated deadaptation and adaptation may differ in some ways from those in healthy subjects and their understanding may help to avoid detrimental effects of deadaptation and to optimize applications of exercise training.

**Chronic Obstructive Pulmonary Disease**

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation associated with the development of secondary systemic manifestations including respiratory and peripheral muscle dysfunction. The prevalence of COPD according to the Global Initiative on Obstructive Lung Disease (GOLD) stage 2 or higher amounts to 9–10% in adults aged 40 years and older, smoking being the most important risk factor. Although reduced FEV\(_1\) represents an important diagnostic criterion, it is only weakly correlated with \( V_{O_{2}} \text{max} \). Exercise intolerance often represents the most striking symptom in these patients. Beside ventilatory limitations, leg fatigue has been suggested to contribute to exercise intolerance in COPD. Conversely, exercise training evidently improves exercise tolerance and \( V_{O_{2}} \text{peak} \). In addition, cycling has been demonstrated to be superior to two legs of utmost importance. One-leg high-intensity interval training and respiratory muscle training will improve ventilatory constraints and thus enable higher training intensities and skeletal muscle and cardiovascular adaptations, resulting in more pronounced increases in \( Q_{\text{max}} \) and \( V_{O_{2}} \text{max} \).
Chronic Heart Failure

The prevalence of chronic heart failure (CHF) increases with age and rises from about 1.5% at the age of 40 to almost 15% in those aged 80 years or above. Myocardial infarction is the leading cause for the development of CHF and the incidence of both myocardial infarction and CHF increases dramatically with age. Heart failure develops along with left ventricular remodeling, i.e. left ventricular dilation, hypertrophy, fibrosis, and infarct expansion, resulting in a dilated and poorly functioning ventricle. CHF is associated with a high mortality rate and a poor quality of life, particularly due to the low exercise tolerance and related fatigue and breathlessness. The inadequate increase in cardiac output and the related reduction in muscle blood flow during exercise may be considered as a main reason for the initiation of the deadaptation of skeletal muscles (fig. 2c). Esposito et al. [28] demonstrated by adopting 1-leg and 2-leg exercise and elevating CaO₂ by administration of hyperoxia that cardiac output and oxygen delivery significantly contributed to exercise limitation. The elegant experimental design elicited both the muscle convective component, defined by the Fick principle [\( VO_2 = \text{blood flow} \times (CaO_2 - CvO_2) \)], and the muscle diffusive component (\( D_{MO_2} \)), defined by Fick’s law of diffusion (\( VO_2 = D_{MO_2} \times PVO_2 \)) to contribute to \( VO_2 \text{peak} \) limitation in CHF patients. Morphological, enzymatic, and functional skeletal muscle abnormalities in those patients are strikingly similar to those observed after prolonged immobilization, e.g. due to bed rest. The reduced myocardial functioning initiates physical inactivity followed by deadaptation of locomotor and probably also of respiratory muscles. On the other hand, many studies provide promising results from exercise training in patients suffering from CHF. Depending on the type of training, skeletal muscle function, and probably cardiac function, will improve. Small muscle mass exercises, e.g. knee extensor exercises, which are not stressing the cardiorespiratory system have been shown to induce various peripheral structural and functional adaptations improving \( VO_2 \text{peak} \) without changing cardiac output [29]. Muscle training increased muscle capillarity and mitochondrial density (21 and 25%) and leg oxygen delivery and diffusive conductance. At similar submaximal exercise intensities, these peripheral adaptations are associated with improved exercise tolerance characterized by diminished production of lactate and lesser leg fatigue accompanied by reduced cardiorespiratory responses, e.g. lower heart rates and VE. Several whole-body training studies demonstrated beneficial effects on skeletal muscle function, reversal of left ventricular remodeling, \( VO_2 \text{max} \), exercise performance, and quality of life [30]. Most important, however, high-intensity training in particular seems to provoke coordinated adaptations at peripheral and systemic levels, i.e. skeletal muscle adaptations, left ventricular remodeling, and \( VO_2 \text{max} \) increase even in elderly patients with CHF and severely impaired cardiovascular function [30]. These observations are in line with the concept that adaptations are coordinated at the level where stimuli are acting, i.e. peripherally or peripherally and systemically.

General Training Recommendations

The maintenance or the attainment of high aerobic exercise capacity and exercise tolerance are important training goals for aging individuals. Healthy elderly after prolonged detraining periods or those with cardiorespiratory diseases may especially benefit from starting with training of small muscle groups, e.g. one-leg or arm exercises including resistance training, primarily resulting in improved skeletal muscle function and exercise tolerance. Subsequently, individuals will better tolerate whole-body exercises, e.g. walking, running, cycling, and swimming at intensities challenging the cardiorespiratory system, particularly favoring cardiovascular adaptations and \( VO_2 \text{max} \) increases. High-intensity interval training seems often to be superior to low- or moderate-intensity continuous training.

Conclusion

Increasing physical inactivity in aging persons initiates a circulus vitiosus resulting in coordinated deadaptation of the oxygen delivery and utilization systems mainly affecting the heart-muscle axis. Whereas in the healthy elderly the circulus vitiosus starts from inactive locomotor muscles, the lung or the heart represent the origin in patients suffering from respiratory or cardiovascular diseases. Specific exercise training programs, considering the state of cardiorespiratory health and physical activity, are the most important and almost the only effective intervention to avoid or to break the circulus vitiosus, thereby promoting quality and expectancy of live in aging humans.

Disclosure Statement

There is no conflict of interest.
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