



UNIVERSITY OF LEEDS

This is a repository copy of *Exercise, Ageing and The Lung*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/101583/>

Version: Accepted Version

Article:

Roman, MA, Rossiter, HB orcid.org/0000-0002-7884-0726 and Casaburi, R (2016) Exercise, Ageing and The Lung. *European Respiratory Journal*, 48 (5). pp. 1471-1486. ISSN 0903-1936

<https://doi.org/10.1183/13993003.00347-2016>

© ERS 2016. This is an author-submitted, peer-reviewed version of a manuscript that has been accepted for publication in the *European Respiratory Journal*, prior to copy-editing, formatting and typesetting. This version of the manuscript may not be duplicated or reproduced without prior permission from the copyright owner, the European Respiratory Society. The publisher is not responsible or liable for any errors or omissions in this version of the manuscript or in any version derived from it by any other parties. The final, copy-edited, published article, which is the version of record, is available without a subscription 18 months after the date of issue publication.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Exercise, Ageing and The Lung

Michael A. Roman¹, Harry B. Rossiter^{2,3} and Richard Casaburi²

In the State of the Art Series: Multimorbidity and the Lung

Edited by L.M Fabbri and J.M. Drazen

¹ Division of Respiratory Medicine, Rockyview Hospital, University of Calgary, Calgary, Alberta, Canada T2V 1P9

² Rehabilitation Clinical Trials Center, Division of Respiratory and Critical Care Physiology and Medicine, Los Angeles Biomedical Research Institute, Torrance, CA 90502, USA

³ Faculty of Biological Sciences, University of Leeds, Leeds, LS2 9JT, UK

Summary Message:

Exercise performance depends on an integrated organ-system response, each subject to differential age-associated decline.

Correspondence:

Richard Casaburi, Ph.D, MD.

Rehabilitation Clinical Trials Center

Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center

1124 W Carson St. Torrance, CA 90502, USA

Tel: 310 222-8200

Fax: 310 222-8249

e-mail: casaburi@ucla.edu

Abstract

This review provides a pulmonary-focused description of the age-associated changes in the integrative physiology of exercise, including how declining lung function plays a role in promoting multimorbidity in the elderly through limitation of physical function. We outline the ageing of physiologic systems supporting endurance activity: 1) coupling of muscle metabolism to mechanical power output; 2) gas transport between muscle capillary and mitochondria; 3) matching of muscle blood flow to its requirement; 4) oxygen and carbon dioxide carrying capacity of the blood; 5) cardiac output; 6) pulmonary vascular function; 7) pulmonary oxygen transport; 8) control of ventilation; 9) pulmonary mechanics and respiratory muscle function. Deterioration in function occurs in many of these systems in healthy ageing. Between the ages of 25 and 80 pulmonary function and aerobic capacity each decline by ~40%. While the predominant factor limiting exercise in the elderly likely resides within the function of the muscles of ambulation, muscle function is (at least partially) rescued by exercise training. The age-associated decline in pulmonary function, however, is not recovered by training. Thus, loss in pulmonary function may lead to ventilatory limitation in exercise in active elderly, limiting the ability to accrue the health benefits of physical activity into senescence.

Abbreviations

ATP	adenosine triphosphate
CO ₂	carbon dioxide
D _L CO	diffusing capacity of the lung for carbon monoxide
$\Delta\dot{V}O_2/\Delta$ power output	the change in oxygen uptake for a given change in power output
EELV	end expiratory lung volume
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
IC	inspiratory capacity
IRV	inspiratory reserve volume
LT	lactate threshold
LV	left ventricle
MVV	maximal voluntary ventilation
NO	nitric oxide
O ₂	oxygen
P ₅₀	the oxygen partial pressure at which haemoglobin is half saturated
PA	pulmonary artery
P _{A-a} O ₂	alveolar to arterial oxygen partial pressure difference
P _a CO ₂	arterial carbon dioxide partial pressure
P _a O ₂	arterial oxygen partial pressure
PCr	phosphocreatine
pH _a	arterial pH

P_{O_2}	oxygen partial pressure
$\dot{Q}/\dot{V}O_2$	ratio of perfusion to oxygen uptake
TLC	total lung capacity
\dot{V}_A/\dot{Q}	ventilation to perfusion ratio
$\dot{V}CO_2$	carbon dioxide output
V_D/V_T	deadspace to tidal volume ratio
\dot{V}_E	minute ventilation
$\dot{V}_E/\dot{V}CO_2$	ventilatory equivalent for carbon dioxide output
V_T	tidal volume
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_{2peak/max}$	peak oxygen uptake in a symptom limited exercise test/maximum oxygen uptake or aerobic capacity

Introduction

Human ageing is a condition satisfying four principles: it is intrinsic, universal, progressive, and usually detrimental to the host.[1] The proportion of the world's population over 60 years increased from 9.2% in 1990 to 11.7% in 2013 and is projected to be 21.1%, or 2 billion people, by 2050.[2] Ageing is associated with loss of physical function. The complex interplay between age-associated reduction in habitual physical activity and intrinsic ageing processes complicates interpretation of the aetiology of physical function decline. Nevertheless, that physical inactivity is a primary cause of most chronic diseases[3] means that ability to maintain physical function into older age is vital to extend the time lived in optimal health: the 'healthspan'.[4] Increasing older adults' healthspan could dramatically lessen the individual and societal impact of an ageing population. Indeed, prevalence of multimorbidity (two or more long-term disorders) is much greater in the elderly: present in 65% of individuals aged 65-84, and 82% of people above 85 years old.[5] This review will explore contributors to exercise limitation in senescence, with a special focus on the lung.

Muscular exercise poses a systemic stress to homeostasis that demands an integrated multi-organ response. While physical activity was a key evolutionary stressor that contributed to shaping structure and function of human organ systems, prevalence of both chronic inactivity and increasing longevity poses a new challenge for the modern human to meet systemic demands of exercise into old age. Poor performance on cycle, treadmill or endurance walking tests in old age indicates proximity to future health decline.[6] This suggests a fundamental connection between aerobic capacity ($\dot{V}O_{2max}$) and longevity.

Animal studies of artificial selective breeding for running capacity show that high $\dot{V}O_{2max}$ is associated with an ~25% survival increase, lower mean arterial pressure, circulating cholesterol and triglycerides, and increased glucose tolerance, among many other health-associated effects.[7] Interestingly, while the lung is often touted as ‘overbuilt’ for exercise, selective breeding for aerobic capacity hints otherwise. Allometrically scaled lung volume is greater in rats bred for high $\dot{V}O_{2max}$ while, at maximal exercise, alveolar ventilation and effective pulmonary diffusing capacity are greater, and arterial CO_2 partial pressure (P_aCO_2) and pulmonary vascular resistance are less than in rats bred for low $\dot{V}O_{2max}$. [8] These findings support case reports in humans that supra-normal pulmonary function is required to allow adequate breathing reserve for youthful $\dot{V}O_{2max}$ maintenance into old age.[9]

$\dot{V}O_{2max}$ declines with age (Fig 1a).[10-13] This is likely related, in part, to physical inactivity co-incident with advancing age: octogenarian endurance athletes can maintain $\dot{V}O_{2max}$ close to the median of those 40 years younger ($38 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$)[14] and in some cases younger still ($50 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$).[9] Nevertheless, cross-sectional studies suggest that $\dot{V}O_{2max}$ declines with a rate between 0.2 to $0.5 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}\cdot\text{year}^{-1}$ (~0.5% per year) after the age of 30, while longitudinal studies suggest that $\dot{V}O_{2max}$ decline may accelerate after ages 40-50.[10, 15] The 810 healthy men and women studied in the Baltimore Longitudinal Study of Ageing between 1978 and 1998 (median follow-up 7.9 years) revealed that $\dot{V}O_{2max}$ decline accelerated from ~0.3-0.6% per year in the 20-30s decade, to >2% per year in septuagenarians and beyond, even when scaled to fat free mass.[10] Aetiology of accelerated loss in older age is multifactorial, and may be consequent to

greater rate of decline in stroke volume and muscle O₂ extraction after 50 years of age[15-18], compared with relatively linear, and smaller magnitude, decline in maximal heart rate.[10] Despite accelerated $\dot{V}O_{2\max}$ decline in older age, greater habitual physical activity at any age is accompanied by greater $\dot{V}O_{2\max}$. [10, 14] Even in octogenarians, habitual endurance exercise is associated with greater muscle oxidative capacity and expression of transcription factors associated with mitochondrial biogenesis.[14] Thus, maintaining physical activity in older age is associated with greater central (cardiac output) and peripheral (muscle O₂ extraction) capacity compared with sedentary senescence.

The lactate threshold (LT) also declines with age.[19, 20] Cross-sectional studies suggest that LT decline (both in absolute terms, and relative to mass) is less rapid than $\dot{V}O_{2\max}$, such that LT/ $\dot{V}O_{2\max}$ in untrained subjects increases from ~40-50% in youth to ~55-70% in septuagenarians; an effect that may be more pronounced in women than men.

Pulmonary function, however, does not respond to exercise training.[21] Therefore, age-related decline in pulmonary function (Fig 1b) may become an increasingly important limiting factor for physical activity and $\dot{V}O_{2\max}$ in the elderly. Inevitable loss in lung elastic recoil associated with ageing leads to pulmonary mechanics alterations and a tendency to ventilatory limitation in older individuals. In most elderly subjects, physical activity decline may be considered protective against development of exertional symptoms and exercise limitation. However, typical lifelong pulmonary function and $\dot{V}O_{2\max}$ declines are roughly proportional (Fig 1), meaning that ventilatory limitation may

become more noticeable in elderly who maintain high levels of physical activity.

In order to appropriately interpret constraints that the ageing lung may pose for physical function, systemic adaptations associated with older age also demand consideration. Systemic integration of physiologic mechanisms underlying exercise response was described by Wasserman et al. in 1967 (Fig 2).[22] Physiologic systems directly involved in the response to maximal aerobic exercise include: 1)coupling of muscle metabolism to mechanical power output; 2)gas transport between muscle capillary and mitochondria; 3)matching of muscle blood flow to its requirement; 4) O_2 and CO_2 carrying capacity of the blood; 5)cardiac output; 6)pulmonary vascular function; 7)pulmonary O_2 and CO_2 transport; 8)control of ventilation; 9)pulmonary mechanics and respiratory muscle function. This review will describe ageing-associated changes in each of these links, and how declining lung function may play a role in promoting multimorbidity in the elderly through limitation of physical function.

Before embarking on an exploration of the effects of ageing on each of these physiologic systems, it is worth stressing that cardiopulmonary exercise testing (CPET) can be a helpful clinical tool to evaluate the common complaint of dyspnea on exertion in the elderly. CPET can often separate dyspnea related to ageing from pathologic causes. For example, potential contributors to increased dyspnea in the elderly include incipient pathology, obesity, medications such as β -blockers and deconditioning. Reduced $\dot{V}O_{2max}$ and LT is seen in all these conditions, but distinguishing features may well be present. Obese subjects have increased $\dot{V}O_2$ during unloaded exercise but preserved

$\Delta\dot{V}O_2/\Delta$ power output. A blunted heart rate response to exercise can be seen in β -blockade. A reduced $\Delta\dot{V}O_2/\Delta$ power output slope on the other hand should trigger investigations for cardiovascular abnormality. On the other hand, deconditioning and ageing often yield cardiopulmonary exercise test findings that are difficult to distinguish. These observations stress the importance of knowledge the appropriate inter-relationships among the pulmonary-cardio-metabolic systems during exercise, and how these relationships may change with deconditioning and with age.

1. Coupling of Muscle Metabolism to Mechanical Power Output

The transfer of metabolic to mechanical power output at rates necessary to meet sustained exercise task requirements can be usefully considered in three stages: 1) coupling of mitochondrial oxygen consumption to ATP production (mitochondrial coupling); 2) coupling of ATP hydrolysis to mechanical power production (mechanical coupling); 3) economy of application of mechanical power to fulfil task requirements (biomechanic coupling or 'skill'). Ageing influences each of these steps.

Muscle size, architecture and metabolism are altered with advancing adult age.[23] Limb muscles, particularly large locomotor muscles, are 25-35% smaller in older age and have more fat and connective tissue than those of younger individuals.[24] This decline is accompanied by a 30-40% decrease in muscle fibre number between the second and eighth decades.[25] Type II (fast-twitch) fibres are 10-40% smaller in the elderly, while type I (slow-twitch) fibre size is less affected. Remodelling of motor units associated with type IIx fibre loss [26], selective type IIa fibre denervation and collateral re-innervation

of type I muscle fibres, results in type I fibre grouping in elderly muscle. This contributes to altered biomechanics of locomotor activity, reducing skill and increasing energy cost.[27-30] An additional component of skill deficit and muscle weakness in the elderly is disruption of excitation-contraction coupling, likely due to neuromuscular junction function loss, dihydropyridine receptor loss, impaired calcium release, and oxidative modification of myosin.[31, 32] Overall, these changes reduce available muscle mass for maximal aerobic exercise, and can lower economy of its application for external locomotion (impaired biomechanical coupling).[33]

Whether changes occur in mitochondrial and mechanical coupling of elderly muscles is more controversial. At the fibre level, total mitochondrial content tends to be reduced in both type I and II elderly fibres.[34, 35] Sensitization to permeability transition and release of mitochondrial-derived pro-apoptotic factors may be responsible.[36] Importantly, reduced mitochondrial oxidative capacity is not fully reversible by endurance training after late middle age,[37-39] and overall mitochondrial content in quadriceps muscle of 70-80 year olds, estimated using magnetic resonance spectroscopy, is correlated with $\dot{V}O_{2max}$ reduction.[40] Mild mitochondrial uncoupling of oxidative muscle fibres, possibly in response to age-associated oxidative stress increase, is proposed as a protective mechanism contributing to the relative longevity of the most active fibres.[41] It is unclear, however, whether reduction in mitochondrial coupling, observed in resting muscle, is maintained during exercise. Additionally, an ~37% increase in ATP cost of power production (reduced mechanical coupling) is proposed in septuagenarians based on magnetic resonance spectroscopic measurements of plantar

flexion exercise,[42] perhaps consequent to slower contractile relaxation, greater ATP cost of ion transport, and/or greater instantaneous stiffness (reduction in elasticity) in single fibres and whole muscles of elderly participants.[43-45] The effect of this mitochondrial and mechanical uncoupling, observed in small muscle groups, would increase O₂ cost of power production during exercise. This, however, appears not to be the case in cycle ergometry in elderly humans up to 80 years old, where O₂ cost is unchanged compared to young (~10 mL.min⁻¹.W⁻¹).[46] Conversely, some male septuagenarians were found to have reduced ATP cost of force production during electrically evoked plantar flexion exercise[47] and eight, non-smoking, female centenarians, actually showed lower O₂ cost of power production during incremental exercise than young controls.[48] These findings are consistent with improved mechanical or mitochondrial efficiency during exercise in the very old: an adaptation that may offset the influence of decreasing lung function with age.[48] However, $\Delta\dot{V}O_2/\Delta$ power output slope in incremental exercise is sensitive to both kinetics and efficiency of oxidative phosphorylation,[49] and it seems plausible that slowed $\dot{V}O_2$ kinetics in the elderly[50] may increase the contribution of substrate level phosphorylation to ATP provision (phosphocreatine breakdown and glycogenolysis accumulating lactate) during incremental exercise in these centenarians. Precise determination of mitochondrial and mechanical efficiency in the very old awaits resolution.

Overall, therefore, reduced mass and mitochondrial content in elderly locomotor muscles limit maximal power output, aerobic capacity and thus greatly reduce total ventilatory

demand at $\dot{V}O_{2\max}$ compared to younger individuals. Muscle fibrosis, reduced elasticity and reduced biomechanical coupling may, however, contribute to increasing locomotor activity ATP cost, and thus contribute to increasing ventilatory requirement at any given submaximal power output.[51]

2. Gas Transport Between Muscle Capillary and Mitochondria

Diffusive O_2 transport between muscle capillary and mitochondria is an important site of limitation to maximal O_2 flux.[52-54] Diffusive O_2 conductance is dependent on several variables including muscle capillarity (specifically, area of apposition between capillary and fibre, and mean distance between capillary and mitochondrion over which O_2 has to diffuse), capillary haematocrit (red blood cell volume contacting muscle capillaries), gas solubility (as influenced by muscle structural variations, such as increased lipid concentration that facilitates O_2 diffusion), temperature, and muscle myoglobin and mitochondrial concentrations. Of these, the main site of resistance to diffusive O_2 flux in muscle is likely to be the distance between haemoglobin and muscle sarcolemma.[55, 56] Myoglobin spectroscopy measurements in exercising human muscle[57, 58] show a large drop in PO_2 between capillary blood and myocyte interior, highlighting both the large resistance to O_2 flux at the capillary/fibre interface and the importance of maintaining high capillary PO_2 to facilitate O_2 diffusion.

In this context, recent reanalysis of data from the seminal 1966 Dallas Bedrest Study is pertinent.[59] Muscular and cardiovascular responses to exercise were established in 5 healthy 20 year-old men subjected to 3 weeks of supine bedrest followed by 8 weeks of

high-intensity endurance exercise training,[16] and reassessed after 40 years follow-up.[15, 17, 18] Longitudinal $\dot{V}O_{2\max}$ decline (~25%), accelerating after age 50, was similar to the decline seen following 3 weeks of bedrest in youth, and was associated with reductions in both convective O_2 delivery (~10% reduction in peak cardiac output, stroke volume, heart rate) and O_2 extraction (~18% reduction in arterio-venous O_2 concentration difference). This age-associated reduction in $\dot{V}O_{2\max}$ would also be sensitive to reductions in muscle O_2 diffusing capacity,[59] should muscle capillarity regression exceed decline in muscle oxidative capacity in older age. However, changes in human muscle capillarity in the elderly are equivocal: ~10-30% lower capillary/fibre ratio in older muscles is common, either in cross-sectional studies or across 12 years of ageing between mid 60s to mid 70s.[28, 60-62] On the other hand, capillary geometry and hematocrit, determined in young and old Fischer 344 \times Brown Norway hybrid rats, appear unaffected by ageing, with increase in red blood cell flux compensating for potential reduction in convective O_2 delivery imposed by reduced capillarity, at least at rest.[63] During exercise, a lower microvascular PO_2 in the elderly (either by fluorescence quenching in rat or near-infrared spectroscopy in human muscles) suggest that blood-to-tissue O_2 movement may be impaired in elderly muscle, therefore placing greater reliance on substrate-level phosphorylation during exercise.[64-67] However, fractional contribution of glycogenolysis and phosphocreatine (PCr) breakdown to total ATP production is similar during maximal aerobic exercise in muscle from old and young participants, though this was observed in plantar flexion exercise where relative perfusion of active muscle is much greater than during locomotor exercise.[42] Therefore, considering that age-associated capillary rarefaction is somewhat less than decrease in oxidative capacity

of elderly muscle, it seems unlikely that anatomic size of capillary/fibre interface and O_2 diffusional conductance plays a major role in limiting muscle aerobic performance in the elderly.[68]

CO_2 is approximately 20 times more diffusible than O_2 in biological tissues, and high capillary CO_2 concentration may facilitate capillary oxyhemoglobin unloading. Slowed kinetics of oxidative metabolism in the elderly require greater phosphocreatine breakdown for a given power output, and ensuing transient intramuscular alkalosis contributes to temporally slowing kinetics of CO_2 output relative to its production.[42, 47, 69, 70] This, together with intra- and extra-muscular CO_2 buffers, slow muscular $\dot{V}CO_2$ kinetics compared with those of $\dot{V}O_2$, and therefore may lessen ventilatory demands for CO_2 clearance. Interestingly, expression of monocarboxylate lactate transporters 1 and 4, and the ratio of oxidative to glycolytic enzyme activity, are increased in older muscles, independent of physical activity.[71, 72] These adaptations may help ameliorate intramuscular acidosis and increase muscle fatigue resistance in high-intensity exercise in the elderly,[73] but accelerate blood lactate appearance and onset of increased ventilatory demands associated with systemic metabolic acidosis.[74] Consequently, potential benefit from increased proton sequestration rate by PCr breakdown slowing CO_2 flux towards the lung may be moderated by enhanced lactate and proton transport rate, contributing to driving ventilatory compensation for metabolic acidosis as $\dot{V}O_{2max}$ is approached. On balance, therefore, the influence of the aged muscle/capillary interface on exercise ventilatory demands is likely small.

3. Matching of Muscle Blood Flow to its Requirement

Although age-associated muscle microvascular anatomy changes may be less influential than reduced mitochondrial function in limiting maximal aerobic capacity in the elderly,[68] there is strong evidence that muscle blood flow is attenuated during submaximal large muscle mass or locomotor exercise in older humans (~55-80 years).[75, 76] The locus of attenuated increase in active muscle blood flow in the elderly, which is accomplished through a combination of systemic sympathoexcitation and local metabolically-mediated vasodilatation, is controversial. However, a sex difference may exist in that older oestrogen-deficient women are particularly prone to blunting of leg vasodilator responsiveness and more rapid muscle deoxygenation compared to younger controls.[77-84] Importantly, this disruption impairs the ability of elderly muscle to deliver O₂ in appropriate proportion to its requirement ($\dot{Q}/\dot{V}O_2$ ratio), which may contribute to transient microvascular deoxygenation during submaximal exercise and increased demand for substrate level phosphorylation.[83, 85-87] Reduced amplitude and kinetics of cholinergic, shear stress and endothelial-mediated relaxation, particularly in feed arteries of oxidative muscles, has been implicated;[88, 89] although the effect of older age on reactivity of muscle microvessels varies with branch order and vasoactive stimulus.[90] Response to metabolic dilators is also attenuated in the elderly, e.g. ATP-induced vasodilatation is lower in sedentary elderly,[91] although whether alterations in nitric oxide (NO) contribute to limiting exercise hyperaemia in the elderly is debated.[75] The metabolically-activated group III/IV muscle afferent contribution to exercise hyperaemia appears to be absent in older individuals, which may further impair blood flow distribution and reduce regional $\dot{Q}/\dot{V}O_2$ in the elderly.[92] α 1-adrenergic

vasoconstrictor tone appears to be similar between old and young, but may be less attenuated during exercise in the elderly simply due to lower absolute power outputs achieved.[78]

While impaired exercise vasodilatation is observed in many elderly, lifelong physical activity protects against this effect:[93] only in sedentary elderly was limb muscle lactate release associated with an attenuated exercise hyperaemia. Interestingly, in men aged 62-73 years, where absolute locomotor muscle exercise hyperaemia was well preserved, a greater proportion of submaximal cardiac output was directed towards the legs at a given $\dot{V}O_2$ compared to 20-25 year olds.[82, 94] This implies that competition for blood flow by other regional circulations could, at least as maximal cardiac output is approached, attenuate locomotor muscle blood flow rise in exercising older adults.[95] This may be particularly important in relation to competition for blood flow from respiratory muscles where greater deadspace ventilation and impaired pulmonary mechanics increases work of breathing for a given $\dot{V}O_2$ (see below), and may contribute to limiting respiratory and/or locomotor muscle $\dot{Q}/\dot{V}O_2$ in the elderly, as it can in athletes and patients with heart failure.[96, 97]

4. Oxygen and Carbon Dioxide Carrying Capacity of the Blood

Anaemia is prevalent in the ageing population with over 10% of individuals above age 65 affected.[98] Most cases of anaemia in older subjects are mild, but even mild decline in haemoglobin will decrease O_2 carrying capacity and reduce $\dot{V}O_{2max}$. Less is known about haemoglobin O_2 affinity changes with ageing. A study of healthy male and female 18-89

year olds revealed an increase in P_{50} (the PO_2 at which haemoglobin is half saturated) in 60-89 year olds compared to 18-39 year olds, in keeping with age-related haemoglobin O_2 affinity decrease. There was no significant change in 2,3 diphosphoglycerate concentration seen in this population. [99] Other work has shown that haemoglobin O_2 affinity does not appear related to age in men.[100] There seems to be no data available regarding blood CO_2 carrying capacity or buffering capacity changes with ageing.

5. Cardiac Output

Maximal cardiac output decreases with age.[10, 11] Decline in maximal heart rate (~ 0.7 beats/minute/year[101]) appears to be less severe than rate of $\dot{V}O_{2max}$ decline, suggesting that decreased sinoatrial node sensitivity to β -adrenergic stimulation in older individuals[102] is not a primary cause of aerobic capacity loss. Measurements of intrinsic heart rate, using intravenous infusions of propranolol and atropine to achieve autonomic blockade, reveal linear intrinsic heart rate decrease over ages 16-70.[103] Animal models show that the ageing sinoatrial node has decreased conduction velocity and contains fewer pacemaker myocytes.[104] Remaining sinoatrial myocytes demonstrate altered ion channel activity, leading to depressed excitability and consequently lower heart rate.[104] Similar changes may occur in ageing human sinoatrial myocytes, but further study is needed.

Ageing hearts may utilize a different mechanism to increase stroke volume during exercise than younger hearts. In elderly subjects, end-diastolic volume increases with exercise with minimal change in end-systolic volume; while in younger individuals, the

increase in stroke volume with exercise is primarily due to a decrease in end-systolic volume.[105] Increasing end-diastolic volume may lead to larger stroke volume increase during exercise in older subjects, mitigating the influence of peak heart rate decline.[105] Age does not alter the cardiac output- $\dot{V}O_2$ relationship although, for a given cardiac output, older subjects have lower leg blood flow.[106]

Peak cardiac output falls ~25% with age.[10] Despite significant structural heart changes with age,[107-109] global left ventricle (LV) systolic function appears unaffected by healthy ageing. [110-112] Peak stroke volume also appears largely unchanged throughout life.[109] If one accepts a 50% drop in $\dot{V}O_{2max}$ from ages 20-80[10], 25% may be attributable to cardiac output decline. As stroke volume response to exercise is unchanged, reduced heart rate, as well as maldistributed cardiac output (see above), are responsible for the cardiac contribution to age related decline in $\dot{V}O_{2max}$. The exercise cardiac response of the ageing individual has been likened to that of a young person on β -blockers.[105]

6. Pulmonary Vascular Function

Ageing related pulmonary circulation changes influence exercise response in the elderly subject. Pulmonary vascular stiffness increases with age.[113, 114] Decreased pulmonary vascular compliance, along with decreased LV compliance,[112] leads to increased pulmonary arterial (PA) pressure, pulmonary wedge pressure and pulmonary vascular resistance in older individuals.[115, 116] PA pressure increase appears to be secondary to vascular stiffening and decreased LV compliance.[116]

In a recent right heart catheterization study, subjects older than 55 years showed resting hemodynamics similar to those of younger individuals. However, significant differences developed during exercise. The older group displayed lower cardiac output and greater mean PA pressure. Increased mean PA pressure during exercise with advancing age was the consequence of increased pulmonary vascular resistance and elevated LV filling, due to age-related diastolic dysfunction.[117]

7. Pulmonary Oxygen Transport

The assumption that arterial O₂ partial pressure (P_aO₂) declines at a constant rate between ages 20 and 100 is founded on prediction equations based on a small number of individuals above age 60.[118] These equations may underestimate values for elderly subjects, with a wide prediction range of 63-84mmHg for an 82 year old subject.[118] There is evidence to the contrary: Blom et al.[119] reported a plateau in P_aO₂ decline after age 70. Similarly, other recent studies show age-related decline in P_aO₂ between ages 40 and 74 with no significant association between P_aO₂ and age greater than 70 or 74.[120-122] There is potential for survival bias in these results, however, as individuals with lower P_aO₂ may die earlier.[123, 124] There are also gender differences for P_aO₂ in the elderly population. A well-done study by Hardie et al.[121] demonstrated mean P_aO₂ of 77mmHg (lower 95% confidence limit of 62mmHg) and 73.5mmHg (lower 95% confidence limit of 59.6mmHg), respectively, for men and women over age 70.

P_aO_2 changes with ageing may be mechanistically related to gas diffusion properties of the lung and also to ventilation-perfusion distribution. There appears to be little effect on exercise gas exchange capabilities in older individuals, as exercise-induced arterial hypoxemia is infrequent. However, exercise-induced hypoxemia occurs more frequently in highly fit elderly individuals.[21] The mechanism is not known, but plausibly may be related to physiologic changes noted above, and the high power outputs achieved in fit individuals (and therefore greater cardiac output and reduced capillary transit time), compared to elderly subjects of average fitness. As discussed below, increased alveolar deadspace and increased alveolar ventilation to pulmonary perfusion (\dot{V}_A/\dot{Q}) mismatch in older subjects likely contribute to exercise-induced hypoxemia seen in elderly athletes.

a. Pulmonary Trans-Capillary Gas Diffusion

Ageing leads to decreased capacity for pulmonary gas exchange, reflected in decline in diffusing capacity of the lung for carbon monoxide (D_LCO).[125] D_LCO decline may be in part related to gradual reduction in alveolar-capillary density to alveolar diameter ratio in the older lung, along with decreased pulmonary capillary blood volume and increased \dot{V}_A/\dot{Q} mismatch that are seen in the elderly.[126]

b. Matching of Ventilation to Perfusion

Smaller studies have demonstrated that ageing results in an increase in lung areas with high \dot{V}_A/\dot{Q} (physiologic deadspace) and low \dot{V}_A/\dot{Q} (shunt).[127, 128] Older subjects have shown increased alveolar to arterial PO_2 difference ($P_{A-a}O_2$).[129, 130] $P_{A-a}O_2$ can be widened by development of right-to-left shunting, diffusion limitation, or ventilation-

perfusion mismatch. Cardus et al.[131] attempted to determine whether increasing \dot{V}_A/\dot{Q} mismatch with age causes age-related P_aO_2 decline and found a small P_aO_2 decrease with age (6 mmHg between ages 20 and 71) that was explained by a small \dot{V}_A/\dot{Q} mismatch increase. Increased intra-pulmonary shunting (low \dot{V}_A/\dot{Q}) did not appear to contribute to lower P_aO_2 . Unfortunately, this was a relatively young population: only 4 of 64 subjects were above age 60. As closing volume does not equal functional residual capacity until the age of 65[171], it is possible there may be additional low \dot{V}_A/\dot{Q} (shunt) units in more elderly subjects.

c. Distribution of Ventilation

Deadspace to tidal volume ratio (V_D/V_T) is elevated at rest in older individuals. V_D/V_T decreases with exercise but the nadir value is higher in older than in younger subjects. In young athletes, maximal exercise V_D/V_T averages 13%, while in older subjects, V_D/V_T averages 30%.[132]

Ventilation is primarily distributed to the lower lung in younger subjects.[133] Xenon distribution measurement of elderly lungs reveals that in older lungs all airways are open above 65% of total lung capacity.[134] Electrical impedance tomography of aged lung demonstrates absence of posture-dependent changes in gas distribution normally seen in younger lungs.[135] As a consequence, at resting tidal volumes, ventilation to dependent lung is decreased in older individuals, leading to greater ventilation of the upper lung and increased upper lung perfusion that improves \dot{V}_A/\dot{Q} matching

8. Control of Ventilation

The respiratory control system adjusts minute ventilation (\dot{V}_E) to respond to changes in metabolic rate and other perturbations in order to maintain, as much as possible, arterial homeostasis. Resting pulmonary ventilation is adjusted to regulate $P_a\text{CO}_2$ (and thus pH_a) within a narrow range. $P_a\text{O}_2$ only becomes an appreciable ventilatory stimulus when $P_a\text{O}_2$ drops well below the normal range. Though few systematic studies have been reported, at rest the elderly appear to regulate $P_a\text{CO}_2$ within the same range as the young; $P_a\text{O}_2$ is somewhat lower mostly because of increased \dot{V}_A/\dot{Q} inhomogeneity.[51, 136].

Challenges to the respiratory control system include exercise, inhalation of hypercapnic and hypoxic mixtures and resistive and elastic loads to breathing. Of these, exercise is the most commonly encountered challenge and has, therefore, received the most study.

Interestingly, though, in comparison to the relatively preserved functional characteristics of exercise ventilatory control (see below), the elderly exhibit substantial degradation of response to these other challenges. Response to inhaled CO_2 is blunted[136-140]; Brischetto et al.[137] found that \dot{V}_E - $P_a\text{CO}_2$ slope was almost one-third lower in the elderly. Similarly, hypoxic response is reduced in older individuals[138-140]; Peterson et al.[140] found hypoxic ventilatory response to be reduced about 50%. Responses to both resistive and elastic loaded breathing are also reduced[141, 142].

Alterations in exercise ventilatory response are more subtle. A consistent observation is that ventilatory response to exercise at a given $\dot{V}\text{CO}_2$ is elevated in elderly subjects as compared to the young[74, 137, 143-145]. Inbar et al.[144] reported cardiopulmonary

responses to incremental exercise of 1,424 men, 43 of whom were aged 60-70 years.

$\dot{V}_E/\dot{V}CO_2$ was distinctly greater across metabolic rates in the older group. Similarly Poulin et al.[145] studied the incremental treadmill exercise response in 128 men and 96 women aged 55-86 years. On average, $\dot{V}_E/\dot{V}CO_2$ slope was 12.3% greater per decade in men and 9.3% greater per decade in women.

The source of enhanced ventilatory response can be evaluated by considering the alveolar mass balance equation:

$$\dot{V}_E/\dot{V}CO_2 = k/[P_aCO_2 \cdot (1-V_D/V_T)]$$

where k is a constant. This equation dictates that the greater $\dot{V}_E/\dot{V}CO_2$ can have only two sources: lower P_aCO_2 or greater V_D/V_T . Brischetto et al.[137] sampled arterial blood serially during incremental exercise in two older subjects and found an isocapnic response. Mummery et al.[146] drew arterial blood samples at rest and after 6 minutes of moderate and heavy exercise from 10 older (average age 63 years) and 10 young subjects. Moderate exercise was isocapnic, and P_aCO_2 fell with heavy exercise (presumably in response to metabolic acidosis), with no differences between older and younger participants. Calculations using measurements of P_aCO_2 suggest that deadspace is greater in elderly subjects than in young[51, 146]. Review of the literature for the source of elevated deadspace ventilation reveals only inconsistent alterations in the tidal volume-breathing frequency relationship[74]. Therefore, deadspace ventilation elevation during exercise seen in the elderly seems likely related to increased alveolar deadspace.

In contrast to moderate intensity steady-state exercise responses, dynamic exercise ventilatory responses are distinctly modified in the elderly. In studies of young subjects, dynamic response of \dot{V}_E is closely correlated with $\dot{V}CO_2$ dynamics[147, 148], with the result that P_aCO_2 fluctuation during the dynamic phase of exercise is small[148]. The observation that \dot{V}_E kinetics are substantially slowed in the elderly (with response time constants averaging 40-56% greater)[149, 150] might suggest that P_aCO_2 regulation in the non-steady state is greatly degraded, but this is likely not the case. The key observation is that $\dot{V}O_2$ kinetics are slowed in the elderly[149-151]. This is primarily related to low muscle oxidative capacity in ageing, but may also be influenced by wider muscle $\dot{Q}/\dot{V}O_2$ distribution (see above). $\dot{V}O_2$ kinetics are the prime determinant of $\dot{V}CO_2$ kinetics, with the latter being slowed with respect to the former by muscle-alkalinizing effects of phosphocreatine breakdown and fluctuation in the body's large CO_2 stores[152]. Thus, $\dot{V}CO_2$ kinetics are also markedly slowed in the elderly[149, 150]. Importantly, the ratio of \dot{V}_E and $\dot{V}CO_2$ time constants are somewhat greater in elderly compared to younger subjects[149, 150], implying a slightly “looser” control of P_aCO_2 . An important observation from 8 older subjects (aged 65-78 years) undergoing a rigorous exercise-training program was that training speeded $\dot{V}O_2$, $\dot{V}CO_2$ and \dot{V}_E kinetics (each time constant was reduced by ~50%), with correlation between the change in \dot{V}_E and $\dot{V}CO_2$ time constants being strong ($r=0.65$).[149] This supports the concept that slower \dot{V}_E kinetics in the elderly are mostly related to slowed metabolic rate kinetics, but a small degradation of P_aCO_2 control cannot be excluded.

9. Pulmonary Mechanics and Respiratory Muscle Function

With age, lung structural changes occur that affect exercise ventilatory response. These changes have the potential to contribute to decreased exercise performance and decline in $\dot{V}O_{2\max}$ seen with increasing age.[10, 144, 153-155] The lung's ageing process is difficult to generalize, given differences in individual environmental and genetic factors that influence how an individual ages. Gender differences in lung ageing may also be significant. The increase in resting lung and residual volumes and reduced vital and inspiratory capacities that occur with age have been well described in the literature and are beyond this review's scope.[136, 156-159]

Pulmonary function begins to decline at approximately age 25. In healthy non-smoking individuals, spirometric measures forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) decrease by $\sim 30 \text{ mL}\cdot\text{year}^{-1}$ in men and $23 \text{ mL}\cdot\text{year}^{-1}$ in women, with accelerated loss after age 65.[160, 161] Mean bronchial diameter also decreases with age, yielding increased airway resistance, particularly in peripheral airways.[162] Pulmonary static elastic recoil pressure decreases by approximately $0.1\text{-}0.2 \text{ cm}\cdot\text{year}^{-1}$ after age 20 due to chest wall stiffness increase and lung tissue elasticity loss.[163, 164] Elasticity loss is thought to represent remodelling of both spatial arrangement and cross-linking of the lung's elastin-collagen network.[165] Elastic recoil loss leads to alteration in the expiratory portion of the maximal flow-volume loop and results in the characteristic "scalloped" loop seen in elderly non-smokers. Elastic recoil loss appears proportional to peak expiratory flow decrease with age.[166]

Over time, chest wall compliance decreases due to calcification of costal cartilage, with increased prevalence of both spinal kyphosis and osteoporosis-associated vertebral fractures potentially contributing.[167-169] Obesity is prevalent in the ageing population, affecting more than one-third of adults older than 65.[170] Obese individuals have lower respiratory system compliance.[171-173] Expiratory reserve volume clearly decreases with increasing body mass index; functional residual capacity is reduced to a lesser extent. Total lung capacity does not appear to be affected significantly, except in extreme obesity. Decreased compliance is expected to contribute to increased dyspnoea during exercise in obese individuals.[174, 175]

Respiratory muscle strength decreases with age.[176, 177] Maximal effort transdiaphragmatic pressure gradients in older individuals are lower than in younger subjects, reflecting decreased diaphragmatic strength.[178, 179] In one study, diaphragm strength in the elderly was 13% less than in a younger group by maximal sniff and 23% less using cervical magnetic stimulation. Other measurements have shown 25% lower diaphragmatic strength in the elderly.[179] Strength loss does not appear related to diaphragmatic fibre type change or muscle atrophy.[180-182]. Diaphragm and intercostal muscle stiffness increase with age[183], decreasing chest wall compliance. Diaphragm collagen metabolism changes (collagen concentration and cross-linking increases) appear responsible for increased stiffness.[184] Spinal kyphosis and increased chest anterior-posterior diameter that occur with age likely contribute to decreased diaphragmatic function.[156]

Airspace size increases with age.[185] The term “senile emphysema” that has been used to describe this age-related pulmonary morphologic change is inaccurate; although ageing results in alveolar duct enlargement and distal duct ectasia, the ageing lung does not develop alveolar wall destruction and inflammation that is a hallmark of smoking-related emphysema.[186]

In healthy adults, peak ventilation during exercise typically approaches 70% of measured maximal voluntary ventilation (MVV), demonstrating appreciable breathing reserve. Aging is associated with a greater \dot{V}_E and dyspnoea for a given power output (Fig 3) due to mechanisms discussed earlier, including reduced lactate threshold, and increased V_D/V_T and \dot{V}_A/\dot{Q} mismatching (likely reflected in the increased \dot{V}_E/\dot{V}_{CO_2}). Breathing reserve tends to decrease in athletes and with normal ageing.[187] In a recent study of 759 maximal treadmill exercise tests performed in healthy Norwegian adults aged 20-85, peak ventilation decrease started at ages 40-49.[188] While peak \dot{V}_E decreased, predicted MVV (based on both FEV_{1-35} and FEV_{1-40})[154, 189] also decreased due to age-related FEV_1 reduction. This led to breathing reserve preservation. There is also an age related decline in vital capacity that leads to relative limitation in tidal volume (Fig 3), meaning, for a given ventilation, breathing frequency tends to be greater, especially at higher intensities.[159, 190]

During exercise in youth, tidal volume increase is achieved through decreases in both inspiratory and expiratory reserve volumes.[191, 192] There is initially a drop in end-expiratory lung volume (EELV) in both young and old subjects to optimize inspiratory

muscle function.[193] During severe intensity exercise in fit, young athletes, expiratory flow limitation can develop,[191] although increased EELV does not appear until very high rates of ventilation.[21, 193] Airway diameter decrease and static recoil pressure reduction that occur in ageing suggest that flow limitation may also become a factor limiting exercise in older individuals. Accurate measurement of expiratory flow limitation during exercise is challenging. The most common method involves demonstrating impingement of exercise flow-volume loops on the maximum-effort resting expiratory flow-volume relationship. This method, however, does not account for thoracic gas compression and may overestimate flow limitation during exercise.[190, 194] Taking several expirations at variable efforts from TLC (total lung capacity) to residual volume may help correct for dynamic gas compression.[194] Using a post-exercise maximal expiratory flow volume curve also helps by accounting for exercise-induced bronchodilation.[190] Wilkie et al. reported that older women exhibit exercise expiratory flow limitation more frequently than younger women.[193] Older subjects also report greater breathlessness and a steeper slope of the dyspnoea-power output relationship, suggesting that age-related lung changes have symptomatic consequences (Fig 3). Interestingly, this study found an EELV increase at power outputs between 80-100% $\dot{V}O_{2max}$ only in younger women. The authors hypothesize that impending flow limitation in older women may have an effect on EELV regulation.[193] This contrasts with findings of another study of trained individuals (14 men, 4 women aged 62-82) where older subjects increased EELV during moderate intensity exercise, but EELV did not increase in younger subjects until \dot{V}_E exceeded 110-120 L.min⁻¹. [21] Increased EELV compromises operating length-tension relationships of diaphragm and respiratory

muscles, leading to less force generation capacity. Increased EELV during exercise results in the subject breathing on the flattened portion of the lung pressure-volume relationship, reducing inspiratory muscle length, increasing work of breathing and potentially decreasing inspiratory muscle endurance.[190] In line with these effects, inspiratory reserve volume (IRV) is consistently lower in the elderly at rest, and remains lower, along with IC, for any given level of \dot{V}_E compared with young subjects (Fig 3), likely contributing importantly to the greater sensation of breathlessness in the elderly. [159, 195, 196]

While flow limitation and EELV behave in a similar fashion during low intensity exercise in older and younger lungs, expiratory flow limitation seems to develop at lower intensity exercise in older subjects.[21, 51, 193] There may be a gender difference, with women developing expiratory flow limitation more frequently than men during high intensity exercise,[197] presumably related to decreased lung size and lower maximal expiratory flow rates in women. Guenette et al.[198] describe an 86 year old female lifelong competitive swimmer (former Olympian) with moderate airflow obstruction (FEV_1/FVC 53%; FEV_1 54% predicted) who continued regular exercise into old age. Despite severe ventilatory limitation (dynamic hyperinflation of 780 mL and end inspiratory lung volume of 96% TLC) the participant only reported moderate dyspnoea and achieved $\dot{V}O_{2max}$ of 175% predicted ($19.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). The authors speculate reduced ventilatory requirements, breathing pattern alterations and improved respiratory muscle strength may each contribute to reduced dyspnoea in this athletic octogenarian. While only a case report, these findings emphasize that relative preservation throughout

life of aerobic capacity may be possible with regular high-intensity exercise, even when expiratory flow and ventilatory limitation is present.

Conclusions

Maintaining a high level of physical activity is an important part of healthy ageing and minimisation of multimorbidity. Deterioration in various components of the multi-organ system response to exercise conspires to make this difficult. Decreases in pulmonary system function likely contribute to exercise intolerance in healthy elderly, particularly those who maintain physical activity into senescence. However, loss of muscle oxidative capacity and cardiac output in sedentary elderly outstrips decline in pulmonary function, such that the relatively small contribution of pulmonary function to exercise limitation is preserved over a wide range of ages. Training programs for muscles of ambulation remains the most effective way to retain aerobic capacity in older individuals. However, the degree to which maintenance of training past 70 years of age – which is associated with considerable health-benefits – causes encroachment upon pulmonary limits requires further study.

Acknowledgements

Dr. Richard Casaburi holds the Grancell/Burns Chair in the Rehabilitative Sciences.

Figure Captions

Figure 1. a) Decline in maximal oxygen consumption ($\dot{V}O_{2\max}$) with age. $\dot{V}O_{2\max}$ is expressed as a percentage of predicted value[153] of a 25 year old individual of average weight and height (male 177 centimetres (cm) height and 82 kilograms (kg) weight; female 164cm height and 65kg weight). b) Decline in forced expiratory volume in one second (FEV_1) with age. FEV_1 is expressed as a percentage of predicted value[199] for a 25 year old individual of the same weight and height as in Figure 1a.

Figure 2. The interaction of physiologic mechanisms during exercise. The figure is modified from the classic 1967 conceptualization of Wasserman et al.[22] The ability to perform exercise is dependent on the performance of a number of linked systems, each of which is subject to deterioration with ageing.

Figure 3. Perceptual, ventilatory and respiratory mechanical responses to incremental treadmill exercise in healthy older (OM, aged 60–80 years) compared with younger men (YM, aged 40–59 years). Data points are mean \pm SEM for measurements at rest, during each stage of exercise and at peak exercise. $\dot{V}O_2$, oxygen uptake; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide output; V_T , tidal volume; IRV, inspiratory reserve volume; TLC, total lung capacity; IC, inspiratory capacity. Reproduced with permission from Jensen et al.[159]

References

1. Strehler BL, Mark DD, Mildvan AS. GEE MV: Rate and magnitude of age pigment accumulation in the human myocardium. *J Gerontol* 1959; 14: 430-439.
2. Sander M, Oxlund B, Jespersen A, Krasnik A, Mortensen EL, Westendorp RG, Rasmussen LJ. The challenges of human population ageing. *Age Ageing* 2014.
3. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2012; 2(2): 1143-1211.
4. Van Norman KA. Exercise programming for older adults. Human Kinetics, Champaign, Ill., 1995.
5. Chatterji S, Byles J, Cutler D, Seeman T, Verdes E. Health, functioning, and disability in older adults-present status and future implications. *Lancet* 2014.
6. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346(11): 793-801.
7. Koch LG, Kemi OJ, Qi N, Leng SX, Bijma P, Gilligan LJ, Wilkinson JE, Wisloff H, Hoydal MA, Rolim N, Abadir PM, van Grevenhof EM, Smith GL, Burant CF, Ellingsen O, Britton SL, Wisloff U. Intrinsic aerobic capacity sets a divide for aging and longevity. *Circ Res* 2011; 109(10): 1162-1172.
8. Kirkton SD, Howlett RA, Gonzalez NC, Giuliano PG, Britton SL, Koch LG, Wagner HE, Wagner PD. Continued artificial selection for running endurance in rats is associated with improved lung function. *J Appl Physiol* (1985) 2009; 106(6): 1810-1818.

9. Karlsen T, Leinan IM, Baekkerud FH, Lundgren KM, Tari A, Steinshamn SL, Stoylen A, Rognmo O. How to Be 80 Year Old and Have a VO₂max of a 35 Year Old. *Case Rep Med* 2015; 2015: 909561.
10. Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation* 2005; 112(5): 674-682.
11. Rosen MJ, Sorkin JD, Goldberg AP, Hagberg JM, Katzell LI. Predictors of age-associated decline in maximal aerobic capacity: a comparison of four statistical models. *J Appl Physiol* (1985) 1998; 84(6): 2163-2170.
12. Ogawa T, Spina RJ, Martin WH, 3rd, Kohrt WM, Schechtman KB, Holloszy JO, Ehsani AA. Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* 1992; 86(2): 494-503.
13. Toth MJ, Gardner AW, Ades PA, Poehlman ET. Contribution of body composition and physical activity to age-related decline in peak VO₂ in men and women. *J Appl Physiol* (1985) 1994; 77(2): 647-652.
14. Trappe S, Hayes E, Galpin A, Kaminsky L, Jemiolo B, Fink W, Trappe T, Jansson A, Gustafsson T, Tesch P. New records in aerobic power among octogenarian lifelong endurance athletes. *J Appl Physiol* (1985) 2013; 114(1): 3-10.
15. McGavock JM, Hastings JL, Snell PG, McGuire DK, Pacini EL, Levine BD, Mitchell JH. A forty-year follow-up of the Dallas Bed Rest and Training study: the effect of age on the cardiovascular response to exercise in men. *J Gerontol A Biol Sci Med Sci* 2009; 64(2): 293-299.

16. Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Jr., Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation* 1968; 38(5 Suppl): VII1-78.
17. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise. *Circulation* 2001; 104(12): 1350-1357.
18. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bedrest and Training Study: II. Effect of age on cardiovascular adaptation to exercise training. *Circulation* 2001; 104(12): 1358-1366.
19. Pollock RD, Carter S, Velloso CP, Duggal NA, Lord JM, Lazarus NR, Harridge SD. An investigation into the relationship between age and physiological function in highly active older adults. *J Physiol* 2015; 593(3): 657-680; discussion 680.
20. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs A, Silva AC, Whipp BJ. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. *Eur Respir J* 1999; 14(6): 1304-1313.
21. McClaran SR, Babcock MA, Pegelow DF, Reddan WG, Dempsey JA. Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. *J Appl Physiol* (1985) 1995; 78(5): 1957-1968.
22. Wasserman K, Van Kessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol* 1967; 22(1): 71-85.

23. Miljkovic N, Lim JY, Miljkovic I, Frontera WR. Aging of skeletal muscle fibers. *Ann Rehabil Med* 2015; 39(2): 155-162.
24. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *J Appl Physiol* (1985) 2001; 90(6): 2157-2165.
25. Lexell J. Human aging, muscle mass, and fiber type composition. *J Gerontol A Biol Sci Med Sci* 1995; 50 Spec No: 11-16.
26. Wang Y, Pessin JE. Mechanisms for fiber-type specificity of skeletal muscle atrophy. *Curr Opin Clin Nutr Metab Care* 2013; 16(3): 243-250.
27. VanSwearingen JM, Studenski SA. Aging, motor skill, and the energy cost of walking: implications for the prevention and treatment of mobility decline in older persons. *J Gerontol A Biol Sci Med Sci* 2014; 69(11): 1429-1436.
28. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* (1985) 2000; 88(4): 1321-1326.
29. Clark BC, Taylor JL. Age-related changes in motor cortical properties and voluntary activation of skeletal muscle. *Curr Aging Sci* 2011; 4(3): 192-199.
30. Frontera WR, Suh D, Krivickas LS, Hughes VA, Goldstein R, Roubenoff R. Skeletal muscle fiber quality in older men and women. *Am J Physiol Cell Physiol* 2000; 279(3): C611-618.
31. Lowe DA, Thomas DD, Thompson LV. Force generation, but not myosin ATPase activity, declines with age in rat muscle fibers. *Am J Physiol Cell Physiol* 2002; 283(1): C187-192.

32. Manini TM, Clark BC. Dynapenia and aging: an update. *J Gerontol A Biol Sci Med Sci* 2012; 67(1): 28-40.
33. Venturelli M, Saggin P, Muti E, Naro F, Cancellara L, Toniolo L, Tarperi C, Calabria E, Richardson RS, Reggiani C, Schena F. In vivo and in vitro evidence that intrinsic upper- and lower-limb skeletal muscle function is unaffected by ageing and disuse in oldest-old humans. *Acta Physiol (Oxf)* 2015; 215(1): 58-71.
34. Chabi B, Ljubicic V, Menzies KJ, Huang JH, Saleem A, Hood DA. Mitochondrial function and apoptotic susceptibility in aging skeletal muscle. *Aging Cell* 2008; 7(1): 2-12.
35. Carter HN, Chen CC, Hood DA. Mitochondria, muscle health, and exercise with advancing age. *Physiology (Bethesda)* 2015; 30(3): 208-223.
36. Hepple RT. Mitochondrial involvement and impact in aging skeletal muscle. *Front Aging Neurosci* 2014; 6: 211.
37. Ljubicic V, Joseph AM, Adihetty PJ, Huang JH, Saleem A, Ugucioni G, Hood DA. Molecular basis for an attenuated mitochondrial adaptive plasticity in aged skeletal muscle. *Aging (Albany NY)* 2009; 1(9): 818-830.
38. Ljubicic V, Hood DA. Diminished contraction-induced intracellular signaling towards mitochondrial biogenesis in aged skeletal muscle. *Aging Cell* 2009; 8(4): 394-404.
39. Betik AC, Thomas MM, Wright KJ, Riel CD, Hepple RT. Exercise training from late middle age until senescence does not attenuate the declines in skeletal muscle aerobic function. *Am J Physiol Regul Integr Comp Physiol* 2009; 297(3): R744-755.

40. Santanasto AJ, Glynn NW, Jubrias SA, Conley KE, Boudreau RM, Amati F, Mackey DC, Simonsick EM, Strotmeyer ES, Coen PM, Goodpaster BH, Newman AB. Skeletal Muscle Mitochondrial Function and Fatigability in Older Adults. *J Gerontol A Biol Sci Med Sci* 2015; 70(11): 1379-1385.
41. Amara CE, Shankland EG, Jubrias SA, Marcinek DJ, Kushmerick MJ, Conley KE. Mild mitochondrial uncoupling impacts cellular aging in human muscles in vivo. *Proc Natl Acad Sci U S A* 2007; 104(3): 1057-1062.
42. Layec G, Trinity JD, Hart CR, Kim SE, Groot HJ, Le Fur Y, Sorensen JR, Jeong EK, Richardson RS. Impact of age on exercise-induced ATP supply during supramaximal plantar flexion in humans. *Am J Physiol Regul Integr Comp Physiol* 2015; 309(4): R378-388.
43. Hunter SK, Thompson MW, Ruell PA, Harmer AR, Thom JM, Gwinn TH, Adams RD. Human skeletal sarcoplasmic reticulum Ca²⁺ uptake and muscle function with aging and strength training. *J Appl Physiol* (1985) 1999; 86(6): 1858-1865.
44. Layec G, Hart CR, Trinity JD, Le Fur Y, Jeong EK, Richardson RS. Skeletal muscle work efficiency with age: the role of non-contractile processes. *Clin Sci (Lond)* 2015; 128(3): 213-223.
45. Ochala J, Frontera WR, Dorer DJ, Van Hoecke J, Krivickas LS. Single skeletal muscle fiber elastic and contractile characteristics in young and older men. *J Gerontol A Biol Sci Med Sci* 2007; 62(4): 375-381.
46. DeLorey DS, Paterson DH, Kowalchuk JM. Effects of ageing on muscle O₂ utilization and muscle oxygenation during the transition to moderate-intensity exercise. *Appl Physiol Nutr Metab* 2007; 32(6): 1251-1262.

47. Tevald MA, Foulis SA, Lanza IR, Kent-Braun JA. Lower energy cost of skeletal muscle contractions in older humans. *Am J Physiol Regul Integr Comp Physiol* 2010; 298(3): R729-739.
48. Venturelli M, Schena F, Scarsini R, Muti E, Richardson RS. Limitations to exercise in female centenarians: evidence that muscular efficiency tempers the impact of failing lungs. *Age (Dordr)* 2013; 35(3): 861-870.
49. Keir DA, Benson AP, Love LK, Robertson TC, Rossiter HB, Kowalchuk JM. Influence of muscle metabolic heterogeneity in determining the $\dot{V}O_{2p}$ kinetic response to ramp-incremental exercise. *J Appl Physiol (1985)* 2015: jap 00804 02015.
50. Grey TM, Spencer MD, Belfry GR, Kowalchuk JM, Paterson DH, Murias JM. Effects of age and long-term endurance training on $\dot{V}O_2$ kinetics. *Med Sci Sports Exerc* 2015; 47(2): 289-298.
51. Johnson BD, Reddan WG, Pegelow DF, Seow KC, Dempsey JA. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis* 1991; 143(5 Pt 1): 960-967.
52. Wagner PD. Determinants of maximal oxygen transport and utilization. *Annu Rev Physiol* 1996; 58: 21-50.
53. Saltin B, Calbet JA. Point: in health and in a normoxic environment, $\dot{V}O_2$ max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol (1985)* 2006; 100(2): 744-745.

54. Wagner PD. Counterpoint: in health and in normoxic environment VO_2max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol* (1985) 2006; 100(2): 745-747; discussion 747-748.
55. McAllister RM, Terjung RL. Training-induced muscle adaptations: increased performance and oxygen consumption. *J Appl Physiol* (1985) 1991; 70(4): 1569-1574.
56. Bebout DE, Hogan MC, Hempleman SC, Wagner PD. Effects of training and immobilization on VO_2 and DO_2 in dog gastrocnemius muscle in situ. *J Appl Physiol* (1985) 1993; 74(4): 1697-1703.
57. Richardson RS, Wary C, Wray DW, Hoff J, Rossiter HB, Layec G, Carlier PG. MRS Evidence of Adequate O_2 Supply in Human Skeletal Muscle at the Onset of Exercise. *Med Sci Sports Exerc* 2015; 47(11): 2299-2307.
58. Mole PA, Chung Y, Tran TK, Sailasuta N, Hurd R, Jue T. Myoglobin desaturation with exercise intensity in human gastrocnemius muscle. *Am J Physiol* 1999; 277(1 Pt 2): R173-180.
59. Wagner PD. A re-analysis of the 1968 Saltin et al. "Bedrest" paper. *Scand J Med Sci Sports* 2015; 25 Suppl 4: 83-87.
60. Groen BB, Hamer HM, Snijders T, van Kranenburg J, Frijns D, Vink H, van Loon LJ. Skeletal muscle capillary density and microvascular function are compromised with aging and type 2 diabetes. *J Appl Physiol* (1985) 2014; 116(8): 998-1005.

61. Chilibeck PD, Paterson DH, Cunningham DA, Taylor AW, Noble EG. Muscle capillarization O₂ diffusion distance, and VO₂ kinetics in old and young individuals. *J Appl Physiol* (1985) 1997; 82(1): 63-69.
62. Coggan AR, Spina RJ, King DS, Rogers MA, Brown M, Nemeth PM, Holloszy JO. Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. *J Gerontol* 1992; 47(3): B71-76.
63. Russell JA, Kindig CA, Behnke BJ, Poole DC, Musch TI. Effects of aging on capillary geometry and hemodynamics in rat spinotrapezius muscle. *Am J Physiol Heart Circ Physiol* 2003; 285(1): H251-258.
64. Gravelle BM, Murias JM, Spencer MD, Paterson DH, Kowalchuk JM. Adjustments of pulmonary O₂ uptake and muscle deoxygenation during ramp incremental exercise and constant-load moderate-intensity exercise in young and older adults. *J Appl Physiol* (1985) 2012; 113(9): 1466-1475.
65. Chilibeck PD, McCreary CR, Marsh GD, Paterson DH, Noble EG, Taylor AW, Thompson RT. Evaluation of muscle oxidative potential by ³¹P-MRS during incremental exercise in old and young humans. *Eur J Appl Physiol Occup Physiol* 1998; 78(5): 460-465.
66. Costes F, Denis C, Roche F, Prieur F, Enjolras F, Barthelemy JC. Age-associated alteration of muscle oxygenation measured by near infrared spectroscopy during exercise. *Arch Physiol Biochem* 1999; 107(2): 159-167.
67. Behnke BJ, Delp MD, Dougherty PJ, Musch TI, Poole DC. Effects of aging on microvascular oxygen pressures in rat skeletal muscle. *Respir Physiol Neurobiol* 2005; 146(2-3): 259-268.

68. Hepple RT, Hagen JL, Krause DJ, Jackson CC. Aerobic power declines with aging in rat skeletal muscles perfused at matched convective O₂ delivery. *J Appl Physiol* (1985) 2003; 94(2): 744-751.
69. Tevald MA, Foulis SA, Kent JA. Effect of age on in vivo oxidative capacity in two locomotory muscles of the leg. *Age (Dordr)* 2014; 36(5): 9713.
70. Chuang ML, Ting H, Otsuka T, Sun XG, Chiu FY, Beaver WL, Hansen JE, Lewis DA, Wasserman K. Aerobically generated CO₂ stored during early exercise. *J Appl Physiol* (1985) 1999; 87(3): 1048-1058.
71. Cartee GD. Aging skeletal muscle: response to exercise. *Exerc Sport Sci Rev* 1994; 22: 91-120.
72. Masuda S, Hayashi T, Egawa T, Taguchi S. Evidence for differential regulation of lactate metabolic properties in aged and unloaded rat skeletal muscle. *Exp Gerontol* 2009; 44(4): 280-288.
73. Kent-Braun JA. Skeletal muscle fatigue in old age: whose advantage? *Exerc Sport Sci Rev* 2009; 37(1): 3-9.
74. Prioux J, Ramonatxo M, Hayot M, Mucci P, Prefaut C. Effect of ageing on the ventilatory response and lactate kinetics during incremental exercise in man. *Eur J Appl Physiol* 2000; 81(1-2): 100-107.
75. Wray DW, Richardson RS. 'Fine-tuning' blood flow to the exercising muscle with advancing age: an update. *Exp Physiol* 2015; 100(6): 589-602.
76. Proctor DN, Parker BA. Vasodilation and vascular control in contracting muscle of the aging human. *Microcirculation* 2006; 13(4): 315-327.

77. Poole JG, Lawrenson L, Kim J, Brown C, Richardson RS. Vascular and metabolic response to cycle exercise in sedentary humans: effect of age. *Am J Physiol Heart Circ Physiol* 2003; 284(4): H1251-1259.
78. Wray DW, Nishiyama SK, Richardson RS. Role of α 1-adrenergic vasoconstriction in the regulation of skeletal muscle blood flow with advancing age. *Am J Physiol Heart Circ Physiol* 2009; 296(2): H497-504.
79. Trinity JD, Groot HJ, Layec G, Rossman MJ, Ives SJ, Morgan DE, Gmelch BS, Bledsoe A, Richardson RS. Passive leg movement and nitric oxide-mediated vascular function: the impact of age. *Am J Physiol Heart Circ Physiol* 2015; 308(6): H672-679.
80. Barrett-O'Keefe Z, Ives SJ, Trinity JD, Morgan G, Rossman MJ, Donato AJ, Runnels S, Morgan DE, Gmelch BS, Bledsoe AD, Richardson RS, Wray DW. Endothelin-A-mediated vasoconstriction during exercise with advancing age. *J Gerontol A Biol Sci Med Sci* 2015; 70(5): 554-565.
81. Proctor DN, Koch DW, Newcomer SC, Le KU, Smithmyer SL, Leuenberger UA. Leg blood flow and VO₂ during peak cycle exercise in younger and older women. *Med Sci Sports Exerc* 2004; 36(4): 623-631.
82. Proctor DN, Newcomer SC, Koch DW, Le KU, MacLean DA, Leuenberger UA. Leg blood flow during submaximal cycle ergometry is not reduced in healthy older normally active men. *J Appl Physiol* (1985) 2003; 94(5): 1859-1869.
83. Parker BA, Smithmyer SL, Ridout SJ, Ray CA, Proctor DN. Age and microvascular responses to knee extensor exercise in women. *Eur J Appl Physiol* 2008; 103(3): 343-351.

84. Proctor DN, Koch DW, Newcomer SC, Le KU, Leuenberger UA. Impaired leg vasodilation during dynamic exercise in healthy older women. *J Appl Physiol* (1985) 2003; 95(5): 1963-1970.
85. DeLorey DS, Kowalchuk JM, Paterson DH. Effects of prior heavy-intensity exercise on pulmonary O₂ uptake and muscle deoxygenation kinetics in young and older adult humans. *J Appl Physiol* (1985) 2004; 97(3): 998-1005.
86. Behnke BJ, Ramsey MW, Stabley JN, Dominguez JM, 2nd, Davis RT, 3rd, McCullough DJ, Muller-Delp JM, Delp MD. Effects of aging and exercise training on skeletal muscle blood flow and resistance artery morphology. *J Appl Physiol* (1985) 2012; 113(11): 1699-1708.
87. Murias JM, Keir DA, Spencer MD, Paterson DH. Sex-related differences in muscle deoxygenation during ramp incremental exercise. *Respir Physiol Neurobiol* 2013; 189(3): 530-536.
88. Park SY, Ives SJ, Gifford JR, Andtbacka RH, Hyngstrom JR, Reese VR, Layec G, Bharath LP, Symons JD, Richardson RS. The Impact of Age on the Vasodilatory Function of Human Skeletal Muscle Feed Arteries. *Am J Physiol Heart Circ Physiol* 2015: ajpheart 00716 02015.
89. Behnke BJ, Delp MD. Aging blunts the dynamics of vasodilation in isolated skeletal muscle resistance vessels. *J Appl Physiol* (1985) 2010; 108(1): 14-20.
90. Sinkler SY, Segal SS. Aging alters reactivity of microvascular resistance networks in mouse gluteus maximus muscle. *Am J Physiol Heart Circ Physiol* 2014; 307(6): H830-839.

91. Mortensen SP, Nyberg M, Winding K, Saltin B. Lifelong physical activity preserves functional sympatholysis and purinergic signalling in the ageing human leg. *J Physiol* 2012; 590(Pt 23): 6227-6236.
92. Sidhu SK, Weavil JC, Venturelli M, Rossman MJ, Gmelch BS, Bledsoe AD, Richardson RS, Amann M. Aging alters muscle reflex control of autonomic cardiovascular responses to rhythmic contractions in humans. *Am J Physiol Heart Circ Physiol* 2015; 309(9): H1479-1489.
93. Taddei S, Galetta F, Viridis A, Ghiadoni L, Salvetti G, Franzoni F, Giusti C, Salvetti A. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation* 2000; 101(25): 2896-2901.
94. Proctor DN, Beck KC, Shen PH, Eickhoff TJ, Halliwill JR, Joyner MJ. Influence of age and gender on cardiac output-VO₂ relationships during submaximal cycle ergometry. *J Appl Physiol* (1985) 1998; 84(2): 599-605.
95. Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, Dempsey JA. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* (1985) 1997; 82(5): 1573-1583.
96. Vogiatzis I, Athanasopoulos D, Habazettl H, Kuebler WM, Wagner H, Roussos C, Wagner PD, Zakyntinos S. Intercostal muscle blood flow limitation in athletes during maximal exercise. *J Physiol* 2009; 587(Pt 14): 3665-3677.
97. Olson TP, Joyner MJ, Dietz NM, Eisenach JH, Curry TB, Johnson BD. Effects of respiratory muscle work on blood flow distribution during exercise in heart failure. *J Physiol* 2010; 588(Pt 13): 2487-2501.

98. Andres E, Serraj K, Federici L, Vogel T, Kaltenbach G. Anemia in elderly patients: new insight into an old disorder. *Geriatr Gerontol Int* 2013; 13(3): 519-527.
99. Tweeddale PM, Leggett RJ, Flenley DC. Effect of age on oxygen-binding in normal human subjects. *Clin Sci Mol Med* 1976; 51(2): 185-188.
100. Mairbaurl H, Weber RE. Oxygen transport by hemoglobin. *Compr Physiol* 2012; 2(2): 1463-1489.
101. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001; 37(1): 153-156.
102. Fleg JL, Schulman S, O'Connor F, Becker LC, Gerstenblith G, Clulow JF, Renlund DG, Lakatta EG. Effects of acute beta-adrenergic receptor blockade on age-associated changes in cardiovascular performance during dynamic exercise. *Circulation* 1994; 90(5): 2333-2341.
103. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc Res* 1970; 4(2): 160-167.
104. Larson ED, St Clair JR, Sumner WA, Bannister RA, Proenza C. Depressed pacemaker activity of sinoatrial node myocytes contributes to the age-dependent decline in maximum heart rate. *Proc Natl Acad Sci U S A* 2013; 110(44): 18011-18016.
105. Cheitlin MD. Cardiovascular physiology-changes with aging. *Am J Geriatr Cardiol* 2003; 12(1): 9-13.
106. Betik AC, Hepple RT. Determinants of VO₂ max decline with aging: an integrated perspective. *Appl Physiol Nutr Metab* 2008; 33(1): 130-140.

107. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004; 110(13): 1799-1805.
108. Fujimoto N, Hastings JL, Bhella PS, Shibata S, Gandhi NK, Carrick-Ranson G, Palmer D, Levine BD. Effect of ageing on left ventricular compliance and distensibility in healthy sedentary humans. *J Physiol* 2012; 590(Pt 8): 1871-1880.
109. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Fail Clin* 2012; 8(1): 143-164.
110. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. *Circulation* 2003; 107(3): 490-497.
111. Forman DE, Manning WJ, Hauser R, Gervino EV, Evans WJ, Wei JY. Enhanced left ventricular diastolic filling associated with long-term endurance training. *J Gerontol* 1992; 47(2): M56-58.
112. Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, Boyd KN, Adams-Huet B, Levine BD. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. *J Am Coll Cardiol* 2014; 64(12): 1257-1266.
113. Gozna ER, Marble AE, Shaw A, Holland JG. Age-related changes in the mechanics of the aorta and pulmonary artery of man. *J Appl Physiol* 1974; 36(4): 407-411.
114. Mackay EH, Banks J, Sykes B, Lee G. Structural basis for the changing physical properties of human pulmonary vessels with age. *Thorax* 1978; 33(3): 335-344.

115. Emirgil C, Sobol BJ, Campodonico S, Herbert WH, Mechkati R. Pulmonary circulation in the aged. *J Appl Physiol* 1967; 23(5): 631-640.
116. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation* 2009; 119(20): 2663-2670.
117. van Empel VP, Kaye DM, Borlaug BA. Effects of healthy aging on the cardiopulmonary hemodynamic response to exercise. *Am J Cardiol* 2014; 114(1): 131-135.
118. Delclaux B, Orcel B, Housset B, Whitelaw WA, Derenne JP. Arterial blood gases in elderly persons with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1994; 7(5): 856-861.
119. Blom H, Mulder M, Verweij W. Arterial oxygen tension and saturation in hospital patients: effect of age and activity. *BMJ* 1988; 297(6650): 720-721.
120. Cerveri I, Zoia MC, Fanfulla F, Spagnolatti L, Berrayah L, Grassi M, Tinelli C. Reference values of arterial oxygen tension in the middle-aged and elderly. *Am J Respir Crit Care Med* 1995; 152(3): 934-941.
121. Hardie JA, Vollmer WM, Buist AS, Ellingsen I, Morkve O. Reference values for arterial blood gases in the elderly. *Chest* 2004; 125(6): 2053-2060.
122. Guenard H, Marthan R. Pulmonary gas exchange in elderly subjects. *Eur Respir J* 1996; 9(12): 2573-2577.
123. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93(3): 391-398.

124. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1(8222): 681-686.
125. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981; 123(2): 185-189.
126. Taylor BJ, Johnson BD. The pulmonary circulation and exercise responses in the elderly. *Semin Respir Crit Care Med* 2010; 31(5): 528-538.
127. Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100 per cent O₂. *J Clin Invest* 1974; 54(1): 54-68.
128. Wagner PD, Saltzman HA, West JB. Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J Appl Physiol* 1974; 36(5): 588-599.
129. Mellempgaard K. The alveolar-arterial oxygen difference: its size and components in normal man. *Acta Physiol Scand* 1966; 67(1): 10-20.
130. Raine JM, Bishop JM. A-a difference in O₂ tension and physiological dead space in normal man. *J Appl Physiol* 1963; 18: 284-288.
131. Cardus J, Burgos F, Diaz O, Roca J, Barbera JA, Marrades RM, Rodriguez-Roisin R, Wagner PD. Increase in pulmonary ventilation-perfusion inequality with age in healthy individuals. *Am J Respir Crit Care Med* 1997; 156(2 Pt 1): 648-653.
132. Johnson BD, Badr MS, Dempsey JA. Impact of the aging pulmonary system on the response to exercise. *Clin Chest Med* 1994; 15(2): 229-246.
133. Ball WC, Jr., Stewart PB, Newsham LG, Bates DV. Regional pulmonary function studied with xenon 133. *J Clin Invest* 1962; 41: 519-531.

134. Holland J, Milic-Emili J, Macklem PT, Bates DV. Regional distribution of pulmonary ventilation and perfusion in elderly subjects. *J Clin Invest* 1968; 47(1): 81-92.
135. Frerichs I, Braun P, Dudykevych T, Hahn G, Genee D, Hellige G. Distribution of ventilation in young and elderly adults determined by electrical impedance tomography. *Respir Physiol Neurobiol* 2004; 143(1): 63-75.
136. Janssens JP. Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. *Clin Chest Med* 2005; 26(3): 469-484, vi-vii.
137. Brischetto MJ, Millman RP, Peterson DD, Silage DA, Pack AI. Effect of aging on ventilatory response to exercise and CO₂. *J Appl Physiol Respir Environ Exerc Physiol* 1984; 56(5): 1143-1150.
138. Garcia-Rio F, Villamor A, Gomez-Mendieta A, Lores V, Rojo B, Ramirez T, Villamor J. The progressive effects of ageing on chemosensitivity in healthy subjects. *Respir Med* 2007; 101(10): 2192-2198.
139. Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. *J Clin Invest* 1973; 52(8): 1812-1819.
140. Peterson DD, Pack AI, Silage DA, Fishman AP. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. *Am Rev Respir Dis* 1981; 124(4): 387-391.
141. Tack M, Altose MD, Cherniack NS. Effect of aging on respiratory sensations produced by elastic loads. *J Appl Physiol Respir Environ Exerc Physiol* 1981; 50(4): 844-850.

142. Tack M, Altose MD, Cherniack NS. Effect of aging on the perception of resistive ventilatory loads. *Am Rev Respir Dis* 1982; 126(3): 463-467.
143. Faisal A, Webb KA, Guenette JA, Jensen D, Neder JA, O'Donnell DE, Canadian Respiratory Research N. Effect of age-related ventilatory inefficiency on respiratory sensation during exercise. *Respir Physiol Neurobiol* 2015; 205: 129-139.
144. Inbar O, Oren A, Scheinowitz M, Rotstein A, Dlin R, Casaburi R. Normal cardiopulmonary responses during incremental exercise in 20- to 70-yr-old men. *Med Sci Sports Exerc* 1994; 26(5): 538-546.
145. Poulin MJ, Cunningham DA, Paterson DH, Rechnitzer PA, Ecclestone NA, Koyal JJ. Ventilatory response to exercise in men and women 55 to 86 years of age. *Am J Respir Crit Care Med* 1994; 149(2 Pt 1): 408-415.
146. Mummery HJ, Stolp BW, de LDG, Doar PO, Natoli MJ, Boso AE, Archibald JD, Hobbs GW, El-Moalem HE, Moon RE. Effects of age and exercise on physiological dead space during simulated dives at 2.8 ATA. *J Appl Physiol* (1985) 2003; 94(2): 507-517.
147. Casaburi R, Whipp BJ, Wasserman K, Beaver WL, Koyal SN. Ventilatory and gas exchange dynamics in response to sinusoidal work. *J Appl Physiol Respir Environ Exerc Physiol* 1977; 42(2): 300-301.
148. Casaburi R, Whipp BJ, Wasserman K, Stremel RW. Ventilatory control characteristics of the exercise hyperpnea as discerned from dynamic forcing techniques. *Chest* 1978; 73(2 Suppl): 280-283.

149. Babcock MA, Paterson DH, Cunningham DA. Effects of aerobic endurance training on gas exchange kinetics of older men. *Med Sci Sports Exerc* 1994; 26(4): 447-452.
150. Cunningham DA, Himann JE, Paterson DH, Dickinson JR. Gas exchange dynamics with sinusoidal work in young and elderly women. *Respir Physiol* 1993; 91(1): 43-56.
151. Bell C, Paterson DH, Kowalchuk JM, Cunningham DA. Oxygen uptake kinetics of older humans are slowed with age but are unaffected by hyperoxia. *Exp Physiol* 1999; 84(4): 747-759.
152. Casaburi R, Weissman ML, Huntsman DJ, Whipp BJ, Wasserman K. Determinants of gas exchange kinetics during exercise in the dog. *J Appl Physiol Respir Environ Exerc Physiol* 1979; 46(6): 1054-1060.
153. Glaser S, Koch B, Ittermann T, Schaper C, Dorr M, Felix SB, Volzke H, Ewert R, Hansen JE. Influence of age, sex, body size, smoking, and beta blockade on key gas exchange exercise parameters in an adult population. *Eur J Cardiovasc Prev Rehabil* 2010; 17(4): 469-476.
154. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129(2 Pt 2): S49-55.
155. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985; 131(5): 700-708.
156. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999; 13(1): 197-205.

157. Miller MR. Structural and physiological age-associated changes in aging lungs. *Semin Respir Crit Care Med* 2010; 31(5): 521-527.
158. Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ. The aging lung. *Clin Interv Aging* 2013; 8: 1489-1496.
159. Jensen D, Ofir D, O'Donnell DE. Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. *Respir Physiol Neurobiol* 2009; 167(1): 87-100.
160. Fowler RW, Pluck RA, Hetzel MR. Maximal expiratory flow-volume curves in Londoners aged 60 years and over. *Thorax* 1987; 42(3): 173-182.
161. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; 127(6): 725-734.
162. Niewoehner DE, Kleinerman J. Morphologic basis of pulmonary resistance in the human lung and effects of aging. *J Appl Physiol* 1974; 36(4): 412-418.
163. Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. *J Appl Physiol* 1968; 25(6): 664-671.
164. Frank NR, Mead J, Ferris BG, Jr. The mechanical behavior of the lungs in healthy elderly persons. *J Clin Invest* 1957; 36(12): 1680-1687.
165. Pierce JA, Hocott JB. Studies on the collagen and elastin content of the human lung. *J Clin Invest* 1960; 39: 8-14.
166. Babb TG, Rodarte JR. Mechanism of reduced maximal expiratory flow with aging. *J Appl Physiol* (1985) 2000; 89(2): 505-511.

167. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *The Lancet* 2002; 359(9319): 1761-1767.
168. Edge JR, Millard FJ, Reid L, Simon G. The Radiographic Appearances of the Chest in Persons of Advanced Age. *Br J Radiol* 1964; 37: 769-774.
169. Estenne M, Yernault JC, De Troyer A. Rib cage and diaphragm-abdomen compliance in humans: effects of age and posture. *J Appl Physiol* (1985) 1985; 59(6): 1842-1848.
170. Fakhouri TH, Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among older adults in the United States, 2007-2010. *NCHS Data Brief* 2012(106): 1-8.
171. Hedenstierna G, Santesson J. Breathing mechanics, dead space and gas exchange in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. *Acta Anaesthesiol Scand* 1976; 20(3): 248-254.
172. Naimark A, Cherniack RM. Compliance of the respiratory system and its components in health and obesity. *J Appl Physiol* 1960; 15: 377-382.
173. Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L. Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. *Chest* 1996; 109(1): 144-151.
174. Sjostrom L, Larsson B, Backman L, Bengtsson C, Bouchard C, Dahlgren S, Hallgren P, Jonsson E, Karlsson J, Lapidus L, et al. Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. *Int J Obes Relat Metab Disord* 1992; 16(6): 465-479.

175. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med* 2002; 162(13): 1477-1481.
176. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *Am J Respir Crit Care Med* 1994; 149(2 Pt 1): 430-438.
177. Watsford ML, Murphy AJ, Pine MJ. The effects of ageing on respiratory muscle function and performance in older adults. *J Sci Med Sport* 2007; 10(1): 36-44.
178. Polkey MI, Harris ML, Hughes PD, Hamnegard CH, Lyons D, Green M, Moxham J. The contractile properties of the elderly human diaphragm. *Am J Respir Crit Care Med* 1997; 155(5): 1560-1564.
179. Tolep K, Higgins N, Muza S, Criner G, Kelsen SG. Comparison of diaphragm strength between healthy adult elderly and young men. *Am J Respir Crit Care Med* 1995; 152(2): 677-682.
180. Caskey CI, Zerhouni EA, Fishman EK, Rahmouni AD. Aging of the diaphragm: a CT study. *Radiology* 1989; 171(2): 385-389.
181. McCool FD, McCann DR, Leith DE, Hoppin FG, Jr. Pressure-flow effects on endurance of inspiratory muscles. *J Appl Physiol* (1985) 1986; 60(1): 299-303.
182. Tolep K, Kelsen SG. Effect of aging on respiratory skeletal muscles. *Clin Chest Med* 1993; 14(3): 363-378.
183. Kelly NG, McCarter RJ, Barnwell GM. Respiratory muscle stiffness is age- and muscle-specific. *Aging (Milano)* 1993; 5(3): 229-238.

184. Gosselin LE, Martinez DA, Vailas AC, Sieck GC. Passive length-force properties of senescent diaphragm: relationship with collagen characteristics. *J Appl Physiol* (1985) 1994; 76(6): 2680-2685.
185. Gillooly M, Lamb D. Airspace size in lungs of lifelong non-smokers: effect of age and sex. *Thorax* 1993; 48(1): 39-43.
186. Fukuchi Y. The aging lung and chronic obstructive pulmonary disease: similarity and difference. *Proc Am Thorac Soc* 2009; 6(7): 570-572.
187. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167(2): 211-277.
188. Edvardsen E, Scient C, Hansen BH, Holme IM, Dyrstad SM, Anderssen SA. Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. *Chest* 2013; 144(1): 241-248.
189. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *J Occup Med* 1982; 24(7): 531-533.
190. Sheel AW, Romer LM. Ventilation and respiratory mechanics. *Compr Physiol* 2012; 2(2): 1093-1142.
191. Johnson BD, Saupe KW, Dempsey JA. Mechanical constraints on exercise hyperpnea in endurance athletes. *J Appl Physiol* (1985) 1992; 73(3): 874-886.
192. Henke KG, Sharratt M, Pegelow D, Dempsey JA. Regulation of end-expiratory lung volume during exercise. *J Appl Physiol* (1985) 1988; 64(1): 135-146.

193. Wilkie SS, Guenette JA, Dominelli PB, Sheel AW. Effects of an aging pulmonary system on expiratory flow limitation and dyspnoea during exercise in healthy women. *Eur J Appl Physiol* 2012; 112(6): 2195-2204.
194. Guenette JA, Dominelli PB, Reeve SS, Durkin CM, Eves ND, Sheel AW. Effect of thoracic gas compression and bronchodilation on the assessment of expiratory flow limitation during exercise in healthy humans. *Respir Physiol Neurobiol* 2010; 170(3): 279-286.
195. Tessier JF, Nejjar C, Letenneur L, Filleul L, Marty ML, Barberger Gateau P, Dartigues JF. Dyspnea and 8-year mortality among elderly men and women: the PAQUID cohort study. *Eur J Epidemiol* 2001; 17(3): 223-229.
196. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J Appl Physiol* (1985) 2008; 104(6): 1583-1593.
197. Guenette JA, Witt JD, McKenzie DC, Road JD, Sheel AW. Respiratory mechanics during exercise in endurance-trained men and women. *J Physiol* 2007; 581(Pt 3): 1309-1322.
198. Guenette JA, Diane Loughheed M, Webb KA, O'Donnell DE. Can an 86-year-old woman with advanced lung disease be a world class athlete? *Respir Physiol Neurobiol* 2012; 181(2): 162-166.
199. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159(1): 179-187.

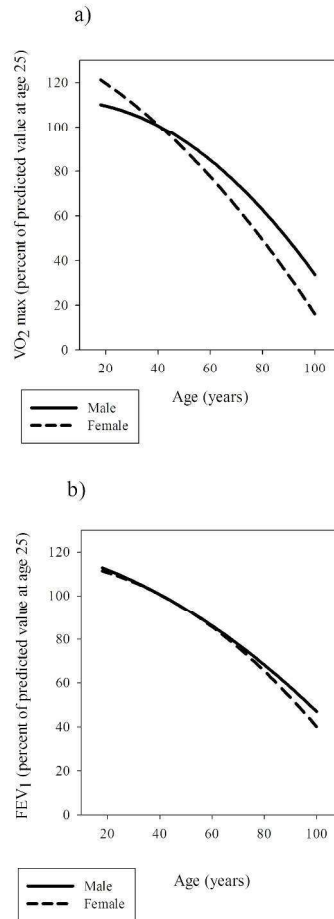


Figure 1. a) Decline in maximal oxygen consumption (VO₂max) with age. VO₂max is expressed as a percentage of predicted value[153] of a 25 year old individual of average weight and height (male 177 centimetres (cm) height and 82 kilograms (kg) weight; female 164cm height and 65kg weight). b) Decline in forced expiratory volume in one second (FEV₁) with age. FEV₁ is expressed as a percentage of predicted[198] value for a 25 year old individual of the same weight and height as in Figure 1a. 149x417mm (300 x 300 DPI)

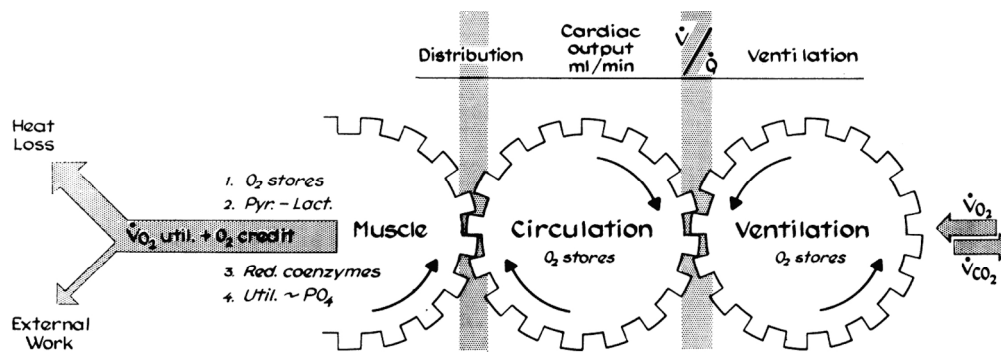


Figure 2. The interaction of physiologic mechanisms during exercise. The figure is modified from the classic 1967 conceptualization of Wasserman et al. [22] The ability to perform exercise is dependent on the performance of a number of linked systems, each of which is subject to deterioration with ageing.
189x64mm (300 x 300 DPI)

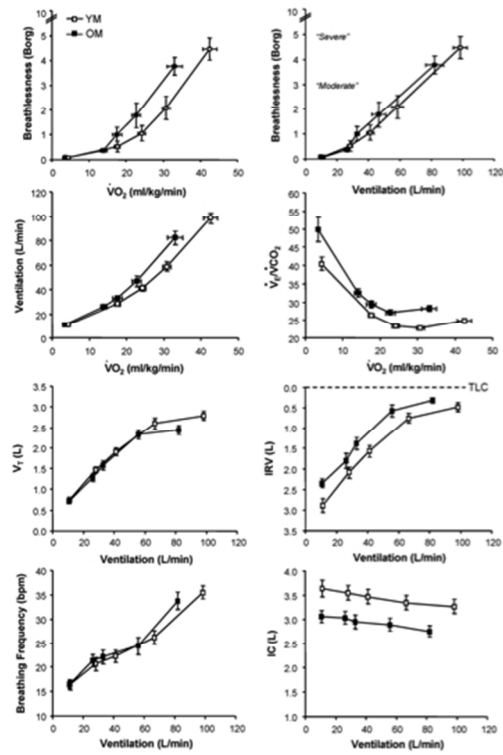


Figure 3. Perceptual, ventilatory and respiratory mechanical responses to incremental treadmill exercise in healthy older (OM, aged 60–80 years) compared with younger men YM, aged 40–59 years). Data points are mean±SEM for measurements at rest, during each stage of exercise and at peak exercise. $\dot{V}O_2$, oxygen uptake; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide output; V_T , tidal volume; IRV, inspiratory reserve volume; TLC, total lung capacity; IC, inspiratory capacity. Reproduced with permission from Jensen et al.[159]

254x190mm (72 x 72 DPI)