

# The effect of age on mechanisms of exercise tolerance: Reduced arteriovenous oxygen difference causes lower oxygen consumption in older people

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**Manuscript title: The effect of age on mechanisms of exercise tolerance: reduced arteriovenous oxygen difference causes lower oxygen consumption in older people**

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## **Abstract**

**Objective** To assess the effect of age on mechanisms of exercise tolerance.

## **Methods**

Prospective observational study recruited 71 healthy individuals divided into two groups according to their age i.e. younger ( $\leq 40$  years of age,  $N=43$ ); and older ( $\geq 55$  years of age,  $N=28$ ). All participants underwent maximal graded cardiopulmonary exercise stress testing using cycle ergometer with simultaneous non-invasive gas-exchange and central haemodynamic measurements. Using the Fick equation, arteriovenous  $O_2$  difference was calculated as the ratio between measured  $O_2$  consumption and cardiac output.

## **Results**

The mean age of younger and older participants was  $26.0 \pm 5.7$  years, and  $65.1 \pm 6.6$  years respectively. Peak  $O_2$  consumption was significantly lower in older compared to the younger age group ( $18.8 \pm 5.2$  vs  $34.4 \pm 9.8$  ml/kg/min,  $p < 0.01$ ). Peak exercise cardiac output and cardiac index were not significantly different between the younger and older age groups ( $22.7 \pm 5.0$  vs  $22.1 \pm 3.9$  L/min,  $p = 0.59$ ; and  $12.4 \pm 2.9$  vs  $11.8 \pm 1.9$  L/min/m<sup>2</sup>,  $p = 0.29$ ). Despite demonstrating significantly lower peak heart rate by 33 beats/min ( $129 \pm 18.3$  vs  $162 \pm 19.9$ ,  $p < 0.01$ ), older participants demonstrated significantly higher stroke volume and stroke volume index compared to the younger age group ( $173 \pm 41.5$  vs  $142 \pm 34.9$  mL/min,  $p < 0.01$ ; and  $92.1 \pm 18.1$  vs  $78.3 \pm 19.5$  mL/m<sup>2</sup>,  $p < 0.01$ ). Arteriovenous  $O_2$  difference was significantly lower in older compared to younger age group participants ( $9.01 \pm 3.0$  vs  $15.8 \pm 4.3$  mlO<sub>2</sub>/ 100 mL blood,  $p < 0.01$ ).

**Conclusion** Ability of skeletal muscles to extract delivered oxygen represented by reduced arteriovenous  $O_2$  difference at peak exercise appears to be the key determinant of exercise tolerance in healthy older individuals.

## List of abbreviations

$O_2$

Oxygen

$\dot{V}O_{2peak}$

Peak oxygen consumption

## Introduction

Age is a major risk factor for developing chronic conditions such as cardiovascular, metabolic and neuromuscular diseases <sup>(1)</sup>. Older individuals (i.e. >65 years of age) with lower exercise tolerance have reduced functional independence, quality of life and increased incidence of cardiovascular and all-cause morbidity and mortality <sup>(2; 3)</sup>. Exercise tolerance is defined as the level of physical exertion an individual may achieve prior to reaching a state of exhaustion, and is commonly represented by peak oxygen consumption ( $\dot{V}O_{2peak}$ )<sup>(4)</sup>. According to the Fick principle, oxygen ( $O_2$ ) consumption is the product of cardiac output and arteriovenous  $O_2$  difference. As a result, the assumption can be made that a reduction in  $\dot{V}O_{2peak}$  is a result of attenuated cardiac output and/or arteriovenous  $O_2$  difference <sup>(5)</sup>. Additionally, with ageing, there is a decrease in lean body mass which correlates with reduced exercise tolerance <sup>(6)</sup>.

$\dot{V}O_{2peak}$  declines with age at the rate of 5-15% per decade after the age of 25, further accelerating with each successive decade <sup>(4; 6)</sup>. Older individuals demonstrate cardiac and vascular remodelling manifested as lower peak heart rate, arteriovenous  $O_2$  difference, early diastolic filling rate, reduced left ventricular contractility, reduced blood volume, increased stiffness and thickness of the myocardium and arteries as well as increased left ventricular end-diastolic volume <sup>(7)</sup>. The evidence available so far, is controversial about age-related decline in arteriovenous  $O_2$  difference, cardiac output and stroke volume <sup>(8; 9; 10; 11; 12; 13)</sup>.

Improved understanding of the physiological mechanisms leading to reduced exercise tolerance in older individuals is warranted as it will inform development of personalised interventions which target individual physiological components of  $\dot{V}O_{2peak}$ . Improved exercise tolerance enhances functional independence, quality of life, and reduces morbidity, mortality and disease progression/development in older individuals <sup>(14; 15; 16)</sup>. Therefore, the aim of the current study is to assess the effect of age on mechanisms of exercise tolerance.

## **Methods**

### **Study design**

This prospective, single-centre, cross-sectional observational study was performed to assess the effects of age on mechanisms of exercise tolerance. The study was conducted at the Clinical Research Facility of the Royal Victoria Infirmary in Newcastle. Data collection began January 2018 and was finalised in July 2019. The study was approved by the National Health Service research ethics committee (North West-Preston Research Ethics Committee), **ethics number 15/NE/0190**, and all procedures were performed according to the declaration of Helsinki. All participants provided written informed consent.

### **Participant involvement**

Participants were not involved in the design and conduct of this research.

### **Participants**

A total of 71 individuals aged between 19-78 years consented to and completed the study, **with participant age groups of <40 years of age and  $\geq$ 55 years of age being based on recruited participants.** Eligible participants attended the research facility on one occasion, which lasted between 90 and 120 minutes.

The study included adult participants with no history of chronic cardiovascular, **respiratory**, neuromuscular, and musculoskeletal disorders. Participants were also excluded if they were current smokers or if their body mass index was <18 or >30 kg/m<sup>2</sup>.

### **Study protocol and measurements**

All study participants were asked to abstain from alcohol or caffeine containing foods and beverages on test days and were asked not to perform vigorous exercise 24 hours prior to the test. Upon arrival at the laboratory, participants completed a health related Physical Activity Readiness questionnaire <sup>(4)</sup>. Blood pressure, O<sub>2</sub> saturation, and heart rate **(Welch Allyn, USA)** were measured in a seated position followed by height and body weight **(Seca, Hamburg, Germany)**. Finally, a resting 12-lead electrocardiogram in supine position was recorded.

Non-invasive bioimpedance technology (TaskForce, CNSystems, Graz, Austria) was used for haemodynamic measurements (i.e. cardiac output, stroke volume, and heart rate) at rest in supine position and during exercise testing, as previously detailed <sup>(17; 18)</sup>. Briefly, the theory behind bioimpedance cardiography is that blood flow through the thorax has a specific resistivity <sup>(17)</sup>. This haemodynamic resistance referred to as bioimpedance could be detected from a high frequency low amplitude current transmitted via electrodes placed in the thoracic cavity <sup>(17)</sup>. The described electrical model is based on Ohm's law.

### **Progressive exercise test and peak oxygen consumption measurements**

Participants completed a progressive exercise test using a semi recumbent cycle ergometer (Corival, Lode, Groningen, Netherlands) with simultaneous gas exchange measurements (Cortex analyzer 3B, Cortex, Leipzig, Germany). At least three minutes of resting (baseline) gas exchange and haemodynamic bioimpedance measurements were recorded before exercising. A ramp protocol was followed until maximal exertion with participants maintaining a pedal frequency of 60-70 revolutions per minute. A warm-up (cycling at 10 watts for 2 min) was included in the exercise test. The workload further increased at the rate of 10 watts per minute until volitional exhaustion. The 12-lead electrocardiography (Custo, CustoMed, Germany) and an automated blood pressure (SunTech Tango, SunTech Medical, Inc., Morrisville, USA) were recorded. The exercise test was terminated i) when respiratory exchange ratio exceeded 1.15 (i.e. universally acknowledged RER threshold <sup>(19)</sup>) ii) upon volitional exhaustion i.e. inability to maintain a cadence of 60 rpm, iii) when  $\dot{V}O_{2peak}$  was achieved, defined as the inability to increase  $O_2$  consumption despite an increase in exercise intensity, and iv) if the patient requested termination of the test.

$O_2$  consumption and cardiac output at peak exercise were defined as the average  $O_2$  uptake and cardiac output during the last 30 seconds of exercise. Anaerobic threshold was automatically calculated using the v-slope method <sup>(20)</sup>. Based on measured  $O_2$  consumption and cardiac output, arteriovenous  $O_2$  difference was calculated using the Fick equation:

$$O_2 \text{ consumption (ml/kg/min)} = \text{Cardiac Output (L/min)} \times \text{Arteriovenous } O_2 \text{ difference (mL/100mL of blood)}$$

The Fick equation has been previously demonstrated to yield equivalent measurements of O<sub>2</sub> consumption, cardiac output and arteriovenous O<sub>2</sub> difference when compared to direct measurement (21).

Stroke volume was calculated using cardiac output and heart rate measurements using the following equation:

$$\text{Stroke volume (mL/beat)} = \frac{\text{Cardiac output (L/min)} \times 1000}{\text{Heart rate (bpm)}}$$

Cardiac power output (Watts), as a measure of overall function and pumping capability of the heart, was calculated as the product of cardiac output and mean arterial blood pressure, using the formulae (20; 22):

$$\text{CPO(W)} = \frac{\text{MAP(mmHg)} \times \text{CO(L/min)}}{451}$$

Where CPO= cardiac power output; MAP= mean arterial pressure; CO= cardiac output.

### **Statistical analyses**

All statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, N.Y., USA). Prior to statistical analysis, data were screened for univariate and multivariate outliers using standard z-distribution cut-offs and Mahalanobis distance tests. A Kolmogorov-Smirnov test evaluated normality of distribution. Differences in demographic, physical and physiological characteristics between younger and older age groups were assessed using independent samples *t*-test. Pearson's coefficient of correlation or Spearman's coefficient of correlation, as appropriate, were used to assess the relationship between variables of interest. The strength of the relationship between two variables is quantified using the absolute value of 'r' i.e., r<0.03 - indicating weak relationship, 0.4-0.6 – moderate, 0.7-1.0 strong. Multiple linear regression analysis was also performed to assess the relationship between demographic indices (i.e., age, body surface area), central haemodynamics (i.e. cardiac output, cardiac power output, stroke volume and peak heart rate) and



arteriovenous O<sub>2</sub> difference. Statistical significance was indicated if  $p < 0.05$ . Data are presented as mean  $\pm$  SD unless stated otherwise.

## Results

A total of 71 participants / 30 women were recruited into the study and divided into two age groups, younger (<40 years of age) and older ( $\geq 55$  years of age). Participants' demographic and physical characteristics are presented in table 1. The mean age of younger participants was  $26 \pm 6$  years, and older  $65 \pm 7$  years. Eighteen participants (64%) in older age group were on angiotensin converting enzyme inhibitors (ACEi) to prevent or treat hypertension. The older age group demonstrated a 12% higher body weight ( $p < 0.01$ ) and 22% higher body mass index ( $p < 0.01$ ) compared with younger participants.

### Metabolic and haemodynamic measurements at rest

Most resting metabolic measurements were not significantly different between the younger and older age groups ( $p > 0.05$ ). There was no significant difference in absolute O<sub>2</sub> consumption between the younger and older participants ( $0.23 \pm 0.05$  vs  $0.24 \pm 0.07$  L/min,  $p = 0.33$ ). However, relative O<sub>2</sub> consumption which accounts for bodyweight, was significantly different and 23% lower in the older age group ( $2.89 \pm 0.57$  vs  $3.74 \pm 1.3$  mL/kg/min,  $p < 0.01$ ). Respiratory exchange ratio ( $0.86 \pm 0.06$  vs  $0.87 \pm 0.06$ ,  $p = 0.53$ ) and arteriovenous O<sub>2</sub> difference ( $6.64 \pm 2.5$  vs  $7.02 \pm 2.0$ ,  $p = 0.49$  mL O<sub>2</sub>/100mL blood) between younger and older participants were also not significant.

Cardiac output and cardiac power output were significantly higher in the younger participants by 41% ( $6.10 \pm 1.4$  vs  $4.33 \pm 1.1$  L/min,  $p < 0.01$ ) and 22% ( $1.05 \pm 0.33$  vs  $0.82 \pm 0.27$  W,  $p < 0.01$ ) as was stroke volume by 42% ( $102 \pm 19.2$  vs  $71.7 \pm 15.0$  mL/min,  $p = 0.01$ ). In contrast, mean arterial blood pressure was significantly higher in older than younger individuals by 9% ( $86.4 \pm 8.5$  vs  $79.6 \pm 8.5$  mmHg,  $p < 0.01$ ). Resting heart rate was not significantly different between the two age groups ( $60.8 \pm 8.1$  vs  $60.9 \pm 11.1$  beats/min,  $p = 0.95$ ). Resting metabolic and haemodynamic measurements at rest are shown in table 2.

## **Metabolic and haemodynamic measurements at peak exercise**

$\dot{V}O_{2\text{peak}}$  and work rate were significantly higher in the younger than older participants by 51% ( $p<0.01$ ) and 61% ( $p<0.01$ ) as shown in Table 3. Peak heart rate was significantly higher in younger participants by 26% ( $p<0.01$ ). Diastolic blood pressure, mean arterial pressure, stroke volume and stroke volume index were significantly higher in the old by 23% ( $p<0.01$ ), 17% ( $p<0.01$ ), 22% ( $p<0.01$ ) and 18% ( $p<0.01$ ) respectively. Systolic blood pressure was not significantly different between the young and old participants ( $p=0.19$ ).

Multiple linear regression analysis revealed that that only age, peak cardiac output, and cardiac power output were only significant predictors of arteriovenous  $O_2$  difference ( $p<0.05$ ).

## **The effect of age on peak oxygen consumption, cardiac output and arteriovenous oxygen difference**

Pearson's coefficient of correlation analysis revealed a significant moderate negative relationship between the age and  $\dot{V}O_{2\text{peak}}$  (Figure 1A) and arteriovenous  $O_2$  difference (Figure 1D). There was no significant relationship between age and peak cardiac output and cardiac power output (Figures 1B and 1C). In addition, there was a significant but weak positive relationship between age and peak stroke volume and stroke volume index ( $r=0.34$ ,  $p<0.01$ ; and  $r=0.32$ ,  $p=0.01$ ).

Figure 2 shows the relationship between  $\dot{V}O_{2\text{peak}}$  and its determinants (i.e. peak arteriovenous  $O_2$  difference and peak cardiac output) in both the young and old age group.

Additionally, there was a significant positive relationship between  $\dot{V}O_{2\text{peak}}$  and peak stroke volume in the young ( $r=0.326$ ,  $p=0.04$ ) but no in older participants ( $r=0.034$ ,  $p=0.88$ ). No significant relationship was found between  $\dot{V}O_{2\text{peak}}$  and heart rate in younger ( $r=0.184$ ,  $p=0.26$ ) or older participants ( $r=0.137$ ,  $p=0.50$ ).

## Discussion

### Study summary and key findings

The present study evaluated the effect of age on exercise tolerance and its determinants in healthy individuals. The major finding suggests that reduced exercise tolerance in older people is caused by reduced ability of skeletal muscles to extract O<sub>2</sub>, represented by arteriovenous O<sub>2</sub> difference. Findings further suggest that cardiac output and cardiac power output is preserved with ageing. Despite significant decline in peak heart rate, stroke volume significantly increases in healthy older people as a compensatory mechanism, allowing for a peak cardiac output similar to that of younger people.

### The effect of age on exercise tolerance

Previous studies have reported reduced  $\dot{V}O_{2peak}$  and heart rate in older people<sup>(13; 23)</sup>. Reduced  $\dot{V}O_{2peak}$  is due to reduction in both central and peripheral physiological mechanisms i.e. arteriovenous O<sub>2</sub> difference and cardiac output<sup>(9; 24; 25)</sup>. The present study found reduced arteriovenous O<sub>2</sub> difference in older individuals further corroborating previous reports<sup>(10; 24; 26)</sup>. The strength of the relationship between arteriovenous O<sub>2</sub> difference and  $\dot{V}O_{2peak}$  was stronger in the older age group compared with the younger group, suggesting that the ability of skeletal muscles to extract delivered O<sub>2</sub> is the major determinant of exercise tolerance in older people<sup>(10)</sup>. With ageing, there is a decline in physical activity volume and intensity, in addition to increased sedentary behaviour<sup>(24)</sup> leading to a reduction in functional fitness, exaggerated age-related changes in the cardiovascular system and a significant reduction in peripheral O<sub>2</sub> extraction<sup>(24; 27)</sup>. However, when training volume and intensity is increased in older individuals, the age-related decrease in arteriovenous O<sub>2</sub> difference is attenuated through improved peripheral mechanisms i.e. microvascular circulation and skeletal muscle function<sup>(24; 28)</sup>.

The major cause of the decline in peak cardiac output with age is a decrease in cardiovascular response to sympathetic stimulation<sup>(8; 10)</sup>. In contrast, we demonstrated preserved cardiac output in the older age group. Such studies<sup>(8; 10)</sup> report that the age-associated decline in  $\dot{V}O_{2peak}$  in healthy individuals is a result of peak heart rate and stroke volume reductions. In the present study, stroke volume increased significantly in older individuals in response to exercise, leading to a significantly higher peak stroke volume in the older age group. A number of studies with participants aged between 20 and 80 years

also conclude that peak cardiac output is unaffected by age through a significant rise in stroke volume under physiological stress, compensating for heart rate attenuation in older individuals <sup>(12; 13; 26)</sup>. Stroke volume increases via a significant increase in end-diastolic volume and Frank Starling mechanism <sup>(13)</sup> <sup>(29)</sup>. It was previously thought that stroke volume plateaus at ~50% of  $\dot{V}O_{2\text{peak}}$  in healthy individuals, but more recently it has been demonstrated that stroke volume progressively increases throughout maximal exercise testing particularly in trained individuals <sup>(13; 26)</sup>.

The most consistently reported physiological change associated with age-related decline in  $\dot{V}O_{2\text{peak}}$  is heart rate. The age-related decline in heart rate is unaffected by lifestyle or gender and occurs at a rate of approximately 5% per decade <sup>(30)</sup>. Because peak heart rate consistently shows a significant relative contribution to decreased  $\dot{V}O_{2\text{peak}}$  in older individuals, there is little doubt that it plays an important role in overall cardiorespiratory performance <sup>(10; 30)</sup>.

## **Conclusions**

Exercise tolerance, represented by  $\dot{V}O_{2\text{peak}}$  is reduced in older people. The present study suggests that the ability of skeletal muscles to extract delivered oxygen (arteriovenous  $O_2$  difference) at peak exercise is significantly reduced in older people and appears to be the key determinant of exercise tolerance in this age group. During exercise, stroke volume increases in older people in order to maintain cardiac output despite significant reduction in peak exercise heart rate.

## **Study limitations**

In the present study the following limitations should be considered. Firstly, haemodynamic measurements were not assessed using the gold standard invasive methods. Previous studies demonstrated acceptable validity and reproducibility of non-invasive haemodynamic measurements using bioimpedance method. Secondly, the gender male to female ratio for the younger age group was 26:17 compared to 15:13 in the older age group. This difference in gender within groups may have modestly impacted end results. In addition, an objective assessment of participants' physical activity levels was not included in the present study. This raises the possibility that lifestyle may have significant impact on overall exercise tolerance and its determinants in both younger and older age participants.

Furthermore, 64% of participants in older age group used ACEi to prevent or treat hypertension and this may have impacted on exercise tolerance.

Lastly, the number of study participants was modest, particularly in the older age group. Considering these limitations, the major findings of the present study should be considered as preliminary.

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### **Authors' Contributions**

DGJ and GAM designed the study. NCO, AF, AB, and CE performed the study and collected the data. AF and DGJ analysed the data and drafted the manuscript. NCO, AB, CE, RV, LCG, and GAM reviewed the manuscript. All authors read and approved the final manuscript.

### **Availability of Data**

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing Interests**

The authors declare that they have no competing interests.

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## List of tables and figures

**Table 1.** Demographic, physical and clinical characteristics of study participants.

	<b>&lt;40 years (N=43)</b>	<b>≥ 55 years (N=28)</b>	<b>P value</b>
<b>Demographics</b>			
Age (years)	26.0±5.66	65.1±6.59	<b>&lt;0.01</b>
Gender (Male/Female)	26/17	15/13	
Height (m)	1.74±0.11	1.67±0.10	<b>0.01</b>
Weight (kg)	69.5±12.0	77.9±10.8	<b>&lt;0.01</b>
Body mass index (kg/m <sup>2</sup> )	22.8±1.97	27.9±2.89	<b>&lt;0.01</b>
Body surface area (m <sup>2</sup> )	1.83±21	1.86±0.17	0.43



**Table 2.** Metabolic and haemodynamic variables at rest

	<40 years (N=43)	≥ 55 years (N=28)	P value
<b>Metabolics</b>			
Oxygen consumption (L/min)	0.24±0.07	0.23±0.05	0.33
Oxygen consumption (mL/kg/min)	3.74±1.27	2.89±0.57	<0.01
Respiratory exchange ratio	0.87±0.06	0.86±0.06	0.53
Arteriovenous oxygen difference (mL <sub>O<sub>2</sub></sub> / 100mL of blood)	6.64±2.48	7.02±2.02	0.49
<b>Haemodynamics</b>			
Heart rate (beats/min)	60.9±11.1	60.8±8.11	0.95
Stroke volume (mL/beat)	102±19.2	71.7±15.1	<0.01
Stroke volume index (mL/beat/m <sup>2</sup> )	56.0±9.16	38.8±9.30	<0.01
Cardiac output (L/min)	6.10±1.36	4.33±1.13	<0.01
Cardiac index (L/min/m <sup>2</sup> )	3.41±0.78	2.36±0.65	<0.01
Cardiac power output (W)	1.05±0.27	0.82±0.27	<0.01
Cardiac power output index (W/m <sup>2</sup> )	0.58±0.13	0.45±0.14	<0.01
Systolic blood pressure (mmHg)	107±11.2	117±13.1	<0.01
Diastolic blood pressure (mmHg)	65.4±8.33	71.8±8.77	<0.01
Mean arterial pressure (mmHg)	79.7±8.5	86.4±9.00	<0.01

**Table 3.** Metabolic and haemodynamic variables at peak exercise

	<40 years (N=43)	≥ 55 years (N=28)	P value
<b>Metabolics</b>			
Oxygen consumption (L/min)	2.38±0.76	1.58±0.57	<0.01
Oxygen consumption (mL/kg/min)	35.05±9.11	18.8±5.24	<0.01
Respiratory exchange ratio	1.12±0.09	1.10±0.06	0.39
Arteriovenous oxygen difference (mL <sub>O<sub>2</sub></sub> / 100mL of blood)	15.8±4.34	9.01±3.01	<0.01
Work rate (watts)	200±64.0	116±44.6	<0.01
<b>Haemodynamics</b>			
Heart rate (beats/min)	162±19.9	129±18.3	<0.01
Stroke volume (mL/beat)	142±34.9	173±41.5	<0.01
Stroke volume index (mL/beat/m <sup>2</sup> )	78.3±19.5	92.1±18.1	<0.01
Cardiac output (L/min)	22.7±4.96	22.09±3.87	0.59
Cardiac index (L/min/m <sup>2</sup> )	12.4±2.91	11.8±1.88	0.29
Cardiac power output (W)	5.31±1.46	6.06±1.52	0.06
Cardiac power output index (W/m <sup>2</sup> )	2.92±0.82	3.22±0.74	0.15
Systolic blood pressure (mmHg)	165±44.8	181±41.3	0.19
Diastolic blood pressure (mmHg)	77.1±13.2	95.0±15.0	<0.01
Mean arterial pressure (mmHg)	106±1.45	124±20.2	<0.01