



# Cardiovascular and peripheral factors affecting the decay of maximal oxygen uptake across the spectrum of age in humans

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## Abstract

**Purpose** Maximal oxygen uptake ( $\dot{V}O_{2\max}$ ) decays with aging due to decreased maximal cardiac output ( $\dot{Q}_{\max}$ ) and the development of progressive sarcopenia and mitochondrial dysfunctions. The study aimed to develop a quantitative analysis of central and peripheral factors in eliciting the observed progressive drop of  $\dot{V}O_{2\max}$  across the spectrum of ages ranging from about 30 yy to 85–90 yy.

**Methods** We applied to  $\dot{V}O_{2\max}$ ,  $\dot{Q}_{\max}$ , and maximal oxygen cardiovascular delivery ( $\dot{Q}_a O_{2\max}$ ) values obtained from literature, a multifactorial model of  $\dot{V}O_{2\max}$  limitation describing the progressive drop of the  $PO_2$  along the pathway from ambient air to mitochondria composed of several steps in series, each of them considered as a resistance ( $R_i$ ) that must be overcome by a pressure gradient ( $\Delta P_i$ ). The proposed analysis allowed us to estimate: (i) the maximal oxygen extraction coefficient ( $O_{2\text{ext}, \max}$ ) and (ii) the changes of the peripheral resistance ( $R_p$ ) hindering  $O_2$  muscular utilization.

**Results**  $O_{2\text{ext}, \max}$  progressively decays from 0.80 at 20 yy to 0.60 at 75–80 yy;  $R_p$  almost doubles over the same interval of inspected ages.

**Conclusions** The analysis implemented using data published in the literature suggests that the progressive increase of  $R_p$  remarkably contributes to the observed gradual decay of  $\dot{V}O_{2\max}$  observed with aging, perhaps more than the progressive drop in the maximal cardiovascular transport of oxygen.

**Keywords** Aging · Maximal aerobic power · Maximal oxygen delivery · Peripheral gas exchanges

## Abbreviations

|                             |                                                                                                                     |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------|
| $C_a O_2$                   | Arterial concentration of $O_2$                                                                                     |
| $(Ca-C\bar{v})_{O_{2\max}}$ | Maximal artero-mixed venous difference in $O_2$ concentration                                                       |
| $F_Q$                       | Fractional limitation to $\dot{V}O_{2\max}$ imposed by cardiovascular $O_2$ flow                                    |
| $F_p$                       | Fractional limitation to $\dot{V}O_{2\max}$ imposed by the peripheral resistance to $O_2$ diffusion and utilization |
| $O_{2\text{ext}, \max}$     | Maximal oxygen extraction coefficient                                                                               |
| $\dot{Q}_{\max}$            | Maximal cardiac output                                                                                              |
| $\dot{Q}_a O_{2\max}$       | Maximal $O_2$ cardiovascular transport                                                                              |
| $R_p$                       | The peripheral resistance limiting $\dot{V}O_{2\max}$                                                               |
| $R_Q$                       | The cardiovascular resistance limiting $\dot{V}O_{2\max}$                                                           |
| $S_a O_2$                   | Arterial oxygen saturation                                                                                          |
| $\dot{V}O_{2\max}$          | Maximal oxygen uptake                                                                                               |

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## Introduction

$\dot{V}O_{2\max}$  decays with aging (Aspenes et al. 2011; Åstrand et al. 1973; Buskirk and Hodgson 1987; Marti and Howald 1990; McGuire et al., 2001, Robinson 1938; Robinson et al. 1975; Rogers et al. 1990; Talbot et al. 2000; Trappe et al. 1996), with athletes keeping a higher  $\dot{V}O_{2\max}$  along the entire life span (Dill et al. 1967; Grimsmo et al. 2010; Maharam et al. 1999; Robinson et al. 1976; Rogers et al., 1990; Trappe et al. 1996) in comparison with non-athletics controls. In elite Master Athletes the progressive drop in maximal cycling speeds over different long track distances (Capelli et al. 2016) and the one-hour unaccompanied cycling record (Capelli 2018) are well justified by the parallel estimated decay of  $\dot{V}O_{2\max}$ .

Classically, the progressive drop of  $\dot{V}O_{2\max}$  was attributed to the decrease of maximal cardiac output ( $\dot{Q}_{\max}$ ) (Fuchi et al. 1989; McGavock et al. 2009; McGuire et al. 2001) and to the development of sarcopenia (Fleg and Lakatta 1988; Proctor and Joyner 1997). Recently, the development of sarcopenia was associated with appearance of mitochondrial dysfunctions (Marcinek and Ferrucci 2025).

The decrease of  $\dot{Q}_{\max}$  appears to be the consequence of the concomitant reduction of maximal heart rate ( $HR_{\max}$ ) occurring across the spectrum of age, whereas the absolute values of maximal stroke volume ( $SV_{\max}$ ) appeared to be preserved (Maharam et al. 1999; McGuire et al. 2001; Rodeheffer et al. 1984; Stamford 1988). Sarcopenia carries along the decrease in muscle force and power in humans and single muscle fibers (Brooks and Faulkner 1994; Canepari et al. 2010; Janssen et al. 2000; Narici and Maffulli 2010).

Although mitochondrial capacity seems to be preserved in active individuals (Kent-Braunn et al., 2000, Russ and Kent-Braun, 2004), the overall oxidative capacity of skeletal muscles seems to decrease with age even after adjusting for the level of physical activity (Marcinek and Ferrucci 2025). Moreover, it has been shown that the rate of synthesis of skeletal muscle mitochondria decreases with age (Johnson et al. 2013) together with resting and maximal ATP production rate (Short et al. 2004), enzyme activity, and respiratory capacity (Bass et al. 1975; Short et al. 2004). These modifications may translate into a drop in mitochondrial oxidative capacity. Therefore, the decline of mitochondrial content and function seems to play a role in the decay of  $\dot{V}O_{2\max}$ .

Although the decay of cardiovascular fitness seems to be the primary cause of the decrease of  $\dot{V}O_{2\max}$  with aging, the contribution of the peripheral factors is far from being understood and quantified. The available data on oxygen extraction and utilization at maximal exercise remain controversial, although they suggest a decrease in the arterial-venous  $O_2$  difference ( $Ca-C\bar{v})_{O_{2\max}}$  and a lower maximal  $O_2$  extraction coefficient ( $O_{2\text{ext}, \max}$ ), (Hagberg et al. 1985;

Hossack and Bruce 1982; McGavock et al. 2009; McGuire et al. 2001; Rivera et al. 1989; Rodeheffer et al. 1984). Within the context of the two main multifactorial models of  $\dot{V}O_{2\max}$  limitation (di Prampero and Ferretti 1990; Wagner 1996), this tendency suggests that peripheral limitation of  $\dot{V}O_{2\max}$  may be greater in old than in young individuals (Ferretti 2014), although the cardiovascular limitation remains predominant.

Unfortunately, the few studies that systematically report  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  in large cohorts of volunteers of different ages (Carrick-Ranson et al. 2013; Farinatti et al. 2018; McGavock et al. 2009; McGuire et al. 2001; Murias et al. 2010; Ogawa et al. 1992; Pandey et al. 2020) do not report arterial  $O_2$  concentration ( $C_aO_2$ ) thus making it impossible to calculate  $O_2$  extraction.

The mishap of the lack of essential data necessary to calculate maximal cardiovascular delivery ( $\dot{Q}_aO_{2\max} = \dot{Q}_{\max} \times C_aO_2$ ) and oxygen extraction may be, however, tentatively circumvented by applying an analysis performed in the light of the multifactorial model of  $\dot{V}O_{2\max}$  limitation proposed by di Prampero and Ferretti (1990) and utilized to understand the role of cardiovascular and muscular adaptations on  $\dot{V}O_{2\max}$  caused by disuse (Bringard et al. 2010; Capelli et al. 2006; Ferretti and Strapazzon 2024; Ferretti et al. 1997); modifications of ventilation and oxygen fraction in inspired air (Esposito and Ferretti 1997) and training (Del Torto et al. 2021).

By estimating  $\dot{Q}_aO_{2\max}$  from  $\dot{Q}_{\max}$ , we propose a quantitative analysis of central and peripheral factors in eliciting the observed progressive drop of  $\dot{V}O_{2\max}$  across the spectrum of ages ranging from about 30 yy to 85–90 yy.

## Methods

### Data sets

The data of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  utilized in the present analysis were derived from the following papers: Adami et al. 2011; Bruseghini et al. 2015; Carrick-Ranson et al. 2013; Farinatti et al. 2018; McGuire et al. 2001; Mitchell et al. 2019; Murias et al. 2010; Ogawa et al. 1992; Pandey et al. 2020. It is noteworthy that the first two papers in this list report data that were collected in the same laboratory utilizing the same techniques and protocols on two different occasions. The data were extracted in the very few papers that reported in parallel values of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  assessed in moderately active healthy men (Table 1). The volunteers investigated in the studies considered in the analysis were non obese, non-smokers men and they were not taking medications. In most of the cases they included moderately active or active men who performed regular aerobic activity (<90 min per week)

**Table 1** Data of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  obtained from the quoted references and used in the analysis of the factors affecting the decay of  $\dot{V}O_{2\max}$  across the spectrum of age

| Source                                        | Age (yy) | $\dot{V}O_{2\max}$ (L min <sup>-1</sup> ) | $\dot{Q}_{\max}$ (L min <sup>-1</sup> ) |
|-----------------------------------------------|----------|-------------------------------------------|-----------------------------------------|
| Adami et al. 2011 and Bruseghini et al. 2015  | <30      | 4.1±0.4                                   | 22.9±5.1                                |
| (Active, moderately active)                   | 69       | 2.4±0.3                                   | 15.8±3.2                                |
| Carrick – Ranson et al. 2013                  | <30      | 2.6±0.5                                   | 18.4±4.0                                |
| (Moderately active)                           | 36±1     | 2.60±0.5                                  | 16.4±2.4                                |
|                                               | 44±3     | 2.4±0.4                                   | 17.5±4.6                                |
|                                               | 53±2     | 2.4±0.4                                   | 16.2±1.7                                |
|                                               | 64±2     | 2.5±0.2                                   | 16.5±2.5                                |
|                                               | 78       | 1.48                                      | 13.1                                    |
|                                               | 84±3     | 1.6±0.5                                   | 14.1±1.8                                |
| Farinatti et al. 2018                         | <30      | 3.5±0.8                                   | 22.1                                    |
| (Moderately active)                           | 69       | 2.0±0.3                                   | 12.5                                    |
| Mcguire et al., 2001 and Mitchel et al., 2019 | 20       | 3.3±1.1                                   | 20. ± 4.1                               |
| (Moderately active)                           | 50       | 2.9±0.7                                   | 21.4±5.1                                |
|                                               | 61       | 2.4                                       | 18.9                                    |
| Murias et al. 2010                            | <30      | 3.8±0.5                                   | 25.9±2.8                                |
| (Moderately active)                           | 68       | 2.3±0.5                                   | 16.8±3.0                                |
| Ogawa et al. 1992 (UT)                        | <30      | 3.4±0.4                                   | 21.2±2.4                                |
| (Healthy sedentaries)                         | 63±3     | 2.2±0.3                                   | 16.3±2.5                                |
| Ogawa et al. 1992 (T)                         | <30      | 4.3±0.5                                   | 27.4±3.2                                |
| (Active)                                      | 63±4     | 3.1±0.4                                   | 20.5±2.1                                |
| Pandey et al. 2020                            | <30      | 2.3±0.5                                   | 17.3±4.0                                |
| (Moderately active)                           | 35±3     | 2.2±0.4                                   | 17.4±2.9                                |
|                                               | 44±3     | 2.1±0.5                                   | 16.5±2.5                                |
|                                               | 54±3     | 1.8±0.6                                   | 14.4±2.0                                |
|                                               | 65±3     | 1.4±0.3                                   | 11.0±2.2                                |
|                                               | 73±3     | 1.6±0.1                                   | 10.8±2.2                                |

The data without the indication of SD were not reported in the original paper with the statistics

with the exceptions of one study (Ogawa et al. 1992), which included trained volunteers.

The diagrams of Fig. 2 in Carrick-Ranson et al. (2013) (men,  $n=48$ ) and Fig. 3 in Pandey et al. (2020) ( $n=104$ , namely 73 males and 31 females) show the decay of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  as a function of age. The diagrams, captured separately with screen snapshots, were saved at high resolution (256 ppi) in pdf format. Afterward, we imported the digitized diagrams into a specific software (Digitizelt version 2.5.10 for Mac OS X, Borman I, Braunschweig, D). This approach allows fixation of the maximum and the minimum of the abscissa and the ordinate by selecting, with a click of the mouse, the corresponding extremes of the two axes displayed on the computer screen. Then, when the operator clicks on each single point, Digitizelt automatically recognizes the x-y coordinates and converts them into the appropriate units. The arrays of data were finally exported to spreadsheets in Excel (Microsoft, Seattle, W, USA) for subsequent analysis. The  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  data obtained

by digitizing the points of the diagrams were then divided by decades, and the corresponding mean values were calculated and utilized for the subsequent numerical analysis. As for the data obtained from the remaining sources, we utilized the values reported by the authors in the tables or text. We then inserted these data in the corresponding decade. Table 1 summarizes the  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  values used as inputs to the data analysis explained in the following lines of the manuscript.

## Data analysis

The analysis is carried out in the context of di Prampero's multifactorial model of  $\dot{V}O_{2\max}$  limitation (di Prampero 1985; di Prampero and Ferretti 1990) and in the following lines we will outline only the essential details needed to understand the reasoning behind our analysis. The model assumes that in normoxia, as is the case for the present study, the resistances to  $O_2$  flow upstream of the heart do not limit  $\dot{V}O_{2\max}$  (for a discussion of this aspect, see Ferretti and di Prampero 1995). Thus, considering only the cardiovascular and peripheral resistances to  $O_2$  flow, if a physiological perturbation yields a given change in the two resistances at stake, the consequent  $\dot{V}O_{2\max}$  change ( $\dot{V}O_{2\max} + \Delta \dot{V}O_{2\max}$ ) with respect to the initial  $\dot{V}O_{2\max}$  value is equal to:

$$\frac{\dot{V}O_{2\max}}{\dot{V}O_{2\max} + \Delta \dot{V}O_{2\max}} = 1 + F_Q \times \frac{\Delta R_Q}{R_Q} + F_P \times \frac{\Delta R_P}{R_P} \quad (1)$$

where:

- 1)  $\dot{V}O_{2\max}$  is the value before the perturbation;
- 2)  $\Delta \dot{V}O_{2\max}$  is the observed change in  $\dot{V}O_{2\max}$  following the perturbation (value after minus value before, so that  $\Delta \dot{V}O_{2\max}$  is negative if  $\dot{V}O_{2\max}$  decreases, positive if it increases);
- 3)  $F_Q$  is the fractional limitation to  $\dot{V}O_{2\max}$  imposed by cardiovascular  $O_2$  flow;
- 4)  $R_Q$  is the cardiovascular resistance before the perturbation, inversely proportional to  $\dot{Q}_a O_{2\max}$ ;
- 5)  $\Delta R_Q$  is the change in  $R_Q$  induced by the perturbation: if  $R_Q$  goes up,  $\Delta R_Q$  is positive; if  $R_Q$  goes down,  $\Delta R_Q$  is negative.
- 6)  $F_P$  is the fractional limitation to  $\dot{V}O_{2\max}$  imposed by the lumped peripheral resistances hindering  $O_2$  diffusion and muscular utilization;
- 7)  $R_P$  is the peripheral resistance before the intervention;
- 8)  $\Delta R_P$  represents the change of the lumped peripheral resistance.

The perturbation that we deal with in this study is ageing. By reducing  $\dot{Q}_{\max}$ , ageing increases  $R_Q$ ; by reducing muscle mass, it increases  $R_p$ . Therefore, the  $\dot{V}O_{2\max}$  ratio on the left hand of Eq. 1 becomes higher, and thus the  $\dot{V}O_{2\max}$  progressively decreases.

$\dot{V}O_{2\max}$  and  $\Delta \dot{V}O_{2\max}$  are measured variables in the reported studies;  $R_Q$  before and after is set as inversely proportional to  $\dot{Q}_{\max}$ , and thus to  $\dot{Q}_a O_{2\max}$ ;  $F_Q$  was demonstrated to be equal to the oxygen extraction coefficient (Ferretti 2014), so it was calculated as the ratio of  $\dot{V}O_{2\max}$  to  $\dot{Q}_a O_{2\max}$ ;  $F_p$  was then obtained as  $1 - F_Q$ ;  $\Delta R_p/R_p$  resulted as a consequence.

Suppose we apply Eq. 1 to the analysis of the progressive drop of  $\dot{V}O_{2\max}$  across the age spectrum, comparing the values of the older adults classified in different decades to the ones of the youngest subjects. In that case, we can write a modified version of Eq. 1 as:

$$\frac{\dot{V}O_{2\max,y}}{\dot{V}O_{2\max,y} + \Delta \dot{V}O_{2\max}} = 1 + F_Q \frac{\Delta R_Q}{R_{Q,y}} + F_p \times \frac{\Delta R_p}{R_{p,y}} \quad (2)$$

Equation 2 represents a particular case of Eq. 1 for the effects of aging on  $\dot{V}O_{2\max}$ , in which the suffix y indicates the youngsters.

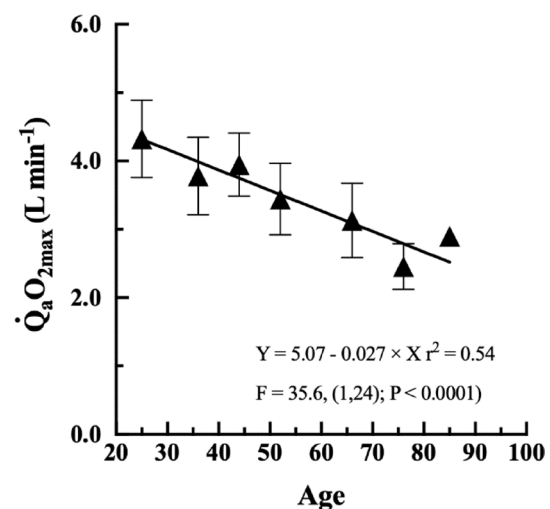
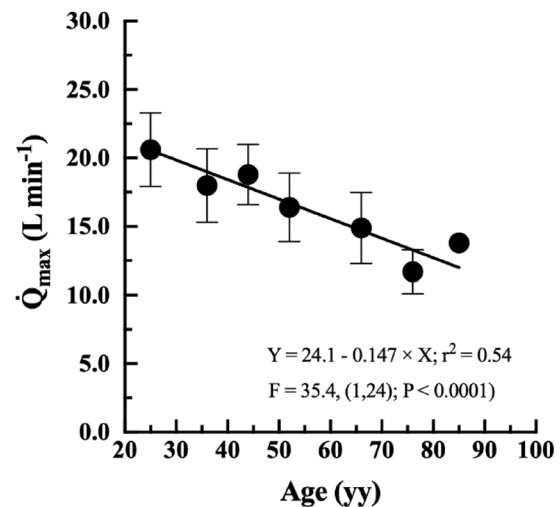
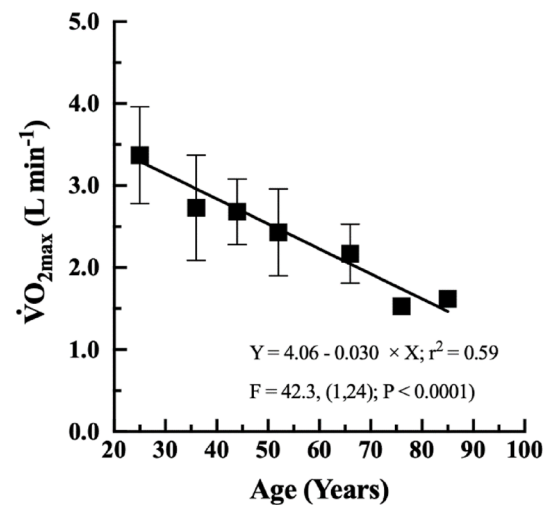
Strengths and weaknesses of this model, as well as the one of the concurrent model (Wagner 1996), have been discussed previously (Ferretti 2014) together with a synthesis of the two models.

## Results

Table 1 reports the values of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$ , plus/minus SD when it was possible, utilized in the analysis.

Figure 1 shows the  $\dot{V}O_{2\max}$ ,  $\dot{Q}_{\max}$  and  $\dot{Q}_a O_{2\max}$  average values calculated for each decade across the spectrum of the ages. Variables significantly and linearly decreased with aging: The values plotted in the graphs are also reported in Table 2 for the sake of the reader.

In Fig. 2, the average values of  $\dot{V}O_{2\max}$  calculated in each decade are plotted as a function of the corresponding  $\dot{Q}_a O_{2\max}$ . The ratio  $\dot{V}O_{2\max}$  to  $\dot{Q}_a O_{2\max} = 1 - C_v O_2 / C_a O_2$  corresponds to  $O_{2\text{ext}, \max}$ , i.e. the maximal extraction coefficient and the straight lines in Fig. 2 represent identical values (isopleths) of  $O_{2\text{ext}, \max}$ . Therefore, the drop in  $\dot{V}O_{2\max}$  and in  $\dot{Q}_a O_{2\max}$  across the age spectrum seems to be paralleled by a progressive decay of  $O_{2\text{ext}, \max}$ , as the values of the older groups cross isopleths corresponding to lower values of  $O_{2\text{ext}, \max}$ . This indicates that a progressive decay of the capacity to extract and utilize oxygen at the periphery may have occurred.



**Fig. 1** Average values plus-minus SD of  $\dot{V}O_{2\max}$  (upper panel),  $\dot{Q}_{\max}$  (intermediate panel), and  $\dot{Q}_{aO_{2\max}}$  (lower panel) calculated for each decade across the spectrum of the considered ages. Age values refer to the median of each decade

In Fig. 3, the values of  $F_Q$  and  $F_p$  across the age spectrum are shown.  $F_Q$  decreased from  $0.77 \pm 0.06$  at <30 yy to 0.56 at 85 yy of age and showed a significant decreasing trend with age ( $y = 0.8158 - 0.0022 \times x$ ;  $r^2 = 0.30$ ;  $F = 13.1$  (1, 31);  $P < 0.001$ ). Obviously,  $F_p$  symmetrically increased from  $0.23 \pm 0.06$  to 0.44 ( $y = 0.1823 + 0.002 \times x$ ;  $r^2 = 0.30$ ;  $F = 12.7$  (1, 31);  $P < 0.001$ ).

In Fig. 4, the calculated values of the ratio  $\Delta R_p/R_p$  are reported as a function of the median value of each decade starting from the 30–40 years decade. The diagram suggests that the weight of the peripheral resistance limiting  $O_2$  utilization and diffusion at maximal exercise intensity increases linearly with age. This trend becomes evident at the beginning of the fourth decade and seems to plateau at ages older than 65.

## Discussion

In this paper, we analysed values of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  collected in various investigations performed in healthy volunteers or patients of different ages. On this basis, we propose a quantitative analysis of the central and peripheral factors that may elicit the progressive drop of  $\dot{V}O_{2\max}$  with age, observed across a spectrum of ages ranging from 30 yy to 85–90 yy. To accomplish this task, we utilized a multifactorial model of  $\dot{V}O_{2\max}$  limitation (di Prampero and Ferretti 1990). This model assumes that the oxygen cascade, i.e., the progressive drop of the  $PO_2$  along the pathway from ambient air to mitochondria, consists of several resistances in series ( $R_i$ ) that are overcome by a pressure gradient ( $\Delta P_i$ ). Each resistance provides a fraction of the total resistance to the oxygen flow from ambient air to mitochondria during maximal exercise and thus corresponds to a specific fraction of the overall limitation of  $\dot{V}O_{2\max}$ . In normoxia, due to non-linearities related to the characteristics of the oxygen equilibrium curve (Ferretti 2014),  $\dot{V}O_{2\max}$  limitation is partitioned between two resistances: cardiovascular ( $F_Q$ ) and peripheral ( $F_p$ ). In young individuals,  $F_Q \approx 0.7$  and  $F_p \approx 0.3$ . The analysis suggests that, from 30 to about 70 years,  $F_Q$  decreases, and  $F_p$  increases with age (see Fig. 3). These changes seem to be linear. The trend becomes evident from the third decade and appears to plateau at ages older than 65. The following paragraphs are devoted to discussing the strengths and weaknesses of the applied approach and the crucial premises on which the implementation of the model is based.

The data extracted from the sources quoted in the Methods showed an average decay of  $\dot{V}O_{2\max}$  of about 37 mL  $\text{min}^{-1}$  per year (Fig. 1). This absolute rate of decay is in agreement with the 10% decay per decade of the maximal aerobic power in healthy active individuals (Hawkins and Wiswell, 2003).

Also  $\dot{Q}_{\max}$  showed a linear decrease of about 151 mL  $\text{min}^{-1}$  per year. Should  $F_Q$  and  $F_p$  not change with age,  $R_Q$  and  $R_p$  would show a consensual and equal increase: in this case, the percent decrease of  $\dot{V}O_{2\max}$  at age 70, with respect to age 20, should be equivalent to the decline of  $R_Q$ , and thus of  $\dot{Q}_{\max}$ . This is not the case. Considering a starting point at 20–30 years, the reduction in  $\dot{V}O_{2\max}$  appears to be greater than that in  $\dot{Q}_{\max}$ . This indicates that a decrease in  $\dot{Q}_{\max}$  alone does not explain the observed decay of  $\dot{V}O_{2\max}$ . Indeed, the latter is more than expected from this assumption (46% instead of 31%). This finding suggests that: (i)  $R_p$  may increase to a greater extent than  $R_Q$ ; (ii)  $F_p$  should be greater at age 70 than at age 20 by an amount equal to the corresponding fall of  $F_Q$ . To sum up, the impairment of peripheral gas exchanges seems to substantially contribute to the decrease in  $\dot{V}O_{2\max}$  with age in parallel with cardiovascular deconditioning.

A study reported  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  in 5 volunteers tested in 1966, 1996, and 2006 (Mitchell et al. 2019). In that study,  $\dot{Q}_{\max}$  seemed to remain preserved for at least 30 years (1966–20 yy: 20.0 L  $\text{min}^{-1}$ ; 1996–50 yy: 21.4 L  $\text{min}^{-1}$ ), to decrease only in the following ten years (2006–60 yy: 18.9 L  $\text{min}^{-1}$ ). Conversely,  $\dot{V}O_{2\max}$  was lower at 50 yy (2.9 L  $\text{min}^{-1}$ ) than at 20 yy (3.3 L  $\text{min}^{-1}$ ), to decrease further in the following decade (2006–60 yy: 2.4 L  $\text{min}^{-1}$ ). These data obtained on the same volunteers are coherent with the conclusions written here above, although the preservation of  $\dot{Q}_{\max}$  resulted from an increase in maximal stroke volume ( $SV_{\max}$ ), suggesting a possible overestimate of  $\dot{Q}_{\max}$  at 50 years.

In this study, we set  $R_Q$  proportional to  $\dot{Q}_{\max}$ , as in Ferretti and di Prampero (1990), because in most of the literature concerning the evolution of  $\dot{V}O_{2\max}$  and  $\dot{Q}_{\max}$  with age, no measurements of blood haemoglobin concentration ([Hb]) are reported. Therefore, we assumed that [Hb] does not change with age, in agreement with some evidence in the literature (Raisinghani et al. 2019). We also assumed  $C_{aO_2} = 210 \text{ ml L}^{-1}$ , which applies to an [Hb] of 155 g  $\text{L}^{-1}$  and an arterial oxygen saturation ( $S_{aO_2}$ ) at maximal exercise of 0.98. These assumptions allowed an estimate of arterial oxygen flow at maximal exercise ( $\dot{Q}_{aO_{2\max}}$ ). The relationship between  $\dot{V}O_{2\max}$  and  $\dot{Q}_{aO_{2\max}}$  shown in Fig. 2, is linear. In the same Figure, isopleths of maximal oxygen extraction coefficient ( $O_{2\text{ext}, \max}$ ) are also indicated.

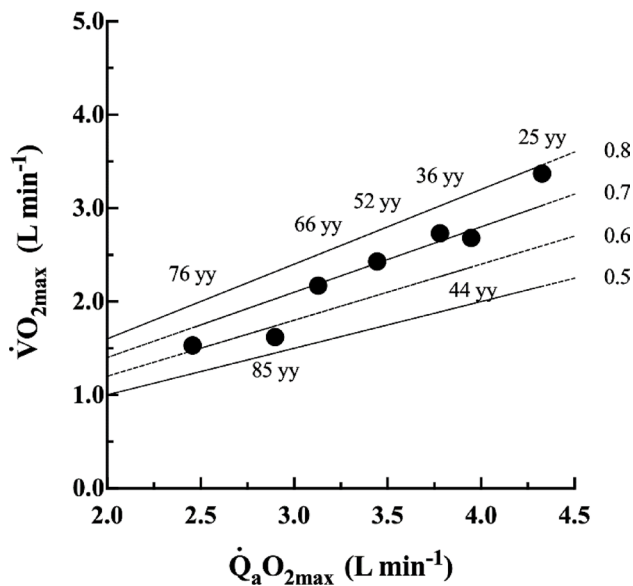
The assumptions of constant [Hb] and arterial saturation across the lifespan are crucial and deserve to be discussed.



**Table 2** Mean values  $\pm$  SD of  $\dot{V}O_{2\max}$ ,  $\dot{Q}_{\max}$  and  $\dot{Q}_aO_{2\max}$  across the spectrum of age

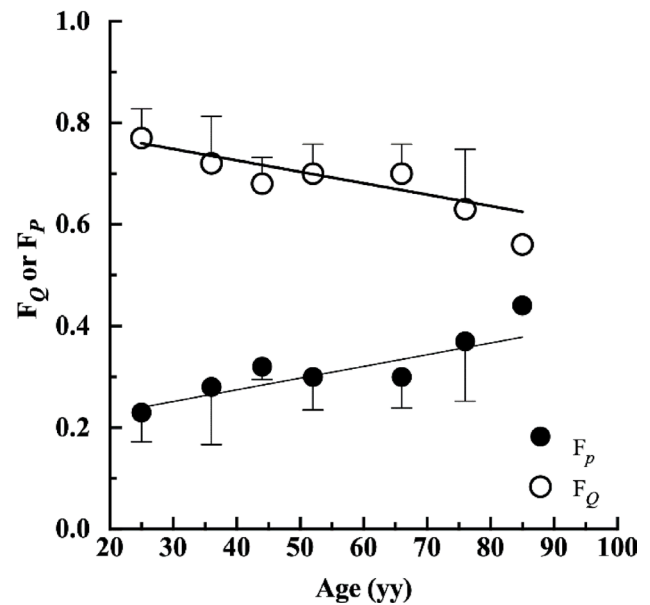
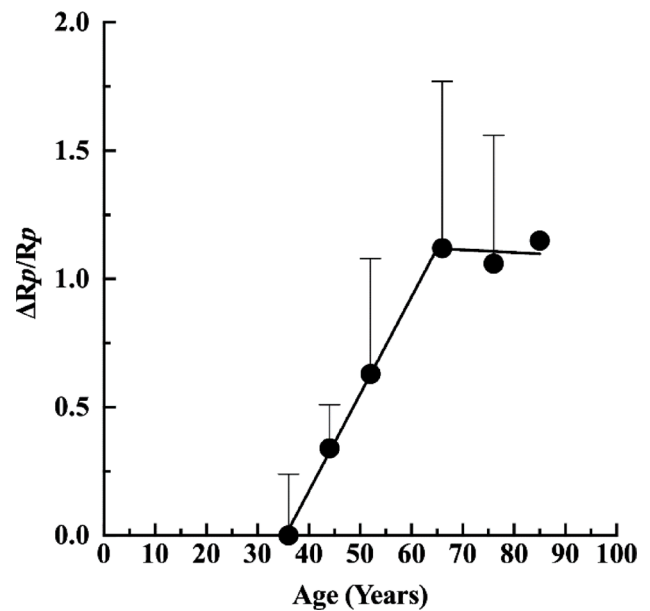
| Age (yy)   | $\dot{V}O_{2\max}$ (L min <sup>-1</sup> ) | $\dot{Q}_{\max}$ (L min <sup>-1</sup> ) | $\dot{Q}_aO_{2\max}$ (L min <sup>-1</sup> ) |
|------------|-------------------------------------------|-----------------------------------------|---------------------------------------------|
| <30        | 3.37 $\pm$ 0.59                           | 20.6 $\pm$ 2.7                          | 4.3 $\pm$ 0.6                               |
| 36 $\pm$ 1 | 2.73 $\pm$ 0.64                           | 18.0 $\pm$ 2.7                          | 3.8 $\pm$ 0.6                               |
| 44 $\pm$ 0 | 2.68 $\pm$ 0.40                           | 18.8 $\pm$ 2.2                          | 3.9 $\pm$ 0.5                               |
| 52 $\pm$ 2 | 2.43 $\pm$ 0.53                           | 16.4 $\pm$ 2.5                          | 3.4 $\pm$ 0.5                               |
| 66 $\pm$ 3 | 2.17 $\pm$ 0.36                           | 14.9 $\pm$ 2.6                          | 3.1 $\pm$ 0.5                               |
| 76 $\pm$ 3 | 1.53 $\pm$ 0.07                           | 11.7 $\pm$ 1.6                          | 2.5 $\pm$ 0.3                               |
| 85*        | 1.62                                      | 13.8                                    | 2.9                                         |

\* For the oldest decade, it was possible to report only one value

**Fig. 2** Average values of  $\dot{V}O_{2\max}$  plotted as a function of the corresponding  $\dot{Q}_aO_{2\max}$  reported in Figure. together with straight isopleths representing a constant value of the maximal  $O_2$  extraction coefficient

The progressive widening of the alveolar-to-arterial gradient of partial pressure of  $O_2$  ( $P_{A}O_2 - P_{a}O_2$ ) with ageing, and hence of  $S_aO_2$ , has been described and it is usually ascribed to the increased inhomogeneity of the ventilation-to-perfusion ratio occurring with age (Sharma and Goodwin 2006). By applying the regression proposed by Marshall and Whyche (1972), we can estimate the  $P_aO_2$  prevailing at each decade. It ranged from 95 to 77 mm Hg from 25 to 85 years of age. In turn, these values, thanks to the particular shape of the dissociation curve of oxyhemoglobin, correspond to  $S_aO_2$  ranging from 97% to 95% (Kelman 1966) and they imply a trivial decay of  $C_aO_2$  from 210 ml L<sup>-1</sup> to of 206 ml L<sup>-1</sup> blood.

Concerning [Hb], a recent paper confirmed that it starts significantly decaying to about 14–14.5 g Hb 100 mL<sup>-1</sup> of blood after 75–80 years of age, but remaining within boundaries of normality until that age (Fig. 2 in Bertolotti et al.

**Fig. 3** Average values plus-minus SD of  $F_Q$  and  $F_p$  across the age spectrum. Age values refer to the median of each decade**Fig. 4** Average values plus-minus SD of the calculated values of the ratio  $\Delta R_p/R_p$  as a function of the median value of each decade

2025). These figures translate, in the case of worst scenario of the single oldest subject considered in the analysis, to a  $C_aO_2$  of 186 ml L<sup>-1</sup>.

On the basis of the reported calculations we dare say that the assumption of invariant values of [Hb] and  $S_aO_2$  did not inject in the calculations of the model any substantial inaccuracy and bias.

Figure 2, as reported above, shows a progressive decrease of  $O_{2\text{ext},\max}$  with age. Ferretti (2014) demonstrated that  $O_{2\text{ext},\max}$  is equivalent to  $F_Q$ . Therefore, the reduction of

$\dot{V}O_{2\text{ext}, \text{max}}$  indicates a decrease of  $F_{\text{O}_2}$ , and thus an increase of  $R_p$  with age. This can mean only one thing: a deterioration of peripheral oxygen diffusion and utilization with ageing. This follows the development of muscle atrophy, the loss of muscle mitochondria, and the reduced muscle capillarity in aged individuals (Fleg and Lakatta 1988; Groen et al. 2014; Johnson et al. 2013; Wiedmer et al. 2021), all leading to a progressively greater  $R_p$ . It's worth noting that  $R_p$  represents a lumped factor that considers and depends on all the mechanisms dictating peripheral  $\text{O}_2$  diffusion and utilization. As such, it cannot disentangle the single contributions of the single steps affecting the efficiency of the peripheral gas exchanges. (di Prampero and Ferretti 1990).

Several adaptations that occur with aging may converge in eliciting the observed increase of the peripheral resistance that decreases maximal oxygen uptake with aging including impaired vasodilation in active muscles (Poole et al. 2003), muscle mass loss (Wiedmer et al., 2021), an extensive cause contributing to the drop in  $\dot{V}O_{2\text{max}}$ , the declines of mitochondrial content and function, together with resting and maximal ATP production rate, (Short et al. 2004), of enzyme activity, and of respiratory capacity (Bass et al. 1975; Short et al. 2004). The decline of mitochondrial oxidative phosphorylation capacity seems to be an intrinsic, unavoidable consequence of aging and it may be considered and additional intensive factor negatively affecting peripheral gas exchanges independently from any loss of muscle mass contributing to the observed increase of  $R_p$ .

In this study we applied a mathematical model that relies on several crucial assumptions. In addition, the database used for the analysis included only the values of  $\dot{V}O_{2\text{max}}$  and  $\dot{Q}_{\text{max}}$ ; therefore, it was not possible to incorporate any further information into the model. On the other hand, the proposed approach tried to shed light on the still-open issue concerning the role of central and peripheral factors in affecting the decay of maximal aerobic power with age. Per se, the proposed analysis would be a call for future investigation that would include, in parallel, the assessment of cardiovascular functions and peripheral  $\text{O}_2$  utilization in healthy volunteers of different age classes.

The future analysis, in addition, would pave the way for studies investigating whether adaptation to training may differ in young and older volunteers and whether the effect of ageing may impact differently the main factors limiting  $\dot{V}O_{2\text{max}}$  in the two sexes. Regarding the adaptation to training, recent data seem to suggest that the amelioration of  $\dot{V}O_{2\text{max}}$  in young and elderly volunteers was positively correlated with improved maximal cardiac performance and peripheral morphological and biochemical adaptations whose entity does not seem to be affected by age (Faricier et al., 2025).

## Conclusions

In conclusion, the analysis proposed in this paper and implemented using data published in the literature suggests that the progressive increase of  $R_p$  contributes to the observed gradual decay of  $\dot{V}O_{2\text{max}}$  occurring with aging in parallel with the decay of the maximal cardiovascular transport of oxygen.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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