Short comunication

The effects of microgravity exposure on maximal oxygen consumption in humans

Efectos de la exposición a la microgravedad en el consumo máximo de oxígeno de los humanos

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ABSTRACT

After a short summary of the multifactorial models of maximal O_2 consumption (VO_{2max}) limitation, microgravity exposure is discussed as a convenient experimental condition to test these models. The following points are highlighted: 1) The decrease of (VO_{2max}) in microgravity concerns specifically exercise performed in upright posture upon resumption of gravity exposure; 2) The decrease of (VO_{2max}) after microgravity exposure has two components: one is fast and is related to cardiovascular adaptation, the other is slow and is related to the development of muscle atrophy; 3) (VO_{2max}) does not decrease during microgravity or in supine posture upon resumption of gravity exposure, if the time in microgravity is sufficiently short; 4) cardiovascular oxygen transport accounts for 70% of (VO_{2max}) limitation also after microgravity exposure.

Keywords: microgravity; exercise; cardiovascular oxygen transport; muscle atrophy; models.

RESUMEN

Luego de un breve resumen de los modelos multifactoriales de la limitación del consumo máximo de oxígeno (VO_{2max}), se analiza la exposición a la microgravedad como condición experimental conveniente para evaluar tales modelos. Se destacan los siguientes aspectos: 1) El decrecimiento en la microgravedad tiene que ver

específicamente con los ejercicios realizados en posición vertical después de reanudar la exposición a la gravedad; 2) El decrecimiento posterior a la exposición a la microgravedad tiene dos componentes: uno es rápido y está relacionado con la adaptación cardiovascular, el otro es lento y está relacionado con la aparición de la atrofia muscular; 3) No decrece durante la microgravedad o en posición supina después de reanudarse la exposición a la gravedad, siempre que el tiempo transcurrido en microgravedad sea suficientemente corto; 4) el transporte de oxígeno cardiovascular representa el 70 % de la limitación también después de la exposición a la microgravedad.

Palabras clave: microgravedad; ejercicios; transporte de oxígeno cardiovascular; atrofia muscular; modelos.

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THE MULTIFACTORIAL MODELS OF VO_{2max} LIMITATION

The concept of maximal O_2 consumption (VO_{2max}) was created, when it became clear that the relationship between O_2 uptake and mechanical power attains a plateau that cannot be overcome despite further power increases, thus implying limitation of VO_{2max}. The discussion on VO_{2max} limitation focused on the identification of a single limiting step for long. Suddenly, the approach changed after *Taylor* and *Weibel* resumed the O_2 cascade theory to describe O_2 transfer from ambient air to mitochondria in mammals. Although they wished to analyse the structural constraints of respiratory systems under maximal stress in animals encompassing a wide range of body size, the seed leading to a new vision of VO_{2max} limitation was implanted. The multifactorial models of VO_{2max} limitation appeared soon afterward.[1,2,3,4,5,6,7,8,9,10] di Prampero's model is a hydraulic model of in-series resistances, relying on the principle that:[2]

$$\dot{V} = \frac{\Delta P_1}{R_1} = \frac{\Delta P_2}{R_2} = \cdots = \frac{\Delta P_n}{R_n} = \frac{\Delta P_T}{R_T} \quad (1)$$

Where $\dot{V}$ is gas flow (at maximal exercise, $V\mathrm{O}_{2max}$), ΔP is the pressure gradient sustaining $\dot{V}$ across the ith resistance R and ΔP_T is the overall pressure gradient, i.e. the difference between inspired and mitochondrial O_2 partial pressure $(P_I\mathrm{O}_2 - P_m\mathrm{O}_2)$. Since $P_m\mathrm{O}_2$ tends to 0, ΔP_T was set equal to $P_I\mathrm{O}_2$. ΔP_T is the sum of the pressure gradients across each resistance:

$$\Delta P_T = \Delta P_1 + \Delta P_2 + \cdots + \Delta P_n \quad (2)$$

In this case, the fraction of the overall limitation imposed by the ith resistance to $\dot{V}$ is given by:

$$F_i = \frac{R_i}{R_T} \quad (3)$$

If we analyse a condition wherein only one resistance is varied by an acute manipulation, as occurs for the cardiovascular resistance to oxygen flow (R_Q) after acute blood reinfusion or withdrawal, we obtain a simplified model, described by:

$$\frac{\dot{V}\mathrm{O}_{2max}}{(\dot{V}\mathrm{O}_{2max}+\Delta\dot{V}\mathrm{O}_{2max})} = 1 + F_Q\frac{\Delta R_Q}{R_Q} \quad (4)$$

Where F_Q is the fractional limitation to $V\mathrm{O}_{2max}$ due to R_Q. Equation (4) tells that there is a linear relationship between the ratio of the $V\mathrm{O}_{2max}$ before to the $V\mathrm{O}_{2max}$ after the manoeuvre (left-hand branch of Equation 4) and the ratio between ΔR_Q and R_Q with y-intercept equal to 1 and slope equal to F_Q (Fig.1). A linear solution of the overall oxygen conduction equation would provide $F_Q = 0.5$ whereas the data showed $F_Q = 0.7$. This means that i) R_Q provides 70% of the fractional limitation of $V\mathrm{O}_{2max}$ instead of 50 %, and ii) the system has a non-linear behaviour.[2] The source of non-linearity was identified in the effects of a non-linear O_2 equilibrium curve and this led to exclude that ventilation and lung diffusion limit $V\mathrm{O}_{2max}$ in normoxia.[3]

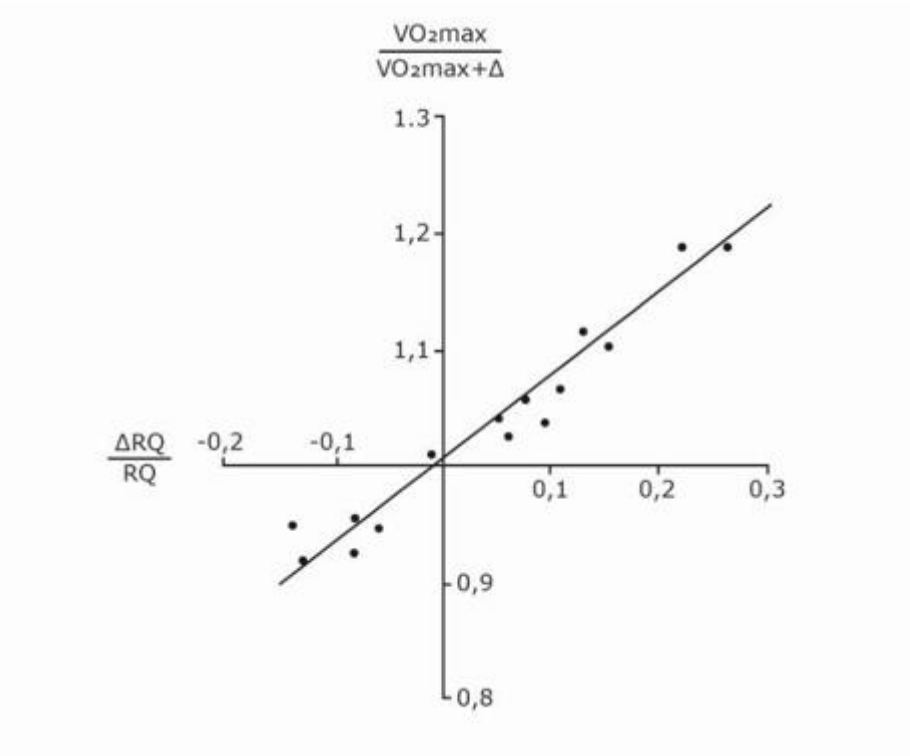

Fig. 1. Graphical representation of di Prampero's model. The changes in *V*O2max that follow an acute manoeuvre acting on the cardiovascular resistance to oxygen flow (R_Q) are expressed as the ratio of the *V*O2max before to the *V*O2max after the manoeuvre at stake $(\dot{V}O_{2max} + \Delta)$. This ratio is plotted as a function of the ratio between the induced change in R_Q (ΔR_Q) and the R_Q before the manoeuvre. Points are mean values from different sources in the literature. The continuous straight line is the corresponding regression Equation (y = 1.006 + 0.7 x, r = 0.97, n = 15). The slope of the line indicates that 70% of the overall limitation to *V*O2max is imposed by cardiovas*cular oxygen transport. Modified after di Prampero and* Ferretti (1990).

Wagner,[10] by combining the mass conservation equation for blood (Fick principle) and the diffusion-perfusion interaction equations of Piiper and Scheid constructed a three-equation system with three unknowns: alveolar (P_AO_2) arterial (P_aO_2) and mixed venous $(P_{\bar{v}}O_2)$ O_2 partial pressure.[3] At steady state, these equations must provide equal *V*O2max values. On this basis, he obtained an algebraic solution for P_AO_2, P_aO_2 and $P_{\bar{v}}O_2$[10] *Wagner*'s vision of the O_2 cascade implied two mass balance equations responsible for convective O_2 transfer, associated with two conductive components, described by the diffusion-perfusion interaction equations. Proximally, the interaction of

a convective component with a diffusive component sets the maximal flow of O_2 in arterial blood$^{(Q a O_{2max})}$. Distally, the interaction of a convective component with a diffusive component (the diffusion-perfusion interaction equation setting O_2 flow from peripheral capillaries to the muscle fibres,[8] sets VO_2max, as reported graphically in figure 2. So, also Wagner focused on what happens distally in the respiratory system.

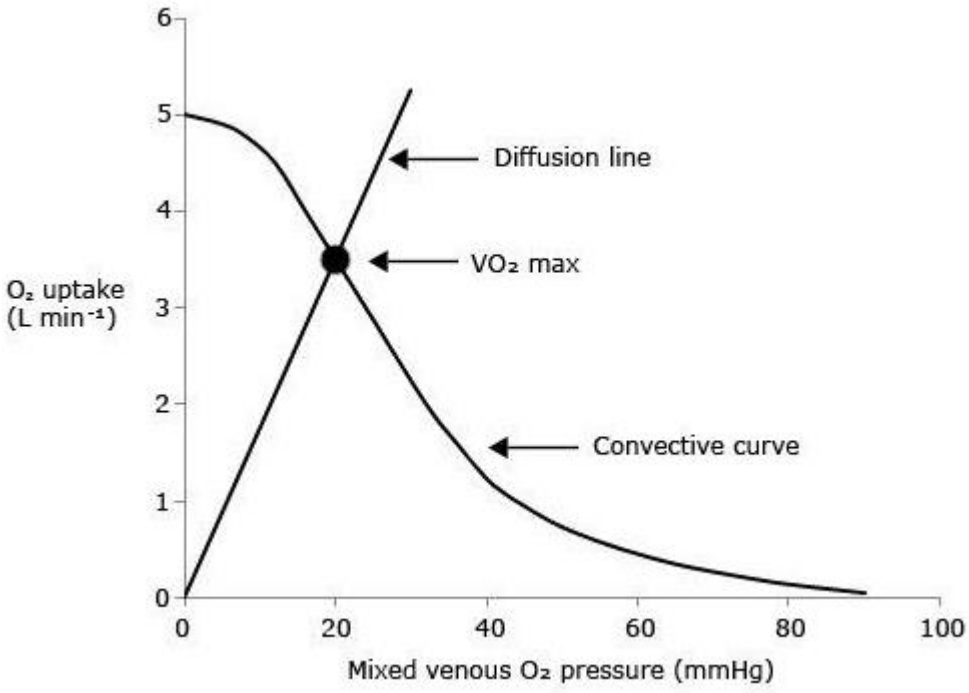

Fig. 2. Graphical representation of Wagner's model. O_2 uptake (VO_2) is plotted as a function of mixed venous O_2 pressure ($P_{\bar{v}}O_2$). The curve with negative slope is Wagner's convective curve. The straight line with positive slope is Wagner's diffusion line, whose slope is equal to Wagner's constant K_W. The convective curve intercepts the y-axis at a $\dot{V}O_2$ equal to arterial O_2 flow $(\dot{Q} a O_2)$, which is the case when $K_W = \infty$. The same curve intercepts the x-axis when $P_{\bar{v}}O_2$ is equal to arterial O_2 pressure, which is the case when $K_W = 0$. The VO_2max value is found on the crossing of the convective curve with the diffusion line (full dot). After *Ferretti* (2014).

Although *Wagner* and *di Prampero* have different visions of the O_2 cascade, their models share a multifactorial vision of VO_2max limitation. Both exclude that VO_2max may be limited by ventilation and O_2 diffusing capacity in healthy humans in normoxia, and

focus on what goes on distally to P_aO_2. If we accept this as an axiom, the simplified version of *di Prampero's* model, represented by Equation 4, can be further developed to obtain:

$$F_Q = \frac{(P_aO_2 - P_\bar{v}O_2)}{P_aO_2} = \frac{R_Q}{(R_Q + R_p)} \quad (5) \qquad (4.20)$$

Whence

$$\frac{1}{F_Q} = \frac{(R_Q + R_p)}{R_Q} = 1 + \frac{R_p}{R_Q} = 1 + \frac{G_Q}{G_p} \quad (6) \qquad (4.21)$$

Where *G* is conductance. Moreover, using Fick principle, we can demonstrate that:

$$\frac{\dot{V}O_{2max}}{\dot{Q}aO_{2max}} = \frac{(P_aO_2 - P_\bar{v}O_2)}{P_aO_2} \quad (7) \qquad (4.23)$$

Whence, because of Equation (5):

$$\frac{\dot{V}O_{2max}}{\dot{Q}aO_{2max}} = F_Q \quad (9) \qquad (4.24)$$

This means that F_Q in normoxia is equal to the O_2 extraction coefficient!

It follows from what precedes that, if $\dot{V}O_{2max} = \dot{Q}aO_{2max}$ (y-axis intercept of the convective curve in Figure 2), $F_Q = 1$ and $F_Q = 0$: all oxygen delivered to peripheral capillaries is consumed by mitochondria. At the other extreme, when $VO_2max = 0$ (x-axis intercept of the convective curve in figure 2, where $P_\bar{v}O_2 = P_aO_2$, $F_Q = 0$, $F_p = 1$, and $R_p = \infty$: the diffusive line of figure 2, the slope of which defines Wagner's constant K_W, coincides with the x-axis and no O_2 flows from capillaries to mitochondria. All intermediate F_Q values fall between these two extremes on the convective curve, where it intersects the diffusion line. The lower is K_W, the higher is R_p and the lower is R_Q So, these two models agree on the conclusion that both F_p and F_Q are necessary determinants

of VO_{2max}, the latter being responsible for the larger fraction of the overall VO_{2max} limitation.

VO_{2max} LIMITATION IN BED REST AND SPACE FLIGHT

Nobody doubts that $\dot{V}O_{2max}$ in upright posture is lower after than before bed rest.[3] The size of the VO_{2max} fall, which is larger the longer is bed rest duration, is fast in the first days, and progressively slower as bed rest proceeds. Thus, the VO_{2max} decline in upright posture after bed rest, as a function of bed rest duration, is non-linear, tending to an asymptote.[4] This is not so during bed rest (or space flight), or in supine posture after bed rest, since very small changes, if any, in VO_{2max} were found in these conditions.[1,6,9]

Ferretti and *Capelli* assumed an exponential VO_{2max} decay upright as a function of bed rest duration.[4] They clearly identified two components in the VO_{2max} decline, characterised by time constants of 8.4 and 70.7 days, respectively. This means that the distal part of the respiratory system, from arterial blood to mitochondria, includes two capacitances of different size, connected in-series. When an adaptive change affects the overall system, the effects on the smaller capacitance initially prevail, imposing fast changes in VO_{2max} since the first days, leading to an asymptote for the fast component within perhaps three weeks. Thereafter, the effects on the second, larger capacitance prevail, whence a further, albeit slower, VO_{2max} decline. The fast component of the VO_{2max} decrease after bed rest was attributed to R_Q (cardiovascular adaptation), whereas the slow component reflects changes in R_P and thus to muscle atrophy.

The fall of VO_{2max} reported by Levine et al in upright posture after a 17-day space flight was not accompanied by changes in VO_{2max} on the same subjects in space.[6] They attributed the VO_{2max} decline upon return to the effects of sudden blood volume redistribution toward the lower limbs after gravity resumption, which are stronger after cardiovascular adaptation to microgravity than before. Due to the short duration of the flight, they were unable to highlight the effects of R_P related to muscle atrophy. Yet Trappe et al did, over similar space flight duration:[9] we are playing at the boundary of muscle atrophy identification. Moore et al reported a 17% decrease in VO_{2max} after only 15 days in space, which is in contrast not only with theory but also with previous experimental results.[7] Hughson et al pointed to cardiac atrophy as source of the VO_{2max} decrease inflight in Moore's study,[5] yet cardiac atrophy is a slow phenomenon, which

should not generate a VO_{2max} fall in such a short time. I would suggest that the anti-ergonomic posture in which Astronauts exercise in the International Space Station might artificially reduce VO_{2max}.

Figure 3 describes the effects of prolonged bed rest in the context of di *Prampero's* model, using the data of Bringard.[1] The continuous line reports the theoretical F_Q value of the model (0.7). The open symbols lying on it refer to the acute manoeuvre of moving from supine to upright, before and after 35-day bed rest. The full dots refer to the overall effect of bed rest, in supine – lower left point – and upright – upper right point – posture. The vertical distance between open symbols and full dots is the same for both postures, indicating that the factor that caused the VO_{2max} decrease supine after bed rest acted by the same extent also in upright posture, resulting independent of posture. *Bringard* concluded that the upward data shift after bed rest reflects the effects of the change in R_p.[1] According to *Wagner's* model, the R_p increase implies a decrease in K_W whereas the R_Q increase causes the downward shift of the $\dot{Q}aO_2$ point, and the consequent slope change of the convective curve.

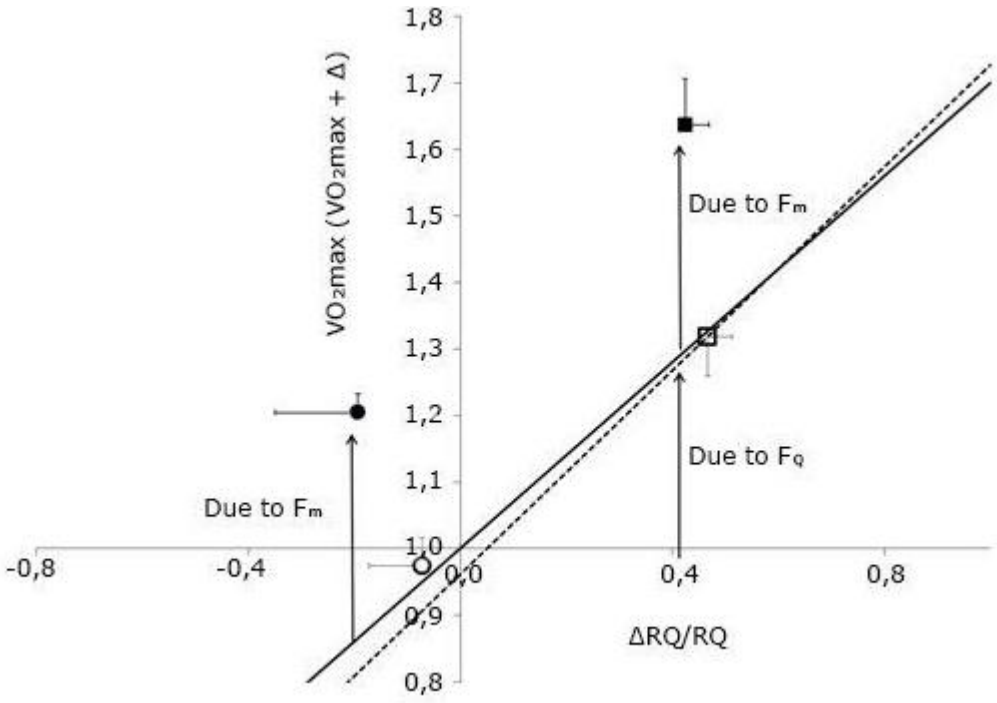

Fig. 3. The ratio between maximal oxygen consumption (VO_{2max}) before and after a given manoeuvre $[(\dot{V}O2max)/(\dot{V}O2max+\Delta), \text{y-axis}]$ is plotted as a function of the relative change in the cardiovascular resistance to oxygen flow $[(\Delta R_Q)/R_Q, \text{x-axis}]$. The

continuous line, with a slope of 0.7, is the theoretical line obtained by di *Prampero* and *Ferretti* (1990) after an analysis of the literature. The open symbols concern the effects of postural changes from supine to upright before (open dot) and after (open square) bed rest. The dashed line is experimental and represents the regression equation calculated on the data of *Bringard* after bed rest (y = 0.76x + 0.96). The slope of the experimental line did not differ significantly from that of the theoretical line. The y-intercept of the experimental line was not significantly different from 1. The filled symbols, located above the experimental line, refer to the effects of bed rest in supine (filled dot) and upright (filled square). Error bars indicate standard error. The arrows highlight the effect on VO_{2max} due to cardiovascular F_Q and peripheral F_P ($\dot{V}O_{2max}$) limitation. Modified after *Bringard*(2010).

In conclusion, when an overall adaptive phenomenon modifies the size of the resistances along the entire O_2 cascade, the time course of the ensuing VO_{2max} changes is characterised by more than one exponential. If changes are in opposite directions, they may compensate each other: if compensation were complete, no effect on VO_{2max} would be visible. If changes are homodirectional, they are additive and the final effect on VO_{2max} would depend on the ensuing fractional limitation of VO_{2max} imposed by each resistance, or on the intersection of the modified convective curve and diffusion line.

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Conflict of interests

There is no conflict of interest in relation to the research presented.