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Slow age-related phase II on-transient $\dot{V}O_2$ and heart rate kinetics during ramp exercise in adult men

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ABSTRACT

We assessed for differences of the phase II cardiopulmonary (ϕ_{II} CRP) on-transient kinetics in terms of mean response time (MRT, s) for the expired ventilation (MRT $\dot{V}e$), pulmonary oxygen uptake (MRT $\dot{V}O_2$), carbon dioxide output (MRT $\dot{V}CO_2$) and heart rate (MRT HR) and also did the ϕ_{II} $\dot{V}O_2$ on-transient kinetics degree of entropy (ϕ_{II} $\dot{V}O_2$ MRT S, kcal•°C^{-1}•s^{-1}), between young (YG = 8, 25 ± 2.9; mean ± SD) and old adult men (OG = 9, 70.9 ± 4.7) men during legs cycling exercise computerized ramp test (YG: 25W•min^{-1}; OG: 15W•min^{-1}), in the search for determinant mechanisms or factors possibly involved in the $\dot{V}O_2$ kinetics of adult men. The provided breath-by-breath pulmonary data and the beat-by-beat data were modelled by non linear regression. We observed ramp slow (MRT difference = OG - YG, s) ϕ_{II} on-transient age-related for both $\dot{V}O_2$ (23 s) and HR kinetics (30 s), and also increased age-related ϕ_{II} $\dot{V}O_2$ MRT S (3.1 kcal•°C^{-1}•s^{-1}) for ramp exercise. The ramp test on-transient phase two of both the slow $\dot{V}O2$ kinetics and slow HR kinetics were age- related, and they were accompanied by an increased $\dot{V}O_2$ kinetics entropy for ramp exercise, meaning that old adults could thermodynamically resists less the energy-transitions and thus increase their entropy in terms of kcal•°C^{-1}•s^{-1}. The amount of heat energy un-available for conversion into useful work (S) in the human body increases with ageing, and the human body does it with ageing by slowing down both the pulmonary O_2 uptake and the heart rate on-transient kinetics during ergometric exercise.

Key words: *Ramp, ageing; oxygen, heart rate, kinetics, entropy.*

RESUMEN

En la búsqueda de mecanismos o posibles factores involucrados en la cinética (tiempo de respuesta media exponencial, TRM en s) de captación pulmonar de oxígeno ($\dot{V}O_2$) en el hombre adulto, evaluamos diferencias en la cinética transitoria de la phase II cardiopulmonar (ϕ_{II} TRM CRP) en términos de la ventilación espirada (TRM$\dot{V}e$), TRM $\dot{V}O_2$, eliminación de bióxido de carbono (TRM $\dot{V}CO_2$) y frecuencia cardiaca (TRM FC), así como del grado de "entropía" (S) de la cinética transitoria de cinética de la ϕ_{II} $\dot{V}O_2$ (ϕ_{II} $\dot{V}O_2$ TRM S, kcal•°C^{-1}•s^{-1}), entre hombres adultos jóvenes (GJ = 8, 25 ± 2.9; media ± DE) y mayores (GM = 9, 70.9 ± 4.7) que hicieron una prueba computada de ejercicio tipo rampa en cicloergómetro usando sus dos piernas. Los datos pulmonares de respiración-por-respiración y de latido-por-latido de la FC fueron modelados mediante regresión no lineal. Observamos una cinética lenta de la ϕ_{II} de rampa transitoria relacionada con la edad ($TRM_{diferencia}$ = GM - GJ, s) de 23 s en $\dot{V}O_2$, de 30 s FC, y un aumento de 3.1 kcal•°C^{-1}•s^{-1} en la ϕ_{II} $\dot{V}O_2$ TRM S relacionada con la edad durante el ejercicio tipo rampa. La cinética lenta de la fase dos transitoria de $\dot{V}O_2$ y FC estuvieron relacionadas con la edad, lo mismo que una entropía cinética aumentada de la $\dot{V}O_2$ del ejercicio de rampa, lo que se interpreta como una menor resistencia termodinámica en los adultos mayores para las transiciones energéticas y así se incrementa su entropía en términos de kcal•°C^{-1}•s^{-1}. La cantidad de energía calórica no disponible para su conversión en trabajo útil (S) del cuerpo humano aumenta con el envejecimiento y lo hace con una cinética de la captación pulmonar de O_2 y de la FC transitorias del ejercicio ergométrico que disminuyen con la edad.

Palabras clave: *Rampa, envejecimiento, oxígeno, frecuencia cardiaca, cinética, entropía.*

INTRODUCTION

The work we performed during our daily life depends largely on the dynamics of the pulmonary ventilation ($\dot{V}e$), oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and a heart rate (HR) (CRP, cardiopulmonary) responses to muscular exercise, and these responses are crucial determinants of exercise tolerance. Of the many work rate-

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forcing protocols that have been used in an attempt to educe control features of the CRP dynamics, after the square wave test, the ramp is the most commonly used because it provides four key parameters ($\dot{V}O_{2max}$; T_{VE}, estimated ventilatory threshold; MRT, mean response time; and work efficiency) that make up a subjects aerobic profile[1] in both clinical and research settings. A linear system has the property that the kinetics of response does not depend on the stimulus amplitude. Thus, it is expected that the responses of $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}e$ in the transition between loadless pedaling and higher work rates (WRs) should be linear in this respect,[2] however, both $\dot{V}e$ and $\dot{V}O_2$ kinetics are markedly slower at work rates associated with sustained blood lactate elevations, and this tendency is also detected for $\dot{V}O_2$ (but not $\dot{V}e$) kinetics to be slower as WR increases for exercise intensities not associated with lactic acidosis. $\dot{V}O_2$ kinetics at high WRs are well characterized by the addition of a slower exponential component to the faster component, which is seen at lower WRs. In contrast, $\dot{V}CO_2$ kinetics does not slow at the higher exercise intensities; this may be the result of the coincident influence diminished several sources of $\dot{V}CO_2$ related to lactic acidosis.[2]

Understanding the integrative strategy that the cardiorrespiratory system and its kinetics adopt to meet the metabolic demands during ramp exercise eliciting maximum CRP values (W_{max}, $\dot{V}e_{max}$, $\dot{V}O_{2max}$, $\dot{V}CO_{2max}$, HR_{max}) would significantly contribute to our understanding of muscle energetics and limitations to exercise tolerance in this exercise domain. In fact, it is well known the impact of regular sport activity on CRP fitness; even at 2240 m over sea level, regular sport activity positively affected aerobic power and counteract age-related decreases in HR_{max}, $\dot{V}O_{2max}$, maximum power max, maximum power index and fast transitory CRP kinetics during increasing ergometric exercise.[3] The measurement of $\dot{V}O_2$ kinetics is a good non-invasive estimation both in describing the response of the whole organism and in gaining insight into the skeletal muscle mass $\dot{V}O_2$ ($\dot{V}O_{2M}$) kinetics. Evermore, the exponential MRT of these CRP (MRT Ve, MRT $\dot{V}O_2$, MRT $\dot{V}CO_2$, MRT HR) increases during their transient increments with respect to work rate ($\Delta\dot{V}e/\Delta WR$, $\Delta\dot{V}O_2/\Delta WR$, $\Delta\dot{V}CO_2/\Delta WR$, $\Delta HR/\Delta WR$; $\Delta HR/\Delta\dot{V}O_2$, and $\Delta\dot{V}e/\Delta\dot{V}CO_2$) is determinant of the oxygen deficit and, hence, of the potential requirement for anaerobiosis to supplement the ongoing aerobic component[4] of the energy transfer for muscle contraction.[5] For example, the dynamic relationship $\Delta\dot{V}O_2/\Delta WR$, indicates if the metabolic response is adequate for a given power output; $\Delta HR/\Delta\dot{V}O_2$, could indicate if for a given metabolic demand either the stroke volume or the peripheral $\dot{V}O_2$ extraction or both are matched; and $\Delta\dot{V}e/\Delta\dot{V}CO_2$, indicates if the there is excessive ventilation to the metabolic stress.[4] Consequently, it appears that indices of aerobic[3] and anaerobic exercise performance differentially influence the fundamental and slow components of the $\dot{V}O_2$ kinetics.[6]

The ageing process is related with the participation or absence of many time constants.[7] Ageing is associated with a slowing of $\dot{V}O_2$ kinetics during the on-transition to a step increase in WR of submaximal exercise[8] and the negative-entropy (-S) of a human being decays when his $\dot{V}O_2$ kinetics entropy (S) increases, in units of kcal•°C-1, with ageing also during submaximal exercise.[9] Entropy (from a Greek word meaning "transformation") is a property that an object has in addition to its temperature, and entropy is connected with the amount of heat energy un-available for conversion into useful work.[10] The Φ two $\dot{V}O_2$ kinetics S is another fundamental parameter to study the transient response of gas exchange kinetics. However, it is unclear whether this slowing of $\dot{V}O_2$ kinetics is a consequence of blood flow limitations and/or $\dot{V}O_2$ delivery or of a slowest activation of the biochemical reactions in skeletal muscle, factors that have been implicated as limiting skeletal muscle $\dot{V}O_2$ consumption in old adults.[11] Nevertheless, it has been observed fast-age on transient contraction in artery stimulated with phenylephrine[12] that could have cause-effect relationships with the slow-age $\dot{V}O_2$ on-transient kinetics and its S (increased-age related $\dot{V}O_2$ kinetics S).[9]

We have already described three CRP on-transient phases (Φ_I, cardiodymamic ;Φ_{II}, linear primary component; Φ_{III}, maximum) and the Φ_{II} CRP kinetics in Mexican athletes during a ramp test at 2240 m above sea level.[3] During Φ_{II}, specially the $\dot{V}O_2$ closely match the skeletal muscle active mass $\dot{V}O_2$ because the $\dot{V}O_2$ slope is not discernibly different from that of the response.[1] In addition, it is well known that the kinetic features in the $\dot{V}O_2$ response from above TVE square-wave test have important implications for the response to ramp test.[1] We have already empirically applied the entropy approach the study the O_2 mass rate of chance per unit of time (S Φ_2 $\dot{V}O_2$ τ, S phase two $\dot{V}O_2$ kinetics) in adult men[9]; specially important is the Φ_2 $\dot{V}O_2$, because during this phase both $\dot{V}O_{2M}$ and $\dot{V}O_2$ rise in a near- exponential fashion towards the $\dot{V}O_2$ demand,[13] but it has not been explored for Φ_{II} CRP ramp exercise test nor to study the entropy of the Φ_{II} $\dot{V}O_2$ kinetics (S Φ_{II} $\dot{V}O_2$ τ) in young *versus* old men comparisons, during ramp exercise test.

The purpose of the present work was to assess for differences of the Φ_{II} CRP on-transient kinetics (MRT $\dot{V}e$, MRT $\dot{V}O_2$, MRT $\dot{V}CO_2$, MRT HR) and the Φ_{II} $\dot{V}O_2$ on-transient kinetics degree of entropy (S Φ_{II} $\dot{V}O_2$ MRT), between young and old adult men during a ramp exercise test, in the search for determinant mechanisms or factors possibly involved in the $\dot{V}O_2$ kinetics of adult men.

Hypothesis

If the exponential Φ_{II} $\dot{V}O_2$ and HR on-transient response to the ramp forcing function of maximal exercise are slow-age related in terms of MRT duration, thus the Φ_{II} $\dot{V}O_2$ MRT, the S Φ_{II} $\dot{V}O_2$ MRT and the Φ_{II} HR MRT estimated values, should be significantly high in old compared to young men.

MATERIALS AND METHODS

Subjects

Our eight young (YG, aged 23 to 30 years) and nine old (OG, aged 64 to 78 years) male subjects that participated in this study were also studied for comparison with previous publication.[8] Standard calibrated scales and stadiometers were used to determine height (cm), weight (kg), and body mass index (weight/height2, kg•m-2). All subjects were healthy with no diagnosed CRP disease and were active having above average fitness. None of the subjects were on medication known to affect CRP function during exercise. Informed consent was obtained after the experimental protocol and possible risks were explained to each participant. The research was approved by the University's Review Board for Health Sciences Research Involving Human Subjects.

General protocol

Each subject was studied on one occasion and was tested at the same time of day on his visit to the laboratory.The subjects reported to the laboratory at least two hours after consuming a light meal and at least four hours after consuming caffeinated beverages. The subjects were asked to abstain from performing heavy intensity exercise prior to visiting the laboratory on the day of testing.

On his visit to the laboratory each subject performed an incremental exercise test with power output increased as a ramp function at 15-25 W.min-1 to volitional fatigue for the determination of the ventilatory threshold (T_{VE}), peak O_2 uptake ($\dot{V}O_{2peak}$) and maximal values for HR, CO_2 and $\dot{V}e$. Subjects exercised in the upright position on an electrically-braked cycle ergometer (Lode, Model H-300-R); the resistance on the cycle ergometer was computer-controlled to produce a ramp signal that corresponded to a linear increase in power output. For the older subjects this test was performed under medical supervision and served as part of the medical pre-screening which also included a general medical examination.[14,15]

The $\dot{V}O_2$ averaged over the final 15 s of the incremental test prior to fatigue was taken as $\dot{V}O_{2peak}$. The $T_{\dot{V}E}$ was defined as the $\dot{V}O_2$ at which there was a systematic increase in the ventilatory equivalent for $\dot{V}O_2$ ($\dot{V}_E/\dot{V}O_2$) and end-tidal PO_2 ($P_{ET}O_2$), with no concomitant increase in the ventilatory equivalent for $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$), or decrease in end-tidal PCO_2 ($P_{ET}CO_2$).

Ventilation and gas exchange ($\dot{V}O_2$, $\dot{V}CO_2$) were calculated breath-by-breath by a computer based programme. Inspired and expired airflow and ventilatory volumes were measured by a low-resistance, low deadspace (90 ml), bi-directional turbine and volume transducer (VMM-110, Alpha Technologies); the volume signal was calibrated daily using a syringe of known volume (3.01 l or 0.99 l). Inspired and expired air was sampled continuously (1 ml•s-1) at the mouth, and analysed for fractional concentrations of $\dot{V}O_2$, CO_2, and N2 using a respiratory mass spectrometer (Perkin Elmer MGA-1100 or Airspec MGA2000); the mass spectrometer was calibrated daily using precision analysed gas mixtures (9% O_2, 7% CO_2, 5% air, 79% N2). Analog signals from the mass spectrometer and turbine transducer were sampled and digitized every 20 ms and stored on computer for later analysis. Gas concentration signals were aligned with the inspired and expired gas volumes after correcting for the time delay of the analysis system. Ventilation, $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated with corrections made for breath-by-breath fluctuations in lung gas stores.[16,17] Temperature and water vapour corrections were based on conditions measured near the mouth. Heart rate was monitored continuously via ECG electrodes using a modified V_5 configuration; the heart rate signal was stored on computer for processing.

The dynamic relationships to characterize the metabolic ($\Delta\dot{V}O_2/\Delta WR$, ml•min^{-1}•W^{-1}), cardiovascular ($\Delta HR/\Delta\dot{V}O_2$, beats•min^{-1}•l•min^{-1}), and ventilatory pattern ($\Delta\dot{V}e/\Delta CO_2$, l•min^{-1}•l•min^{-1}) responses were determined during the CRP ramp test4 in YG *vs.* OG comparisons.

Data analysis

The Φ_{II} CRP (HR, $\dot{V}e$, $\dot{V}O_2$, $\dot{V}CO_2$) response was determined by simple linear regression and visual inspection of the entire CRP ramp response.[18] The ramp-component model used to describe the Φ_{II} CRP kinetic response was described previously[18] and provides an estimate of the baseline (a_0), amplitudes (α_x), time delays (TD_x), and time constants (τ_x), where x refers to a specific component in the multi-component model. The kinetic CRP parameters for the on- transition in the ramp output were determined as a function of time [f(t)] using the computerized nonlinear regression techniques to fit a single exponential expressions to each response time course.[18] Thus, we obtained

the on-transient mass rate of change per unit of time for each CRP variable ($d\dot{V}e \cdot dt^{-1}$, $l \cdot min^{-1}$; $d\dot{V}O_2 \cdot dt^{-1}$, $ml \cdot min^{-1}$; $d\dot{V}CO_2 \cdot dt^{-1}$, $ml \cdot min^{-1}$, $HR \cdot dt^{-1}$, $beats \cdot min^{-1}$). Model parameters were determined by least-squares nonlinear regression in which the best fit was defined by minimization of the residual sum of squares (RSS).

The overall time course of the Φ_{II} CRP response was determined from the MRT. The MRT was the only kinetic parameter used for comparisons, which was calculated from a weighted sum of TD and τ for each component. The MRT is equivalent to the time required to achieve approximately 63% of the difference between a^0 and the new steady-state value.

Phase Two $\dot{V}O_2$ Kinetics Entropy

The entropy of the Φ_{II} $\dot{V}CO_2$ MRT (S Φ_{II} $\dot{V}CO_2$ MRT) was calculated in terms of the Boltzmann's constant ($k = 3.2983 \cdot 10^{-4}$, $cal \cdot °C^{-1}$) by empirically substituting the quantitative measure of the atomistic disorder of a living system (D) in the formula of entropy ($S = k \cdot \log D$) by MRT; in other words, S Φ_{II} $\dot{V}O_2$ MRT = $k \cdot \log(\Phi_{II}$ $\dot{V}O_2$ MRT).[8]

Statistical analysis

General statistics, and the Pearson correlation coefficients to assess the degree of relationships between variables were applied to those of interest. The CRP kinetic parameter estimates were analysed using a one-way measures analysis of variance (ANOVA) for on-transitions as the main effects. A significant F-ratio was further analysed using Student-Neuman-Keuls post hoc analysis. Student t-test was applied for YG *versus* OG comparisons.[19] Statistical significance was accepted at $p < 0.05$. All values are reported as the mean ± SD.

RESULTS

The anthropometric data from YG *vs.* OG comparisons showed no differences in height (179.63 ± 5.71 = 174.11 ± 5.53) body mass (79.13 ± 9.3 = 79.78 ± 9.87) and body mass index (24.49 ± 2.32 = 26.32 ± 3.05), but, as expected, in age (25.01 ± 3.95 < 70.87 ± 4.73, $t_{\alpha 0.05} = 23.6$, $P < 0.001$) the difference was -45.85 yrs. The maximal ramp test CRP data, and the transient increments in terms of $\Delta\dot{V}CO_2/\Delta VWR$, $\Delta HR/\Delta\dot{V}CO_2$, and $\Delta\dot{V}e/\Delta\dot{V}CO_2$ caused by a ramp test input in the YG and OG are shown in table 1. The summary data for ramp Φ_{II} kinetic CRP data exercise are presented in table 2. An example of the CRP ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}e$, HR; ramp-component exponential fitting models describing both the $\dot{V}CO_2$ and the HR) ramp on-transient response in one young subject is shown in figure 1. The Φ_{II} MRT kinetic parameter from the CRP variables ($\dot{V}CO_2$, $\dot{V}CO_2$, $\dot{V}e$, HR) quantifying their dynamic responses in YG vs OG adult men, during the on-transient of ramp test are shown in Figure 2. The Φ_{II} MRT kinetic parameter entropy (Φ_{II} $\dot{V}O_2$ MRT S) quantifying the dynamic response of $\dot{V}O_2$ in YG *vs.* OG adult men, during the on-transient of ramp test is shown in figure 3.

Maximal CRP Differences

As expected, all of the maximal ergo-CRP responses to the ramp test resulted significantly high in YG compared OG (Table I) in terms of differences as followed: WR (121.43 W), $\dot{V}O_2$, (1.55 $l \cdot min^{-1}$, 19.24 $ml \cdot kg^{-1}$ $l \cdot min^{-1}$), HR ($beats \cdot min^{-1}$: experimental = 32.42, predicted = 45.78), $\dot{V}CO_2$, (1.93 $l \cdot min^{-1}$), and e (44.5 $l \cdot min^{-1}$). However, only the dynamic cardiovascular relationship ($\Delta HR/\Delta\dot{V}CO_2$) resulted significantly high in OG compared YG (difference = 15.03 $beats \cdot min^{-1} \cdot l \cdot min^{-1}$) (Table 1). The OG ΔHR/

Table I. Maximal ramp test cardiorespiratory data in eight young and nine old adult men.

Group	Work rate (W)	$\dot{V}O_2$ peak ($l \cdot min^{-1}$) ($mL \cdot kg^{-1} \cdot min^{-1}$)	Heart rate experimental ($beats \cdot min^{-1}$)	Heart rate predicted ($beats \cdot min^{-1}$)	$\dot{V}CO_2$ ($l \cdot min^{-1}$)	$\dot{V}_E$ ($l \cdot min^{-1}$)	$\dot{V}O_2/\Delta WR$ ($mL \cdot min^{-1} \cdot W^{-1}$)	$\Delta HR/\dot{V}O_2$ ($beatsl \cdot l^{-1} \cdot min^{-1}$)	$\Delta\dot{V}e/\Delta\dot{V}CO_2$ ($l \cdot l^{-1}$)
Young									
249.88[a]	3.75[b]	47.38[c]	190.75[d]	195.00[e]	4.40[f]	140.50[g]	11.08	38.12h	25.79
± 45.72	± 0.62	± 6.39	± 14.11	± 3.07	± 0.84	± 36.24	± 1.05	± 7.23	± 2.79
Old									
128.44[a]	2.20[b]	28.13[c]	158.33[d]	149.22[e]	2.47[f]	96.00[g]	10.99	53.16h	30.06
± 20.84	± 0.41	± 7.18	± 14.90	± 4.74	± 0.36	± 29.78	± 1.90	± 14.58	± 6.82

Numeric values are mean ± SD. $\dot{V}O_2$: Pulmonary oxygen uptake. Predicted heart rate = 220 years -age in years. $\dot{V}CO_2$: Carbon dioxide output. $\dot{V}_E$: Expired ventilation. WR: Work rate. $\Delta\dot{V}O_2/\Delta WR$, $\Delta HR/\Delta\dot{V}O_2$, and $\Delta\dot{V}e/\dot{V}CO_2$, metabolic, cardiovascular, and ventilatory dynamic relationships, respectively. Student-tα, 0.05 test (Pa to f ≤ 0.001; Pg to h ≤ 0.02): [a]t = 7.2, [b]t= 6.2, [c]t = 5.8, [d]t = 4.6, [e]t = 23.3, [f]t = 6.3; [g]t = 2.8; ht = 2.6.

Table 2. Ramp phase two cardiopulmonary kinetic data in eight young and nine old men.

Parameter	Young	Old	t_{value}	P_{value}
		$\dot{V}O_2$		
"$B_{ase}L_{ine}$", mL	1080.38 ± 254.35	943.68 ± 143.40	1.39	> 0.05
$A_{mplitude}t_{otal}$, mL	290.05 ± 28.14	171.03 ± 32.48	8.02	≤ 0.001
$T_{ime}D_{elayed}$, s	0.53 ± 0.56	0.29 ± 0.29	1.17	> 0.05
$T_{ime}C_{onstant}$, s	18.37 ± 5.71	41.61 ± 5.95	8.20	≤ 0.001
$M_{ean}S_{quare}E_{rror}$	18404.2 ± 6727.3	14012.9 ± 11499.7	–	
$R_{esidual}S_{um}S_{quares}$, x 10^5	27.04 ± 18.05	12.83 ± 11.82	–	
		Heart Rate		
"$B_{ase}L_{ine}$", beats	101.4 ± 10.2	97.4 ± 21.0	0.49	> 0.05
$A_{mplitude}t_{otal}$, beats	12.4 ± 2.1	12.0 ± 2.6	0.32	> 0.05
$T_{ime}D_{elayed}$, s	1.4 ± 3.9	9.6 ± 6.0	3.20	≤ 0.007
$T_{ime}C_{onstant}$, s	32.0 ± 2.9	54.0 ± 7.4	7.80	≤ 0.001
$M_{ean}S_{quare}E_{rror}$	166.6 ± 395	386.9 ± 539.2	–	
$R_{esidual}S_{um}S_{quares}$, x 10^5	0.25 ± 0.59	0.30 ± 0.47	–	
		$\dot{V}CO_2$		
"$B_{ase}L_{ine}$", mL	914.1 ± 237.4	887.2 ± 146.4	0.6	> 0.05
$A_{mplitude}t_{otal}$, mL	397.0 ± 35.7	264.5 ± 70.2	5.0	≤ 0.001
$T_{ime}D_{elayed}$, s	11.9 ± 8.0	9.5 ± 10.4	0.2	> 0.05
$T_{ime}C_{onstant}$, s	36.5 ± 8.7	43.9 ± 10.2	1.9	> 0.05
$M_{ean}S_{quare}E_{rror}$	0.23 ± 0.156	0.26 ± 0.48	–	
$R_{esidual}S_{um}S_{quares}$, x 10^5	36.67 ± 40.37	13.13 ± 10.47	–	
		$\dot{V}e$		
"$B_{ase}L_{ine}$", l	24.6 ± 5.7	28.9 ± 6.3	1.5	> 0.05
$A_{mplitude}t_{otal}$, l	10.5 ± 1.6	9.1 ± 2.3	1.5	> 0.05
$T_{ime}D_{elayed}$, s	9.4 ± 8.1	7.5 ± 8.9	0.5	> 0.05
$T_{ime}C_{onstant}$, s	52.9 ± 8.0	61.6 ± 8.8	2.1	> 0.05
$M_{ean}S_{quare}E_{rror}$	60.2 ± 48.9	28.5 ± 19.9	–	
$R_{esidual}S_{um}S_{quares}$, x 10^5	0.10 ± 0.11	0.03 ± 0.02	–	

Numeric values are mean ± sd. ≤: Significantly different. --: No assessed. "": Virtual base line. $\dot{V}O_2$: Pulmonary oxygen uptake. $\dot{V}CO_2$: Carbon dioxide output. $\dot{V}_E$: Expired ventilation.

$\Delta\dot{V}O_2$ was negatively related with $\dot{V}CO_2p_{eak}$ ($r = -0.72$, $P < 0.043$).

Φ_{II}CRP Kinetic Parameter Differences

The Φ_{II} total amplitude in both the $\dot{V}O_2$ and the $\dot{V}CO_2$ resulted, 119 mL and 131.8 mL, respectively, high in YG compared OG (Table 2). The Φ_{II} HR TD resulted 8.1 s slow in the OG compared YG (Table 2). The Φ_{II} τ in both the $\dot{V}O_2$ and the HR resulted, 23.25 s and 21.9 s, respectively, slow ($P \leq 0.001$) in OG compared YG (Table 2). The Φ_{II} MRT in both the $\dot{V}CO_2$ and the HR resulted, 23 s ($t = 8.3$) and 30 s ($t = 6.2$), respectively, slow in OG compared YG (Figure 2). The Φ_{II} $\dot{V}O_2$ MRT S resulted 3.1 kcal•°C^{-1}•S^{-1} high ($t = 7.1$, $P \leq 0.001$) in OG compared YG (Figure 3).

DISCUSSION

The three CRP phases (Φ_I, Φ_{II}, Φ_{III}) observed in this study agreed with the fact that from sea level[20] to moderate altitude,[17] CRP kinetics are characterized during a ramp exercise by three progressively steeper slopes mainly based on $\dot{V}e$; the first from the beginning of exercise to anaerobic

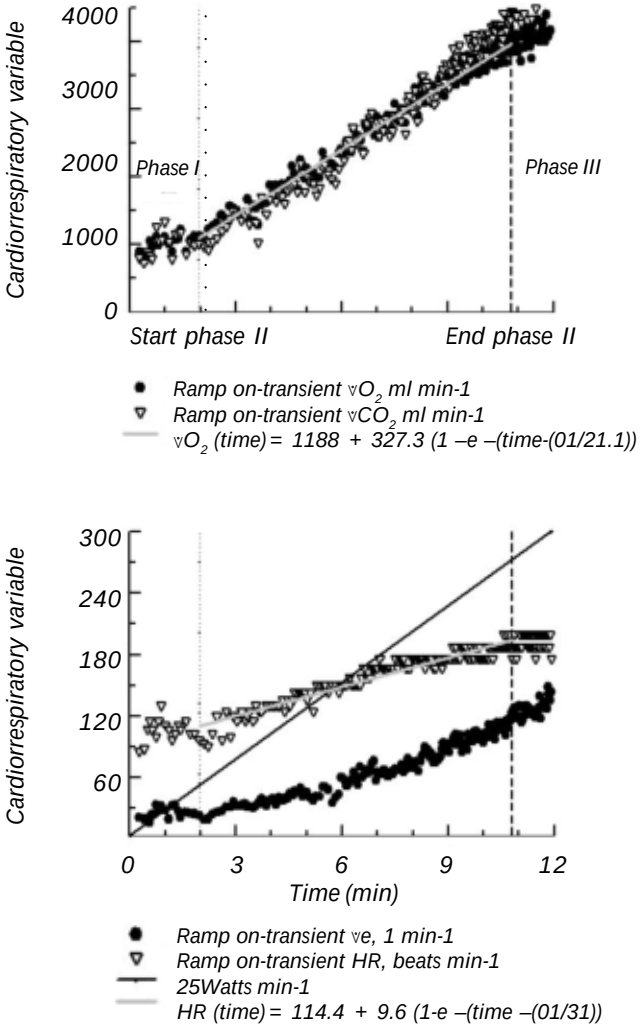

Figure 1. *An example of the three phases of the cardiopulmonary ramp (25 W•min-1) on-transient response in one young subject the pulmonary oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), expired ventilation ($\dot{V}e$), and heart rate (HR) responses; and also the ramp-component exponential fitting models describing the phase two of both the $\dot{V}O_2$ and the HR.*

threshold; the second from anaerobic threshold to respiratory compensation point, where the body CO_2 stores are used to buffer acidosis owing to lactate production and this extra CO_2 production drives the ventilation increase, at high altitude, ventilation increases owing to hypoxia and is characterized by two, instead of three phases,[20] and the third from respiratory compensation point to peak exercise. In the first detailed data on the time course of the CRP responses to exercise in humans[21] it was shown that cardiac output (HR • $S_{troke}V_{olume}$, l •min-1) increases more rapidly following an increase in exercise workload than does arteriovenous O_2 difference, proving that most of the early increase in $\dot{V}O_2$ is due to increased cardiac output, but as exercise continues, increased arteriovenous O_2 difference contributed gradually more to increased $\dot{V}O_2$. Consequently, we used the phase II HR kinetics because it may reflect O_2 delivery to the working muscle in terms of phase II $\dot{V}O_2$

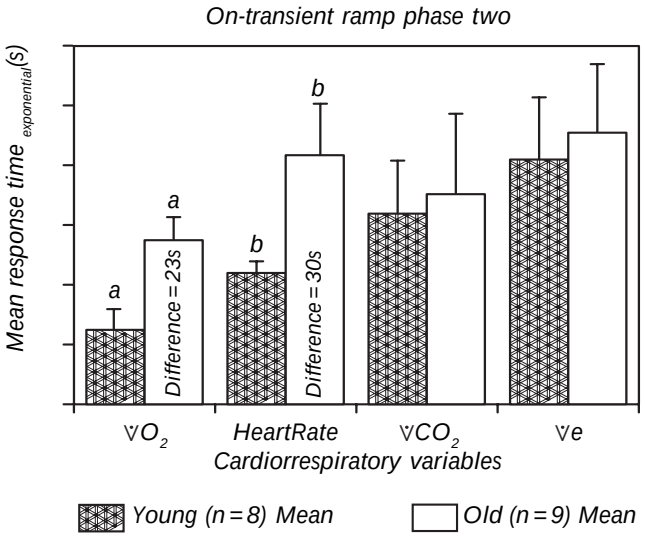

Figure 2. *The phase two mean response time kinetic parameter (Φ_{II} MRT) for the pulmonary oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), expired ventilation ($\dot{V}e$), and heart rate (HR) responses quantifying their dynamic responses in young vs. old adult men, during the on-transient ramp test.*

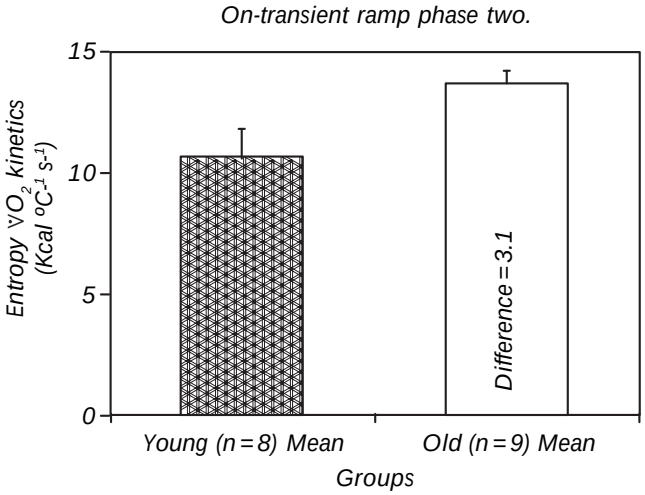

Figure 3. *The phase two mean response time kinetic parameter antropy for the pulmonary oxygen uptake (Φ_{II} $\dot{V}O_2$ MRT S) quantifying the dynamic response of $\dot{V}O2$ in young vs. old adult men, during the on-transient ramp test.*

kinetics at least before the increased arteriovenous O_2 difference contributed gradually more to increased $\dot{V}O_2$.

Maximal CRP Differences

It was not a surprise that all of the maximal ergo-CRP responses to the ramp test resulted significantly high in YG compared OG.[22] These differences in YG > OG for WR, $\dot{V}O_2$,HR, $\dot{V}CO_2$, and $\dot{V}e$ are, in general, the result of a decline with age in $\dot{V}O_{2max}$,10% per decade in sedentary people after the age of 25 yr and between the ages of 50 and 75 yr the decline is ,15% per decade (l•min-[1]); and other parameters of importance for physical fitness is an effect of reduced HR_{max} (8.2 %) that diminished maximal cardiac output accompanied by motoneuropennia and thereby of motor unitpennia and sarcopennia (skeletal muscle system is the most common affected); evermore, the decline in maximal aerobic power is due not only to ageing but also to lifestyle variables such as exercise and body composition.[22,23] Consequently, in this study the high $\Delta HR/\Delta\dot{V}O_2$ in OG compared YG is explained because the age significantly influenced this relationship, and it agreed with a negative correlation between $\Delta HR/\Delta\dot{V}O_2$ and $\dot{V}O_{2peak}$.[4]

Φ_{II} CRP Kinetic Parameter Differences

The slow age related Φ_{II} HR TD contributed to the slow age related ΦII HR MRT. The slow- age related Φ_{II} τ in both the $\dot{V}O_2$ and the HR contributed to their Φ_{II} MRT in both the $\dot{V}O_2$ and the HR as well because their MRTs were calculated by the sum of their τ_{II} + TD_{II}; however, since the τII (the inverse of the rate constant derived through non-linear regression) does not apply as a significant kinetics parameter for ramp test[24] because it is no interchangeable with MRT (solved algebraically), thus, it follows that we will just make a discussion on the Φ_{II} $\dot{V}O_2$ MRT , and Φ_{II} HR MRT only.[25]

Near-infrared spectroscopy and computer simulations revealed a nonlinear relationship between microvascular muscle blood flow and muscle $\dot{V}O_2$ during incremental ramp exercise[26] and, in healthy subjects, muscle blood flow increased at a faster rate than muscle $\dot{V}O_2$ early in the exercise test and slowed progressively as maximal work rate was approached. In addition, De Cort, et al.[21] observed in normal healthy subjects, that blood pressure and afterload change immediately following an increase in exercise workload, however the time course of the changes in blood pressure response was very long compared to those from cardiac output and $\dot{V}O_2$ due to the rapid decrease in afterload, implying a close and probably neurogenic link between increased exercise level and dilatation of blood vessels in the exercising muscles, followed by a subsequent slower time course of afterload changes that may reflected an initial neurogenic component in the decrease in peripheral resistance followed by a more slowly developing metabolic component. Consequently, one possible explanation for our slow age-related Φ_{II} $\dot{V}O_2$ kinetics, and also for the low OG Φ_{II} total amplitude in both the $\dot{V}O_2$ and the $\dot{V}CO_2$, could be in term of this mechanistic implication of a slowed muscle blood flow progressively as maximal work rate was approached26 probably due to a fast age related on-transient arterial contraction[12] suggesting and age-related decline in the regulatory signals to control the intracellular calcium concentration in the vascular reactivity.[27,28] Evermore, in one study on the heart function with either exercise training or phenylalkylamine calcium channel blocker, verapamil, and the consequent effect on $\dot{V}O_2$[29] it was observed increasing ventricular preload with either exercise training or calcium channel blockade that was coincident with faster $\dot{V}O_2$ kinetics (τ) and increased $\dot{V}O_{2max}$ in sedentary elderly individuals; however, even verapamil is a central or cardiac acting drug that did not changed blood pressure in that subjects´ study[29] it is possible to expect some peripheral effect on vascular conductance as exercise should did some how, "counteracting" some age- related decline in the regulatory signals to control the intracellular calcium concentration in the vascular reactivity. Consequently, these calcium channel blockade that was coincident with faster $\dot{V}O_2$ kinetics and increased $\dot{V}O_{2max}$ in sedentary elderly individuals[29] agreed with the a fast age related on-transient arterial contraction[12] suggesting age- related decline in the regulatory signals to control the intracellular calcium concentration in the vascular reactivity[27,28] as one of the causal factors of our slow age-related Φ_{II} $\dot{V}O_2$ kinetics observed in this study. Evermore, probably this fast age related on-transient arterial contraction contributes to make a peripheral entropic barrier sensible different in old compared with young subjects, by changing the tissues metabolic entropic potential in terms of protein-protein thermodynamic interactions because of significant entropic solvatation changes in the body fluids.[7]

We explain in part an slow age-related Φ_{II} HR kinetics because it agrees with the observation that cardiac output is a non-linear function of $\dot{V}O_2$ during ramp-incremental exercise because while the kinetics of cardiac output are faster than those of $\dot{V}O_2$ they progressively symmetry as work rate and $\dot{V}O_2$ increases.[30] Evermore, the slow- age related Φ_{II} MRT in HR was in agreement with both the high OG $\Delta HR/\Delta\dot{V}O_2$ and the negative relationship between OG $\Delta HR/\Delta\dot{V}O_2$ and $\dot{V}O_{2peak}$ because they are significantly influenced by the ageing process.[4] Besides, multi fractal analysis of ageing (and in heart failure pacients) in

heartbeat time series studies showed an age-related monofractal spectrum probably due depressed neuro-autonomic control, and an age-related spectral symmetry; explained by a less dynamic complexity in terms of diminished number of responses to physical efforts, this agrees with the slow age-related Φ_{II} HR kinetics observed in this study, or emotional stress.[7]

Φ_{II} $\dot{V}O_2$ Kinetics Entropy

The Φ two $\dot{V}O_2$ kinetic S parameter is a measure of variability (kcal•°C^{-1}•s^{-1} on-transient) in the age of mass rate of change in $\dot{V}O_2$ per unit of time between two cronobiological states, young and old, during the on-transient response to an ergometric forced function of exercise. Since S is the amount of heat energy un-available for conversion into useful work[10] thus a slow exponential $\dot{V}O_2$ on-transient kinetic causes a unidirectional ("irreversible") trend of increase in entropy (increased- age related Φ two $\dot{V}O_2$ kinetic S). This increased- age related Φ two $\dot{V}O_2$ kinetic S, agrees with the general thermodynamic fact that when a system minimizes its internal energy at the same time maximizes its S, and this has been observed during kinetic studies on protein folding explicitly depending on the environment physicoquemical conditions.[7] The increased-age related Φ_{II} $\dot{V}O_2$ MRT S during ramp test in this study showed more evidence of increased-age related Φ_2 $\dot{V}O_2$ τS during submaximal exercise in the same old men[8] in agreement with comparable $\dot{V}O_2$ kinetic results between ramp test and constant work rate tests.[31] The significant increases in the OG Φ two $\dot{V}O_2$ kinetics S in our studies together with the observations of both age-related decline in vasodilatory capacity[32] and fast age-related on-transient arterial contraction,[12] suggest blood flow limitations implicated as limiting skeletal muscle energy metabolism in old adults in concerted action with an age- related diminished capacity or function (i.e., endothelium, total body water, motor unitpennia, sarcopennia) in the skeletal muscle affecting energy metabolismo[33] during a sudden increases in energy demand (slow age-related $\dot{V}O_{2M}$ kinetics in the human body) may be because of the increased body internal environmental S diminishing at the same time the body internal energy.[7] Exercise is a potent stimulus of the sympathetic system that when accompanied by blood hypo-perfusion metabolites, the chemosensitive afferent nerve fibers (muscle metaboreceptors) are activated causing a positive feedback in sympathetic nerve activity in muscle blood vessels (vasoconstriction) increasing vascular resistance in nonexercising muscles and thereby increasing blood pressure and perfusion pressure, that limits blood flow in exercising muscles[34] compromising O_2 tension and this is also in agreement with our observed increased Φ two $\dot{V}O_2$ kinetics S in the OG.

This increased age- related Φ two $\dot{V}O_2$ kinetics S, suggests a substantial O_2- related on transient slow muscle entropy energy metabolic limitation in terms of 3 kcal•°C^{-1}•s^{-1} (3.1 • 4.184 = 12.55 kJ•°C^{-1}•s^{-1}) to 4 kcal•°C^{-1}•s^{-1} (4 • 4.184 = 16.74 kJ•°C^{-1}•s^{-1}) on-transition lost in useful energy; this does not meant an efficiency problem since efficiency is similar between young and old9,31 because S is a result of an energy rate of change between to states (i.e, young towars old), and efficiency reflects basic energy metabolism yields in terms of $\dot{V}O_2$M kinetics related to phosphocreatine (PCrM) kinetics and $\dot{V}O_2$ (pulmonary) kinetics[5,35] that occurred in homeothermic conditions[10] in both young and old subjects, and efficiency is something depending only upon upper and lower working temperatures.[10] Consequently, an increased age- related Φ two $\dot{V}O_2$ kinetics S, translate into a diminished body energy capacity to keep the energy metabolism of adequate response to on-transitions in energy demands to perform work. Since the increased age-related ΦII $\dot{V}O_2$ MRT S was 3.1 kcal•°C^{-1}•s^{-1} for ramp exercise in this study (4 kcal•°C^{-1}•s^{-1} for Φ_2 $\dot{V}O_2$ τ S submaximal exercise)9 then the OG incresases from 3 to 4 units amount of heating capacity (motion towards entropy) from the energy metabolism per degree Centigrade and per unit of time; in other words, this suggests a slowing age-related in molecular motion to perform work but towards entropy because thermodynamically speaking this heat is just the total energy in the random motion,[10] meaning that three to four units of $\dot{V}O_2$ on-transient kinetics of entropy has been added from young state to the old one cronobiological- ergometric transition. The 3 to 4 amount of heat energy un-available for conversion into useful work in the OG is the "heat energy added in some positive quantity" for a given lost of information implicit in this increased S age-related. This age related-increased Φ_{II} $\dot{V}O_2$ MRT S agreed with the Boltzmann´s formula of entropy that S increases with time.[10] Evermore, because total body water diminishes during the ageing process,[36] and the kcal (Calorie) is the amount of heat that causes the temperature of one kg of water (a highest heat capacity molecule) to raise one degree Centigrade or to increase the water entropy by one unit,[37] it follows that OG could resists less any change of matter motion towards an increase in entropy in terms of kcal•°C^{-1}•s^{-1}. Perhaps this is why also there is a progressively slowing in body motion during the ageing process[36] to death. Finally, since both the Φ_2 $\dot{V}O_2$ Φ for submaximal exercise and the ΦII $\dot{V}O_2$ MRT for ramp test, mathematically describe the profile of the transition non-steady-state pe-

riod during which physiological adaptations adjust to meet the increased metabolic demand, reflecting the response of the hemato-cardiovascular system and muscle mass to a step up in external work rate, then the Φ two $\dot{V}O_2$ kinetics S seem to be another fundamental parameter to specify the age- related energy lost in the study of the transient response of gas exchange kinetics during ergometric forcing functions exercise.

The potential clinical implications from these studies suggest that there is need for caution when exercise training or physical rehabilitation regimens in elderly people are applied for clinical interest; because for that purposes it should be considered both, the peripheral-limb vascular function to whole-body cardiovascular health as an integral medical evaluation and exercise prescription intervention in aged population.

CONCLUSIONS

The ramp test on-transient phase two of both the $\dot{V}O_2$ kinetics (Φ_{II} $\dot{V}O_2$ MRT) and HR kinetics (Φ_{II} HR MRT) were age-related, accompanied with 3.1 kcal•°C^{-1}•s^{-1} $\dot{V}O_2$ kinetics entropy (Φ_{II} $\dot{V}O_2$ MRT S) for ramp exercise, meaning that old adults could thermodynamically resists less the energy-transitions and thus increase their entropy in terms of kcal•°C^{-1}•s^{-1}.The amount of heat energy un-available for conversion into useful work in the human body increases with ageing, and the human body does it with ageing by slowing down both the pulmonary $\dot{V}O_2$uptake and the heart rate on-transient kinetics during ergometric exercise.

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