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Factors determining the time course of $\dot{V}O_{2\,max}$ decay during bedrest: implications for $\dot{V}O_{2\,max}$ limitation

C. Capelli · G. Antonutto · M. Azabji Kenfack ·
M. Cautero · F. Lador · C. Moia · E. Tam ·
G. Ferretti

Abstract The aim of this study was to characterize the time course of maximal oxygen consumption ($\dot{V}O_{2\,max}$) changes during bedrests longer than 30 days, on the hypothesis that the decrease in $\dot{V}O_{2\,max}$ tends to asymptote. On a total of 26 subjects who participated in one of three bedrest campaigns without counter-measures, lasting 14, 42 and 90 days, respectively, $\dot{V}O_{2\,max}$ maximal cardiac output ($\dot{Q}_{max}$) and maximal systemic O_2 delivery ($\dot{Q}aO_{2max}$) were measured. After all periods of HDT, $\dot{V}O_{2\,max}$, $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ were significantly lower than before. The $\dot{V}O_{2\,max}$ decreased less than $\dot{Q}_{max}$ after the two shortest bedrests, but its per cent decay was about 10% larger than that of $\dot{Q}_{max}$ after 90-day bedrest. The $\dot{V}O_{2\,max}$ decrease after 90-day bedrest was larger than after 42- and 14-day bedrests, where it was similar. The $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ declines after 90-day bedrest was equal to those after 14- and 42-day bedrest. The average daily rates of the $\dot{V}O_{2\,max}$, $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ decay during bedrest were less if the bedrest duration were longer, with the exception of that of $\dot{V}O_{2\,max}$ in the longest bedrest. The asymptotic $\dot{V}O_{2\,max}$ decay demonstrates the possibility that humans could keep working effectively even after an extremely long time in microgravity. Two components in the $\dot{V}O_{2\,max}$ decrease were identified, which we postulate were related to cardiovascular deconditioning and to impairment of peripheral gas exchanges due to a possible muscle function deterioration.

Keywords Bedrest · Exercise · Maximal oxygen uptake limitation · Maximal cardiac output · Maximal cardiovascular oxygen transport

C. Capelli (✉) · G. Antonutto · M. Cautero · E. Tam
Dipartimento di Scienze e Tecnologie Biomediche,
School of Medicine, University of Udine,
P.le M. Kolbe 4, 33100 Udine, Italy
e-mail: ccapelli@makek.dstb.uniud.it

C. Capelli · G. Antonutto
M.A.T.I. Center of Excellence, University of Udine,
P.le M. Kolbe 4, 33100 Udine, Italy

M. A. Kenfack · F. Lador · C. Moia · G. Ferretti
Département de Physiologie,
Centre Médical Universitaire,
1 rue Michel Servet, 1211 Genève 4, Switzerland

G. Ferretti
Dipartimento di Scienze Biomediche e Biotecnologie,
School of Medicine, University of Brescia,
V.le Europa 11, 25100 Brescia, Italy

Introduction

Maximal oxygen consumption ($\dot{V}O_{2\,max}$) is reduced by bedrest and its reduction is greater the longer the bedrest duration (Convertino 1996). However, the time course of the $\dot{V}O_{2\,max}$ change induced by bedrest is still unclear for two reasons: (1) most of the bedrest studies carried out so far lasted less than 1 month, which is insufficient to establish a time course of the $\dot{V}O_{2\,max}$ change, and (2) very scarce data exist for repeated $\dot{V}O_{2\,max}$ measurements at various times during bedrest on the same subjects, and only for bedrest duration of 20 and 30 days (Georgievskiy et al. 1966; Greenleaf et al. 1989).

On the basis of a transversal analysis of data from bedrests lasting 7–30 days, Convertino (1996, 1997) proposed a linear decrease of $\dot{V}O_{2\,max}$ with bedrest, with a daily rate of decay of about 1%. With such decay, however, $\dot{V}O_{2\,max}$ would reach zero (100% loss)

within 122 days. This time interval is much shorter than the duration of long-term space missions. Thus, the change in $\dot{V}O_{2max}$ with bedrest duration cannot be linear, but must tend to an asymptote.

With this notion in mind, the aim of the present study was to gain a better understanding of the time course of the $\dot{V}O_{2max}$ changes in bedrests of duration longer than 30 days. The pursuit of this aim was made possible by having had the opportunity of measuring $\dot{V}O_{2max}$ and maximal cardiac output ($\dot{Q}_{max}$) with the same protocols and procedures, after three bedrest campaigns, without countermeasures of increasing duration, up to 90 days.

Methods

Subjects

A total of 26 healthy young male subjects were investigated in three head-down-tilt (HDT, $-6°$ incline) bedrest experimental campaigns, lasting 14, 42 and 90 days, respectively. Their repartition in the three studies, and their anthropometric characteristics, referring to the pre-bedrest condition, are reported in Table 1. None of the subjects underwent physical or pharmacological countermeasures during the bedrest period. None of the subjects were taking cardiovascular medication at the time of the study and all subjects were non-smokers. The subjects underwent a cardiopulmonary stress test during the selection process.

Study designs and methods were approved by the local ethical committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Toulouse) (90- and 42-day bedrest campaigns) and by the ethical committee of the School of Medicine of the University of Udine, Italy (14-day bedrest). All the subjects were informed about the aims of the investigation and the methods applied in the experiments and signed a written informed consent. The data obtained in occasion of the 42-day bedrest were previously published (but not those of the 14- and 90-day bedrests) (Ferretti et al. 1997).

Table 1 Anthropometric characteristics (mean ± SD) of the subjects participating in the study

Bed rest duration (days)	n	Age (years)	Body mass (kg)	Stature (cm)
14	10	24 ± 3.5	78 ± 7.7	182 ± 5.6
42	7	28 ± 1.0	74 ± 3.3	176 ± 1.0
90	9	32 ± 3.6	71 ± 5.4	173 ± 3.0

Study design

Experimental campaigns were organized by the European Space Agency in co-operation with national space agencies. The 42- and 90-day bedrest campaigns took place in Toulouse, France, the former at the Hôpital Purpan in 1994, the latter at the Clinique de l'Espace, Institut de Médecine Spatiale, Hôpital Rangueil, in 2001–2002. The 14-day bedrest was organized in Cologne, Germany at the Aerospace Medicine Institute and was completed over the biennium 2001–2002.

Each bedrest consisted of three different phases: (1) baseline control experiments before bedrest; (2) a period of head down bedrest ($-6°$) without countermeasure: no deviations from the lying position were permitted and neither exercise nor muscular contraction tests were allowed during this period; (3) final experiments after bed rest. Exercise testing after bedrest was performed on day 1, 4 and 3 after reambulation for the 14-, 42- and 90-day bedrests, respectively. For further details on the overall design of the three bedrests the reader is kindly referred to previous papers (Belin de Chantemèle et al. 2004; Biolo et al. 2004; Ferretti et al. 1997).

Protocol

An intermittent graded protocol for $\dot{V}O_{2max}$ determination was used in the three bedrest campaigns. $\dot{V}O_{2max}$ was determined during graded exercise on the cycle ergometer. The lowest power was 50 W. Power was then progressively increased by 50-W steps. The step increase was reduced to 25 W as the individual maximum was approached. The lowest sub-maximal workloads lasted 7 min. As the workload increased, the exercise duration was reduced because the time spent for measuring $\dot{Q}$ was shortened by increasing breathing rate. $\dot{V}O_2$ and heart rate (f_H) were determined at the steady state, during the 6th minute of each work load. Steady-state $\dot{Q}$ was determined immediately after the measurement of $\dot{V}O_2$. Successive work loads were separated by 5 min recovery intervals, during which blood samples were taken at min 1, 3 and 5 for the determination of blood lactate concentration ($[La]_b$).

Individual $\dot{V}O_{2max}$ was established from the plateau attained by the relationship between $\dot{V}O_2$ and power above a given power. If such a plateau was not observed, subsidiary criteria for $\dot{V}O_{2max}$ establishment were (1) a lack of increase in f_H between successive work loads ($\Delta f_H < 5$ min^{-1}); and (2) $[La]_b$ values higher than 10 mM. The maximal aerobic power ($\dot{w}_{max}$) was then calculated as the minimal power requiring a $\dot{V}O_2$ equal to $\dot{V}O_{2max}$. The highest

individual measured steady state $\dot{Q}$ value was retained as the maximal cardiac output ($\dot{Q}_{max}$) for that subject. This corresponded in all cases to a $\dot{Q}$ value attained at the power requiring a $\dot{V}O_2$ equal to $\dot{V}O_{2max}$. The corresponding O_2 flow in arterial blood (systemic O_2 delivery at maximal exercise, $\dot{Q}aO_{2max}$) was then computed as described below.

Methods and techniques

Exercise was carried out either on an electrically braked cycle-ergometer (Ergometrics 800-S, Ergoline, Germany) (42- and 90-day bedrest) or on a mechanically braked ergometer (14-day bedrest) whose work load was independent of the pedalling frequency (Monark 839E, Sweden).

In the 42-day bedrest, $\dot{V}O_2$ at rest and at exercise steady state was computed by standard expiratory mass balance equations. CO_2 output ($\dot{V}CO_2$) and pulmonary ventilation ($\dot{V}_E$) were also calculated. During the 5th minute of each workload, expired gas was collected into Douglas bags and subsequently analysed for gas composition and volume. A paramagnetic O_2 analyser (Oxynos 1-C, Leybold Haereus, Germany), an infrared CO_2 analyser (LB-2, Leybold-Heareus, Germany) and dry gas meter (Singer DTM 15, Wellesley, MA, USA) were employed (Ferretti et al. 1997).

In the 14- and 90-day HDT bedrest, breath-by-breath $\dot{V}O_2$ was determined at alveolar level from respiratory gas fractions and ventilatory flow recorded at the mouth (Grønlund 1984, Capelli et al. 2001). N_2, CO_2 and O_2 fractions were measured in continuo by means of quadrupole mass spectrometers (Airspec 2200, UK at Cologne, Balzers Prisma, Liechtenstein at Toulouse). Respiratory air flows were measured by means of ultra-sound flow transducers (Tuba, GHG, Switzerland at Cologne, and Spiroson, Eco Medics, Switzerland at Toulouse). Mass spectrometers and flow transducers were calibrated before and after each experimental run by means of certified gas mixtures and by means of a 3-l syringe, respectively (Hans Rudolph, Kansas City, MO, USA). The recorded data were digitalized by means of a 16-bit A/D converter (MP100 or MP150 WS, Biopac Systems, Santa Barbara, CA, USA) operated by a commercial software (ACK100W, Biopac Systems) running on PC. A computerized numerical procedure implemented under Labview environment (National Instruments, Austin, TX, USA) and running on PC was used to compute breath-by-breath $\dot{V}O_2$ off-line. Resting and exercise steady-state $\dot{V}O_2$ were then calculated by averaging breath-to-breath $\dot{V}O_2$ values over 1 min.

The f_H was monitored either by means of a short-distance telemetry cardiotachometer (Polar 3000, Polar Electro, Finland) or by electrocardiography (Elmed, ETM, Germany).

In the 14- and 90-day bedrest studies, $\dot{Q}$ was determined by means of an open circuit acetylene technique (Barker et al. 1999). To this aim, the subject breathed a gas mixture containing 21% O_2, 6% He, 1.5% C_2H_2, balanced with nitrogen until equilibration. Gas concentrations while breathing the mixture were continuously monitored by mass spectrometry. Inspired and expired gas volumes were determined by the ultrasonic flow meters. The inspired gas mixture was administered from a high-pressure gas cylinder via 50 l Douglas bag buffers. The gas flow from the cylinders was adjusted to the subject's ventilation. For each subject, the partition coefficient for acetylene was determined separately by mass spectrometry (Meyer and Scheid 1980), on a 5 ml venous blood sample. The recorded data were digitalized as described before.

During the 42-day bedrest campaign, $\dot{Q}$ was determined from f_H and stroke volume measurement (Q_H). The latter was measured by means of the pressure-pulse contour method (Antonutto et al. 1995). To this aim, arteriolar blood pressure profile was continuously monitored by means of a Finapres device (Ohmeda, Englewood, CO, USA). The photo-plethysmographic cuff of the Finapres was applied to the middle phalanx of the middle finger of the right hand. The pressure profiles were recorded on a magnetic tape, digitalized (MP100 WS, Biopac Systems) and subsequently analysed by a PC (ACK100W, Biopac Systems). Calibration of the area described by blood pressure profiles was performed at rest, as previously described (Ferretti et al. 1997).

Blood hemoglobin concentration ([Hb]) was measured by a photometric technique (HemoCue, Sweden) on 10 μl blood samples from an earlobe. Arterial O_2 saturation (S_aO_2) was measured by infrared oximetry (Ohmeda 2350 Finapres, Englewood, CO, USA for the 42- and 90-day bedrests and Siemens MicrO$_2$, Denvers, MA, USA for the 14-day bedrest). $\dot{Q}aO_{2max}$ was finally calculated as

$$\dot{Q}aO_2 = \dot{Q}S_aO_2[\text{Hb}]\sigma \tag{1}$$

where constant σ is the physiological O_2 binding coefficient of hemoglobin (1.34 ml g^{-1}).

Blood lactate concentration in arterialized capillary blood was assessed by means of an electro-enzymatic method (ESAT 6661 Lactat, Eppendorf, Germany for the 42- and 90-day bedrests) or by means of a

colorimetric method (Accusport, Boeheringer, Germany for the 14-day bedrest).

Statistics

Mean values were reported along with their standard deviations (SD). Linear regressions were calculated by using the least square methods. Mean values before and after bedrest were compared by means of the non-parametric signed Wilcoxon rank test. Comparison of data among different bedrests was performed by means of the non-parametric Kruskall–Wallis test. When applicable, a Bonferroni post-hoc test was used to locate significant differences. The level of significance was set at $P < 0.05$ (two-tail test).

The time course of the change of $\dot{V}O_{2max}$ expressed relative to the values observed before bedrest set equal to 100%, was modelled as a function of bedrest duration by means of a bi-exponential function describing the slow and fast component of the time course. The equation was of the form $y = A_1e(-t/\tau_1) + A_2e(-t/\tau_2)$ where A_1 and A_2 are the amplitude, τ_1 and τ_2 represent the time constants of the fast and slow component, respectively. The parameters of the model were calculated by using an iterative, non-linear estimating

procedure (Carson et al. 1983) implemented in the statistical software Statistica for Macintosh (StatSoft, Tulsa, Ok, USA).

Results

The average values of all investigated parameters at maximal exercise, assessed before and after bedrests are reported in Table 2. Before bed rest, $\dot{V}O_{2max}$ was the same in the three studies. After all three bedrests, $\dot{V}O_{2max}$ decreased by about 14, 16 and 32% in comparison with the pre-bedrest control values from the shortest to the longest bedrest. $\dot{w}_{max}$ values were significantly lower than before bedrest and the decrease in $\dot{w}_{max}$ was proportional to that in $\dot{V}O_{2max}$. Cardiac output at maximal exercise ($\dot{Q}_{max}$) dropped by 23, 30 and 23% after the three periods of bedrest. The average values before and after the bedrests of 42 and 90 days were computed only on five out of seven and six out of nine subjects, respectively, since only in these cases it was possible to obtain, for technical reasons, both pre and post $\dot{Q}_{max}$ data. The decrease in $\dot{V}O_{2max}$ was less than that in $\dot{Q}_{max}$ after the two shortest bedrests, whereas it was not the case after the 90-day

Table 2 Mean values (± SD) of maximal oxygen uptake ($\dot{V}O_{2max}$) maximal cardiac output $\dot{Q}_{max}$) maximal heart rate (f_{Hmax}) and maximal oxygen delivery ($\dot{Q}aO_{2max}$) together with lactate concentration ([La]$_b$), mechanical power ($\dot{w}_{max}$) haemoglobin concentration ([Hb]) and per cent saturation of

oxyhaemoglobin (Sat[HbO$_2$]) at $\dot{V}O_{2max}$ before and after 14, 42 and 90 days of head down tilt bedrest. Significances of the differences between pre and post-bedrest conditions, (P values) and average values of per cent decrease are also reported

| Parameter	HDTBR	Before	After	P	Change (%)
$\dot{V}O_{2max}$ l min^{-1}	14	2.80 ± 0.37	2.43 ± 0.31	< 0.05	− 13.9 ± 9.3
	42	2.83 ± 0.20	2.36 ± 0.13	< 0.05	− 15.9 ± 5.4
	90	2.81 ± 0.36	1.90 ± 0.31	< 0.05	− 32.4 ± 6.8
$\dot{Q}_{max}$ l min^{-1}	14	25.3 ± 2.41	19.4 ± 3.04	< 0.05	− 22.8 ± 12.3
	42	23.7 ± 2.42	16.4 ± 1.44	< 0.05	− 29.6 ± 5.0
	90	19.7 ± 3.18	15.3 ± 2.16	< 0.05	− 22.7 ± 7.2
$\dot{Q}aO_{2max}$ l min^{-1}	14	5.6 ± 0.87	4.3 ± 0.86	< 0.05	− 22.6 ± 14.2
	42	5.4 ± 0.77	3.5 ± 0.48	< 0.05	− 34.4 ± 5.6
	90	4.3 ± 0.73	2.9 ± 0.22	< 0.05	− 29.8 ± 9.8
$\dot{w}_{max}$ W	14	225 ± 27.6	175 ± 26.3	< 0.05	− 21.9 ± 10.2
	42	229 ± 17.8	186 ± 11.3	< 0.05	− 17.8 ± 2.1
	90	199 ± 25.0	136 ± 19.9	< 0.05	− 31.8 ± 8.1
f_{Hmax}, min^{-1}	14	188 ± 3.8	183 ± 11.0	NS	− 2.8 ± 5.7
	42	194 ± 1.5	194 ± 2.3	NS	− 0.4 ± 0.9
	90	187 ± 6.5	188 ± 8.5	NS	+ 0.7 ± 1.9
[La]$_b$, mM	14	11.9 ± 3.50	10.0 ± 1.54	NS	− 9.3 ± 32.0
	42	12.0 ± 0.57	11.2 ± 0.68	NS	− 6.9 ± 3.4
	90	10.1 ± 0.93	9.1 ± 2.15	< 0.05	− 6.9 ± 20.8
[Hb], g l^{-1}	14	170.1 ± 2.7	166.5 ± 10.6	NS	− 1.9 ± 5.3
	42	173.3 ± 5.3	156.9 ± 4.9	< 0.05	− 9.3 ± 2.1
	90	174.0 ± 9.2	159.6 ± 10.9	< 0.05	− 8.2 ± 7.0
Sat[HbO$_2$], %	14	95 ± 0.4	97 ± 0.2	NS	+ 1.0 ± 0.05
	42	94 ± 2.8	97 ± 0.8	< 0.05	+ 3.3 ± 3.38
	90	97 ± 0.4	98 ± 0.8	NS	+ 1.0 ± 0.04

bedrest. Observed per cent decreases of maximal oxygen delivery ($\dot{Q}aO_{2max}$) amounted to about 23, 34 and 30% from the shortest to the longest bedrest, respectively. After all three studies, maximal f_H was the same as before. $[La]_b$ after maximal exercise at the end of bedrest was equal to that before in the two shortest studies, yet it was significantly lower after the 90-day bedrest. [Hb] was significantly decreased after the two longest bedrests, although per cent saturation of oxyhaemoglobin ($Sat[HbO_2]$) at maximal exercise was identical before and after bedrests in all the cases. Thus, in these bedrests, the decrease in $\dot{Q}aO_{2max}$ was larger than that in $\dot{Q}_{max}$.

The $\dot{V}O_{2max}$ decrease after the 42-day bedrest did not differ significantly from that after the 14-day bedrest. The $\dot{V}O_{2max}$ decrease after the 90-day bedrest was significantly larger than that after the two other bedrests. The same was the case for $\dot{w}_{max}$. The $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ declines after the 90-day bedrest did not differ significantly from those after the 14- and 42-day bedrest. The greatest apparent $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ decreases were observed after the 42-day bedrest.

The average daily rates of the $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ decay during each of the three bedrests are shown in Fig. 1. The average daily rate of $\dot{V}O_{2max}$ decline decreased from 0.99% per day for the 14-day bedrest, to 0.39% per day for the 42-day bedrest and to 0.35% per day for the 90-day bed rest. $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ showed a faster average daily rate of decay than $\dot{V}O_{2max}$ in the two shortest bedrests. For $\dot{Q}_{max}$ this decay amounted to 1.63% per day for the 14-day bedrest, and 0.70% per day for the 42-day bedrest. For $\dot{Q}aO_{2max}$ it amounted to 1.61% for the 14-day bedrest, and 0.82% per day for the 42-day bedrest. In the lon-
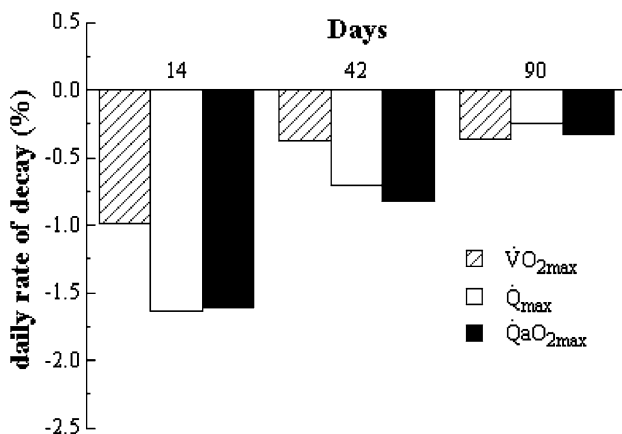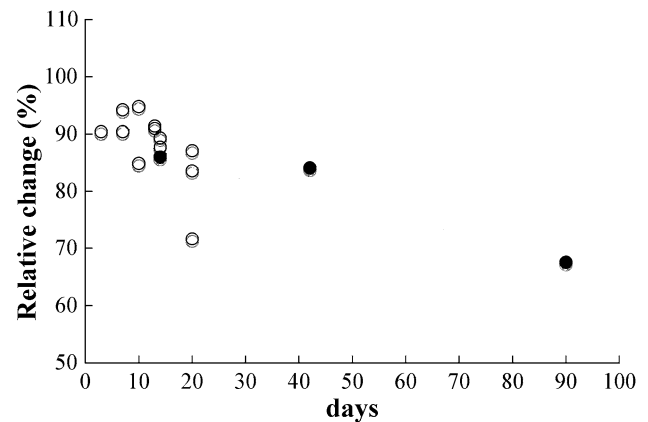
Fig. 2 Changes of $\dot{V}O_{2max}$ expressed relative to the values observed before bedrest set equal to 100%, as a function of bedrest duration in days. *Full symbols* refer to the values computed from the data obtained in the 14-, 42- and 90-day HDTBR; *empty symbols* refer to data collected from different sources in the literature (see text for more details)

gest bedrest, the decay was 0.25% per day and 0.33% per day for $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ respectively. The $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ decreases appeared to be completed within 14 days.

In Fig. 2 the changes of $\dot{V}O_{2max}$ expressed relative to the values observed before bedrest set equal to 100%, are plotted as a function of the days of bedrest. The values computed from the present data are plotted together with those by Greenleaf et al. (1989) obtained at different times during bedrest on the same subjects, and with those taken from different sources in the literature (Convertino et al. 1982; Friman 1979; Georgievskiy et al. 1966; Kakurin et al. 1966; Kashihara et al. 1994; Saltin et al. 1968; Smorawinski et al. 2001; Stremel et al. 1976; Taylor et al. 1949; Trappe et al. 2006, White et al. 1966). The bi-exponential function describing the changes of $\dot{V}O_{2max}$ as a function of bedrest duration was characterized by a fast component, with an amplitude of 10.2% and a time constant of 9.1 days, and by a slow phase, with an amplitude of 88.3% and a time constant of 327 days.

Discussion

In this study, $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ were determined for the first time after a bedrest as long as 90 days. The observed $\dot{V}O_{2max}$ decrease was 32.4%, which is larger than after the two shorter bedrests, but definitely less than predicted by a mere extrapolation from the percent changes in $\dot{V}O_{2max}$ observed after the 14-day bedrest. The same was the case for $\dot{Q}_{max}$ and

Fig. 1 Average daily rates of decay of maximal oxygen uptake ($\dot{V}O_{2max}$) maximal cardiac cardiac output ($\dot{Q}_{max}$) and maximal oxygen delivery ($\dot{Q}aO_{2max}$) observed after the 14, 42 and 90 days of bedrest

$\dot{Q}aO_{2max}$ whose changes did not differ significantly with the bedrest duration from 14 days on.

The results of the present study demonstrate that the rate at which $\dot{V}O_{2max}$ decreases during bedrest becomes progressively smaller as the time of bedrest is prolonged. This is shown by (1) the similar $\dot{V}O_{2max}$ decrement after 14- and 42-day bedrests, and (2) the reduction of the average daily rate of $\dot{V}O_{2max}$ decrease with bedrest duration. The latter finding indicates that most of the $\dot{V}O_{2max}$ decrease occurs within the first 2 weeks of bedrest, the remainder taking place slowly and progressively toward the 90th day.

Greenleaf et al. (1989) reported data of $\dot{V}O_{2max}$ obtained on four subjects at days 7, 14, 21 and 29 of bedrest. Despite the small number of subjects, and despite the fact of having been obtained in supine rather than upright posture, their data compare well with the present ones. The greatest average daily rate of $\dot{V}O_{2max}$ decrease in their study occurred during the 1st week of bedrest (–1.37% per day), to slow down progressively in the following weeks. Their figure for the $\dot{V}O_{2max}$ change on day 14 (–10.7%) was similar to that observed in the present study for the same bedrest duration (–13.9%, see Table 2).

These findings suggest the $\dot{V}O_{2max}$ decrease with bedrest tends toward an asymptote, as hypothesized. Thus, they contradict the concept of a linear $\dot{V}O_{2max}$ decrease with time during bedrest proposed by Convertino (1996, 1997). They rather suggest the possibility of attaining and likely maintaining steady, but low $\dot{V}O_{2max}$ values during very long sojourns in microgravity. Similarly, the changes in $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ from the present study showed a more marked decrease during the early phase of bedrest, with a clear tendency to slow down and stabilize for longer bedrest duration. Indeed, the percent changes of $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$ were the same after all three bedrests.

Our postulate is that the fast component of the $\dot{V}O_{2max}$ decrease during bedrest is related to the reduction of $\dot{Q}aO_{2max}$ consequent to the reduction of both $\dot{Q}_{max}$ and [Hb], whereas the slow component accompanies the impairment of peripheral gas exchange, likely associated, at least in part, to the development of muscle hypotrophy.

In a previous paper (Ferretti et al. 1997), it was demonstrated that the decrease in $\dot{V}O_{2max}$ due to bedrest results from the simultaneous action of at least two factors: the decrease in cardiovascular oxygen transport, and the decrease in muscle oxidative capacity, which parallels the decrease in muscle mass. It is now clear that these two factors follow different time courses during bedrest. In fact a transversal

analysis of the CSA data from different sources in the literature (Ferretti 1997) and of the present subjects after the 42- and 90-day bedrests (Ferretti et al. 1997; Trappe et al. 2004), provided a calculated time constant of CSA decay (128 days) that was much slower than that for $\dot{Q}_{max}$ and $\dot{Q}aO_{2max}$: in fact in the present study both these parameters underwent only minor changes after only 14 days of bedrest. On this basis it is legitimate to postulate that the time course of the $\dot{V}O_{2max}$ changes during bedrest ought to be characterized by at least two components, one fast related to changes in $\dot{Q}aO_{2max}$ the other slow, dictated by the decrease in muscle oxidative potential. Thus, in this study, the decrease of $\dot{V}O_{2max}$ expressed as relative change of the initial value set equal to 100%, was modelled by means of a bi-exponential model with no time delays. The bi-exponential model was characterized by larger r^2 than the simpler mono-exponential model (0.69 vs. 0.61), its residuals distribution was closer to normality and showed a smaller standard deviation (4.5 vs. 4.6) than that of the mono-exponential model. Both these statistical results support the postulate behind the present analysis. Whereas the calculated time constant of the fast component accurately described the time course of the cardiovascular changes induced by bedrest, the time constant of the slow component turned out to be about 11 months long, that is some two and half times more than the calculated time constant for muscle CSA (see above). The paucity of reliable data on long-term bedrests, and its restriction to a time span of less than 90 days implies that the value of the slower time constant estimated on this occasion resulted from extrapolation rather than interpolation of data, and thus should be considered with a pinch of salt. However, despite to these intrinsic limitations, modelling the $\dot{V}O_{2max}$ changes by using a complex time course seems to be legitimate and suggests a multifactorial set of causes for the observed decay of the maximal aerobic power.

Yet the strongest argument in favour of a multifactorial origin of the $\dot{V}O_{2max}$ decrease during bedrest comes from an analysis of the factors that limit $\dot{V}O_{2max}$ (di Prampero 1985; di Prampero and Ferretti 1990). The algebraic solution of this model, for the case in which only the cardiovascular resistance to oxygen flow (R_O) is changed, is given by the following equation :

$$\dot{V}O_{2max}/(\dot{V}O_{2max}+\Delta\dot{V}O_{2max})=1+F_Q(\Delta R_Q/R_Q) \quad (2)$$

where F_Q is the fractional limitation to $\dot{V}O_{2max}$ imposed by cardiovascular oxygen transport. Equation 2 implies that the ratio between the absolute $\dot{V}O_{2max}$ value before and after bedrest is linearly

related to the relative change in R_Q, the y-intercept being equal to 1 and the slope to F_Q. This relationship for the present data is shown in Fig. 3, where the ratio $\Delta R_Q/R_Q$ is estimated from the changes in $\dot{Q}aO_{2max}$. The individual values from the three bedrests are superimposed to the theoretical line for $F_Q = 0.7$ (di Prampero and Ferretti 1990). Whereas the values after the 14- and 42-day bedrests are symmetrically distributed around the theoretical line, the values for the 90-day bedrest are displaced upward with respect to the theoretical line. Likewise, an analysis of residuals, obtained as the difference between theoretical and actual $\dot{V}O_{2max}$ decays for the corresponding changes in R_Q, shows that the theoretical line is a fairly good predictor of the data obtained from the 14- and 42-day bedrests (residuals equal to -0.002 ± 0.153 and -0.050 ± 0.165, respectively, both being not significantly different from 0), but not of those from the 90-day bedrest (residuals equal to 0.333 ± 0.248, $P < 0.05$). Since the theoretical line applies to $\dot{V}O_{2max}$ changes induced by a modification of a single resistance to oxygen flow, the discordance between this line and the data obtained after the 90-day bedrest indicates that additional factors beyond cardiovascular oxygen transport are to be taken into account to explain the observed decay in $\dot{V}O_{2max}$.
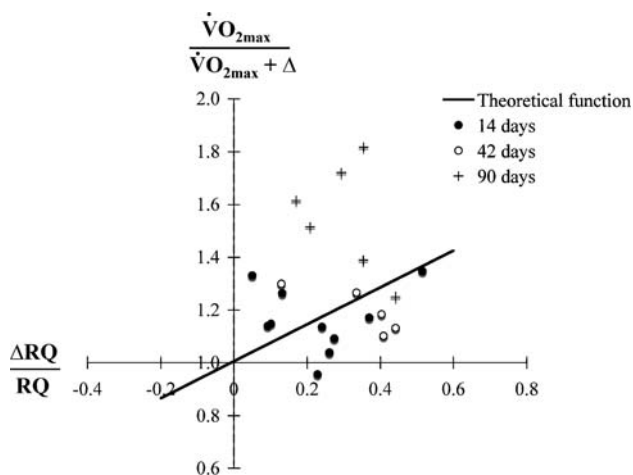
Fig. 3 Changes in maximal oxygen consumption ($\dot{V}O_{2max}$ expressed as the ratio between the values before and after bedrest) as a function of the calculated relative changes in the cardiovascular resistance to $\dot{V}O_{2max}$ (R_Q). Data refer to the three bedrest campaigns, as indicated (14 days, $n = 10$, 42 day, $n = 5$, 90 day, $n = 6$). The line is theoretical and has a slope of 0.70, corresponding to the fractional limitation imposed by the cardiovascular system (F_Q) reported by di Prampero and Ferretti (1990) for humans at sea level. Whereas the points for the 14- and 42-day bedrest lie around the theoretical line, the data for the 90-day bedrest do not: in this case the change in $\dot{V}O_{2max}$ is greater than predicted by assuming changes in R_Q only

Assuming that the lungs do not limit $\dot{V}O_{2max}$ in healthy subjects who do not desaturate at sea level (di Prampero and Ferretti 1990), the overall limitation of $\dot{V}O_{2max}$ is imposed by cardiovascular oxygen transport, which sets R_Q, and by peripheral oxygen diffusion and utilization, setting the peripheral resistance (R_p) in-series with R_Q. The overall resistance to oxygen flow downstream the lungs (R_{TOT}) is thus equal to :

$$R_{TOT} = R_Q + R_p = (F_Q R_{TOT}) + (F_p R_{TOT}) \qquad (3)$$

where F_p is the fractional limitation to $\dot{V}O_{2max}$ imposed by peripheral (muscular) factors. In turn,

$$R_{TOT} = \frac{(PaO_2 - PmO_2)}{\dot{V}O_{2max}} \qquad (4)$$

where PaO_2 is arterial O_2 partial pressure (assumed equal to 100 mmHg after 42-day bedrest, see Ferretti et al. 1997, and unchanged for longer bedrest duration), and PmO_2 is the O_2 partial pressure in the mitochondria, assumed equal to 0 (in fact lower than 3 mmHg, see Connett et al. 1986; Richardson et al. 1999, 2001). F_Q and F_p were calculated after the 42-day bedrest (Ferretti et al. 1997), and turned out to be 0.73 and 0.27, respectively. Since the decrease in $\dot{Q}aO_{2max}$ was the same after the 42- and 90-day bedrests, and since the $\dot{Q}aO_{2max}$ before bedrest was the same in all investigations (see Table 2), it follows that R_Q should be the same after the 42-day as after the 90-day bedrest. On this basis, combination of Eqs. 3 and 4 allows an estimate of R_p after the 90-day bedrest:

$$\frac{PaO_2}{\dot{V}O_{2max_{90}}} = FQ_{42} \frac{PaO_2}{\dot{V}O_{2max_{42}}} + Rp_{90} \qquad (5)$$

where subscripts 42 and 90 indicate the bedrest duration. Since $\dot{V}O_{2max}$ was lower after 90-day than after 42-day bedrest, but the O_2 gradient was the same, R_{TOT}, and thus R_p must be higher in the former than in the latter case. This is demonstrated in Table 3, where the R_{TOT}, R_Q and R_p for the 90-day bedrest, calculated by introducing in Eq. 5 the experimental mean values of the present study and the value assumed for PaO_2, are compared with the corresponding values after the 42-day bedrest. These values carry along a different fractional limitation of $\dot{V}O_{2max}$ after the 90-day bedrest with respect to the 42-day bedrest. In fact F_Q decreased from 0.73 to 0.59, whereas F_p increased from 0.27 to 0.41. These changes in F_Q and F_p mean that the impairment of peripheral gas exchange, which develops during very long bedrest, may have increased the role of peripheral (muscular) factors in limiting maximal aerobic power.

Table 3 Calculated values of (1) the total resistance to oxygen flow downstream the lungs (R_{TOT}); (2) the resistance imposed by the cardiovascular oxygen transport (R_O); (3) the peripheral resistance (R_p) after 42 and 90 days of head-down tilt bedrest and of the fractional limitations imposed to maxymal oxygen uptake by cardiovascular transport (F_O) and peripheral factors (F_p)

Duration (dd)	R_{tot} (mmHg min l^{-1})	R_O (mmHg min l^{-1})	R_p (mmHg min l^{-1})	F_O	F_p
42	42.4	30.9	11.4	0.72	0.28
90	52.6	30.9	21.7	0.59	0.41

These results have important practical implications for future long-term space missions because (1) the tendency toward an asymptote of the $\dot{V}O_{2max}$ decay demonstrates the possibility for humans to keep working effectively even after extremely long time in microgravity, and (2) specific muscular training ought to be added to countermeasures for the cardiovascular system for the entire duration of very long bedrests or space flights in order to counteract the slow decay of maximal aerobic power. Both these aspects should be taken into account in programming a future human mission to Mars.

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