Eur J Appl Physiol
DOI 10.1007/s00421-011-1917-0

ORIGINAL ARTICLE

Effects of acceleration in the G_z axis on human cardiopulmonary responses to exercise

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Received: 12 October 2010 / Accepted: 8 March 2011

Abstract The aim of this paper was to develop a model from experimental data allowing a prediction of the cardiopulmonary responses to steady-state submaximal exercise in varying gravitational environments, with acceleration in the G_z axis (a_g) ranging from 0 to 3 g. To this aim, we combined data from three different experiments, carried out at Buffalo, at Stockholm and inside the Mir Station. Oxygen consumption, as expected, increased linearly with a_g. In contrast, heart rate increased non-linearly with a_g, whereas stroke volume decreased non-linearly: both were described by quadratic functions. Thus, the relationship between cardiac output and a_g was described by a fourth power regression equation. Mean arterial pressure increased with a_g non linearly, a relation that we interpolated again with a quadratic function. Thus, total peripheral resistance varied linearly with a_g. These data led to predict that maximal oxygen consumption would decrease drastically as a_g is increased. Maximal oxygen consumption would become equal to resting oxygen consumption when a_g is around 4.5 g, thus indicating the practical impossibility for humans to stay and work on the biggest Planets of the Solar System.

Keywords Oxygen consumption · Heart rate · Cardiac output · Arterial blood pressure · Hypergravity · Microgravity

Communicated by Susan A. Ward.

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Introduction

Although humans are well adapted to Earth's gravity acceleration (9.8 m s^{-2} or 1 g), exposure to varying durations of increased or decreased acceleration in the G_z axis (a_g) may occur. A deeper understanding of the human cardiopulmonary response to submaximal and maximal exercise in varying gravitational environments has a major impact in aviation and space science in the perspective of high-speed flight and sending humans to outer sidereal bodies, or of colonizing the Moon. In fact, Astronauts who will reach outer sidereal bodies should be able to perform work when reaching them and thus be capable of exercising.

As quantitative data are not available, and difficult to generate, the aim of this paper was to develop a model to predict the cardiopulmonary responses to steady-state submaximal exercise in varying gravitational environments which may actually occur, ranging from 0 to 3 g. This is a

Published online: 25 March 2011

theoretical paper, which relies on experimental data collected by the authors either in their laboratories in hypergravity, or in microgravity during space flight.

In case of higher a_g than on Earth, the easiest way of obtaining physiological data during exercise in varying gravitational conditions is to perform experiments inside a long-radius human centrifuge equipped with a cycle ergometer. Microgravity, by contrast, can only be studied inside a space ship. Thus, experiments at higher or lower a_g than on Earth are expensive, and consequently data obtained in those conditions are scanty. The evolution of space stations in the past 20 years and the installation of equipment, including cycle ergometers and respiratory monitoring systems, have allowed acquisition of some data in microgravity, parts of which have been published (Buderer et al. 1976; Levine et al. 1996; Michel et al. 1977; Shykoff et al. 1996; Girardis et al. 1999). At high a_g, although a few papers reporting metabolic data during exercise in a spinning human centrifuge can be found (Bjurstedt et al. 1968; Nunneley and Shindell 1975; Nunneley 1976; Bonjour et al. 2010), very little is known of the cardiovascular response to exercise. Bjurstedt et al. (1968) and Bonjour et al. (2010) reported only heart rate (f_H) values during exercise at high a_g. Cardiac output ($\dot{Q}$) during increased a_g was reported by Rosenhamer (1967), Bjurstedt et al. (1974) and Pendergast et al. (1987), but the first two of these studies might have had technical limitations, the second presents data at one relative work load only (50% of maximal aerobic power at 1 *g*, without accounting for possible negative effects of a_g on maximal aerobic power), and the last is a partial preliminary report in a book chapter. Linnarsson and Rosenhamer (1968) published some mean arterial pressure ($\bar{P}$) data, but these are difficult to compare with other studies due to methodological differences.

For the present analysis, we used data obtained by the authors during the Euromir '95 long-term flight, jointly organised by European and Russian Space Agencies, and in the human centrifuge at Karolinska Institute, Stockholm, Sweden. Incidentally, both experiments were carried out at the same absolute submaximal powers and at the same pedalling frequency. Metabolic data from both studies have been previously published (Girardis et al. 1999; Bonjour et al. 2010). Cardiovascular data from the same studies are still unpublished. In addition, we used the data collected in the human centrifuge at Buffalo, USA, a preliminary report of which was previously published (Pendergast et al. 1987).

This paper is an attempt to provide preliminary answers to the following: what exercise intensity will be tolerable by Astronauts? What will their maximal aerobic power be? Which is the biggest sidereal body on which men could reasonably land and perform work? These are important questions to exploration of space and thus Space Agencies.

Origin of experimental data

Data obtained in microgravity (Euromir '95)

A total of 10 determinations of steady-state $\dot{V}_{O_2}$ and $\dot{Q}$ during submaximal dynamic leg exercise were obtained on two subjects (age 37 years and body mass before flight 75.1 kg for subject 1; age 39 years and body mass before flight 68.9 kg for subject 2), who flew onboard the Russian Space Station Mir for 6 months. Both subjects were well trained and perfectly aware of the procedures and of their implicit risks and gave their informed consent. Ethical and medical approvals for the experiments were given by the Medical Board of the European Space Agency and the Russian National Committee of Bioethics of the Russian Academy of Sciences.

Protocol

Measurements were carried out at rest and during steady-state exercise. The investigated powers were 50, 75 and 100 W. An electrically braked cycle ergometer (Innovision A/S, Odense, Denmark) was used. The pedalling frequency was 1.0 Hz. The ergometer used during the space flight was identical to that used for control experiments on Earth. Both were calibrated by the manufacturer prior to the study and were shown to maintain their calibrated power levels for longer than 1 year. At each power, rebreathing was performed at 3, 9 and 12 min of exercise. Experiments at 1 *g* were carried out 172, 116 and 73 days before the flight on both subjects. The same protocol was repeated during a 180-day flight on board the Russian Space Station Mir (0 *g*, cabin temperature during the flight ranging between 20.6 and 24.5°C, barometric pressure ranging between 710 and 788 mmHg) on days: 12, 54, 80, 122, 144 and 13, 59, 81, 117, 143 after the launch on subject 1 and 2, respectively. Thus, for each power output, a total of six and ten observations could be performed at 1 and 0 *g*, respectively. However, only the first two measurements at 0 *g* were retained for the present analysis, in order to avoid interferences from possible effects of muscle hypotrophy on maximal O_2 consumption (Capelli et al. 2006).

Methods

Steady-state $\dot{V}_{O_2}$ was measured by a closed circuit method during rebreathing, and $\dot{Q}$ by a CO_2 rebreathing method (Farhi et al. 1976). The rebreathing bag was filled with a

mixture containing CO_2, a soluble (N_2O) and an insoluble (SF_6) inert gas, balanced with N_2. This mixture was diluted with ambient air using a calibrated syringe to spare gas during the flight. The initial O_2 fraction in the bag ranged between 0.326 and 0.375. The volume of the rebreathing bag was empirically established prior to the first experiment; it was increased with the exercise power output and ranged between 2.5 and 3.5 l. During rebreathing, the dry fractions of breathed gases at the mouth were continuously monitored by a photo-acoustic gas analyser (RMS-II, Innovision A/S, Odense, Denmark), stored on a magnetic disk and subsequently analysed by means of the Matlab computation software (Mathworks, USA). The knowledge of bag volume and initial bag SF_6 fraction allowed computation of the overall closed circuit volume, using the dilution principle, as previously described (Girardis et al. 1999). $\dot{V}_{O_2}$ was then computed from the slope of the linear relation between the O_2 volume in the rebreathing bag at end of each expiration and the rebreathing time, as previously described (Girardis et al. 1999). In all experiments, three rebreathing manoeuvres were performed during the exercise steady-state. Application of this procedure provided at least two valid $\dot{V}_{O_2}$ measurements at each power output, which were then averaged. The steady-state $\dot{Q}$ was obtained from off-line analysis of the CO_2 fraction traces at the mouth immediately before and during the rebreathing manoeuvre (Farhi et al. 1976). Computation was performed using the Matlab computation software (Mathworks, USA).

Continuous recordings of arterial pulse pressure were also obtained at a fingertip of the right arm by means of a non-invasive cuff pressure recorder integrated in the RMS-II system. Within each cardiac cycle, the values corresponding to systolic and diastolic blood pressure were retained. Beat-by-beat $\bar{P}$ was computed as the integral mean of each pressure profile. The mean steady-state f_H and $\bar{P}$ values were obtained during the 5th min of exercise. Q_{st} was calculated as the ratio of $\dot{Q}$ to f_H. The steady-state gas exchange ratio (R) was calculated from the time course of O_2 and CO_2 fractions at the mouth during regular breathing, by means of the alveolar gas equations (Otis 1964). For this purpose, the O_2 and CO_2 traces were recorded between the second and the third rebreathing manoeuvres. End-tidal gas fractions were assumed to be equivalent to alveolar gas fractions. The average steady-state $\dot{V}_{CO_2}$ was calculated by multiplying R times the corresponding average $\dot{V}_{O_2}$ value.

Data obtained in hypergravity at Karolinska institute

These data were obtained during experiments carried out on 14 young healthy subjects (characteristics reported in Bonjour et al. 2010) in the human centrifuge of Karolinska Institute, Stockholm, Sweden.

Protocol

The subjects sat in a seat inside the centrifuge gondola, which could be adjusted to be perpendicular to the resultant of the normal G vector and the centrifugal G vector. They were secured on the seat by a five-point safety belt. The feet were fixed on an electrically braked cycle ergometer (Model 380, Siemens-Elema, Sweden) that was located in front of the seat. The ergometer adjusted the force to compensate for changes in frequency, so to keep the workload constant. The ergometer was calibrated by the manufacturer just before the start of the experiments. A signal proportional to the power was recorded continuously. The crank axis was at the level of the seat (Bjurstedt et al. 1968). The subject had both a tachometer and a metronome to indicate the pedalling rate. The rotational radius of the centrifuge was 7.2 m at the middle of the support surface. Slip rings at the centre of rotation allowed for audiovisual monitoring, power supply and transmission of physiological signals between the gondola and a control room.

Methods

In these experiments, $\dot{V}_{O_2}$, carbon dioxide output ($\dot{V}_{CO_2}$) and pulmonary ventilation ($\dot{V}_E$) were determined at the mouth on a breath-by-breath basis, by means of a metabolic cart (K4b^2, Cosmed, Rome, Italy) that allows continuous monitoring and storing of the time course of oxygen and carbon dioxide partial pressures throughout the respiratory cycles. The metabolic cart analysers were calibrated against gas mixtures of known composition. The inspiratory and expiratory ventilations were measured by a turbine flowmeter, dedicated to the metabolic cart, which was calibrated with a 3-l syringe. The alignment of the traces was corrected for the time delay between the flowmeter and the gas analysers. Afterward, the averages of the breath-by-breath $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and $\dot{V}_E$ values measured during the 5th min of exercise were calculated. These data were published in a previous paper on the effects of gravity acceleration on the internal work during cycling (Bonjour et al. 2010).

In the same tests, f_H was measured by electrocardiography. Continuous recordings of arterial pulse pressure were also obtained at a fingertip of the right arm by means of a non-invasive cuff pressure recorder (Portapres, TNO, The Netherlands). Within each cardiac cycle, the values corresponding to systolic and diastolic blood pressure were retained. Beat-by-beat $\bar{P}$ was computed as the integral

mean of each pressure profile, using the Beatscope® software package (TNO, The Netherlands). Then, the averages of the beat-by-beat f_H and $\bar{P}$ measured during the 5th min of exercise were calculated. These data are unpublished.

From the pulse pressure profiles obtained at steady state, beat-by-beat Q_{st} was estimated by the Modelflow method (Wesseling et al. 1993), using the Beatscope® software package. Beat-by-beat $\dot{Q}$ was then computed and a steady-state $\dot{Q}$ value obtained as the mean over 1 min. However, since no calibration of the Modelflow method could be performed in the centrifuge, these values were not used for regression computation.

Experiments were conducted at four a_g levels, corresponding to 1, 1.5, 2 and 2.5 *g* along the longitudinal body axis. Experiments at 1 *g* were carried out in the gondola, while it was staying still in the parking position, using the same experimental set-up as for the hypergravity experiments. At each a_g level, four work loads were studied, namely 25, 50, 75 and 100 W, which were administered in random order. The pedalling frequency was 1 Hz. After having attained the appropriate spinning speed, 5 min at rest were allowed. Then the first exercise was carried out for a 5-min duration, followed by a 2-min resting recovery. Then the second exercise was carried out, again lasting 5 min, after which the gondola was decelerated and parked. All investigated parameters were continuously recorded during the entire experimental session.

Data obtained at Buffalo in hypergravity

These data were obtained during experiments carried out on 12 healthy male subjects (Age = 20 ± 2 years, height = 182 ± 2 cm, body mass = 77.3 ± 3.1 kg) in the human centrifuge at the Center for Research and Education in Special Environments, Buffalo, NY, USA.

Protocol

The experimental protocol was similar to the one performed at Karolinska Institute, with the only difference that a 125-W exercise was performed instead of 100 W. An electrically braked calibrated cycle ergometer was used (Collins Pedalmode, Braintree, MA, USA). The subject was placed in the gondola in the same way as described above for the experiments in Stockholm.

Methods

This gondola was larger than the one in Stockholm, and a mass spectrometer (Perkin Elmer, USA) was located inside it and used for measurement of $\dot{V}_{O_2}$, f_H and $\dot{Q}$ at exercise steady state. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were measured by an open circuit method. The gondola was equipped with a remotely controlled five-way valve that directed expired gas to one of five Douglas bags for individual collections. After the experiment, the expired gas from each individual bag was pushed through a dry gas meter and O_2 and CO_2 fractions were determined by the mass spectrometer. $\dot{Q}$ was determined by the one-step CO_2 rebreathing method (Farhi et al. 1976), using an ultrasonic flowmeter and the mass spectrometer. f_H was measured by electrocardiography. Q_{st} was calculated as the ratio of $\dot{Q}$ to f_H. Mean arterial pressure was measured by an automated blood pressure system (Infrasonde Model D4000, Puritan-Bennett Cor. Wilmington, MA). Experiments were carried out at 1 G, with the gondola slowly rotating (1 *g*), and at 2 and 3 *g*. At increased *g*, the gondola automatically rotated to maintain acceleration along the G_z axis. The data at 2 *g* are unpublished, while preliminary data for 3 *g* were previously published in a symposium report (Pendergast et al. 1987).

Data treatment

Data are presented relative to the corresponding value at 1 *g* from the same study. This approach allowed (1) direct comparison of data from different studies that used subjects, whose results at 1 *g* may have been different; and (2) pooling of data at various powers, assuming that, in any given study, at any given power, the observed changes in each value reflect only the effects of a_g.

In a previous paper (Bonjour et al. 2010), we have demonstrated that $\dot{V}_{O_2}$ is linearly related to a_g, and this relationship was accepted and used in the data treatment for the present paper. In the same previous paper at increased G, f_H was also treated as linear in the 1–2.5 *g* range, but the data at 0 *g* did not fit a linear model, and a quadratic function interpolated the data better. Since

$$\dot{Q} = Q_{st} f H \quad (1)$$

and since Q_{st} appeared to decrease with a_g as a quadratic function, we used a fourth power function to interpolate the relation of $\dot{Q}$ to a_g.

Maximal $\dot{V}_{O_2}$ ($\dot{V}_{O_{2\,max}}$) in the various a_g environments was estimated from the respective relationships of $\dot{V}_{O_2}$ to f_H, assuming that the maximal f_H was invariant among a_gs'. The maximal f_H of the Stockholm study was used (186 ± 12 min^{-1}, Bonjour et al. 2010)—note that no measurements of maximal $\dot{V}_{O_2}$ were carried out in the Euromir and in the Buffalo studies. The corresponding maximal aerobic power ($\dot{w}_{max}$) was then calculated as the minimal power requiring a $\dot{V}_{O_2}$ equal to $\dot{V}_{O_{2\,max}}$ at each a_g. Maximal $\dot{Q}$ at 1 *g* was calculated by extrapolating the submaximal $\dot{Q}$ versus $\dot{V}_{O_2}$ relations up to $\dot{V}_{O_{2\,max}}$. From this value, the maximal $\dot{Q}$ at G ≠ 1 *g* (in the 0–3 *g* range) was

then calculated by means of the equation describing the relation of $\dot{Q}$ to a_g (for details, see Fig. 4).

Total peripheral resistance (in mmHg l^{-1} min) was calculated by dividing each $\bar{P}$ value by the corresponding $\dot{Q}$ value, assuming that the pressure in the right atrium can be neglected as its determinant. The left ventricular stroke work was determined as the product of $\bar{P}$ times Q_{st} and was expressed in J after appropriate unit conversion. The left ventricular power was then obtained as the product of left ventricular stroke work times f_H and expressed in W.

Results

The values at 1 *g* are reported in Table 1. The linear relationships between $\dot{V}_{O_2}$ and a_g are shown in Fig. 1. $\dot{V}_{CO_2}$ followed the same tendency as $\dot{V}_{O_2}$, with a slightly lower slope. *R* was thus always lower than 1 and unaffected by a_g. The quadratic relationships between f_H and a_g, and between Q_{st} and a_g are shown in Figs. 2 and 3, respectively. The relationship between $\dot{Q}$ and a_g is reported in Fig. 4, where the fourth power regression equation is also indicated. This equation was used to estimate mean $\dot{Q}$ values at the a_g investigated at Stockholm. These values are compared in Table 2 with those obtained from the measured f_H and the Q_{st} values reported in Fig. 3.

$\bar{P}$ appeared to increase with a_g non linearly, a relationship that we interpolated with a quadratic function (Fig. 5). From the obtained $\bar{P}$ values, an estimate of the pressure at feet and carotid body at the various investigated a_g is shown in Table 3. Thus, total peripheral resistance turned out to vary linearly with a_g as shown in Fig. 6, whereas the relation of left ventricular stroke work to a_g was best described by a third power function (Fig. 7). The left ventricular power, in turn, was unaffected by a_g.

The estimates of $\dot{V}_{O_{2\,max}}$, together with the corresponding $\dot{w}_{max}$ and maximal $\dot{Q}$ at the various considered a_g levels are reported in Table 4. $\dot{V}_{O_{2\,max}}$, $\dot{w}_{max}$ and maximal $\dot{Q}$ decreased as a function of a_g, being at 3 *g* 34.1, 49.8 and 55.0% lower than at 0 *g*, respectively. On the other hand, at 3 *g*, $CaO_2 - C\bar{v}_{O_2}$ was 49.6% higher than at 0 *g*.

Discussion

This paper attempts to provide a comprehensive picture of the effects of a_g on the cardiovascular response to exercise in humans. It is based on data obtained in three different circumstances, several years apart, in which submaximal exercise was performed with similar power outputs and at the same pedalling frequency. The latter is crucial for comparing data from different experiments, because of its influence on the internal work of cycling and on the $\dot{V}_{O_2}$ versus power relations in hypergravity (Bonjour et al. 2010). The data are presented relative to their corresponding 1 *g* value (delta) at the same exercise power and from the same study, in order to account for inter-subjects and inter-studies data variability at 1 *g*. Moreover, by doing so, we could isolate the effect of a_g on the parameters of interest, independent of the power at which the measurement was made. This is so for variables which in a plot against mechanical power show parallel relationships

Table 1 Data at 1 *g*

		0 W	50 W	75 W	100 W
$\dot{V}O_2$ (l min^{-1})	Stockholm	0.23	0.85	1.10	1.39
	Buffalo	0.34	0.90	1.15	1.47
	Euromir	0.34	0.95	1.17	1.47
$\dot{V}CO_2$ (l min^{-1})	Stockholm	0.19	0.74	0.95	1.24
	Buffalo				
	Euromir	0.30	0.88	1.10	1.39
f_H (min^{-1})	Stockholm	72	91	99	109
	Buffalo	82	98	108	116
	Euromir	83	94	104	117
O_2 pulse (ml per beat)	Stockholm	3.20	9.38	11.18	12.77
	Buffalo	4.15	9.18	10.65	12.67
	Euromir	4.09	10.07	11.25	12.62
$\dot{Q}$ (l min^{-1})	Stockholm	6.6	10.3	11.7	13.4
	Buffalo	6.3	13.5	13.8	17.0
	Euromir	6.9	11.0	12.7	13.6
Q_{st} (ml)	Stockholm	92	113	119	123
	Buffalo	77	138	128	147
	Euromir	82	116	122	116
$\bar{P}$ (mmHg)	Stockholm	85	87	94	94
	Buffalo				
	Euromir	78	83	85	90
Total peripheral resistance (mmHg l^{-1} min)	Stockholm	12.81	8.53	8.01	7.03
	Buffalo				
	Euromir	11.36	7.60	6.67	6.63
Left ventricular stroke work (J)	Stockholm	1.05	1.31	1.48	1.54
	Buffalo				
	Euromir	0.85	1.29	1.38	1.39
Left ventricular power (W)	Stockholm	1.05	1.31	1.48	1.54
	Buffalo				
	Euromir	1.18	2.02	2.39	2.70

$\dot{V}O_2$ oxygen consumption, $\dot{V}CO_2$ carbon dioxide output, *R* gas exchange ratio, f_H heart rate, $\dot{Q}$ cardiac output, Q_{st} stroke volume, $\bar{P}$ mean arterial pressure

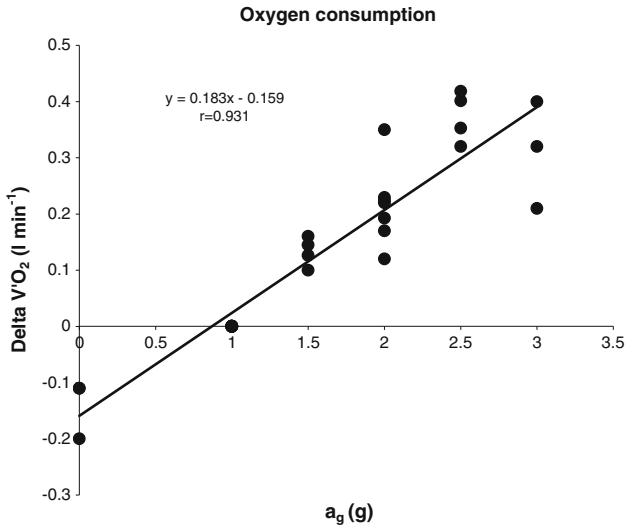

Fig. 1 Oxygen consumption ($\dot{V}O_2$), expressed as the difference (delta) with respect to the corresponding value observed at 1 *g*, as a function of acceleration in the G_z axis, from the three considered studies. Each point is the mean value from a given study at a given power. The line (linear model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

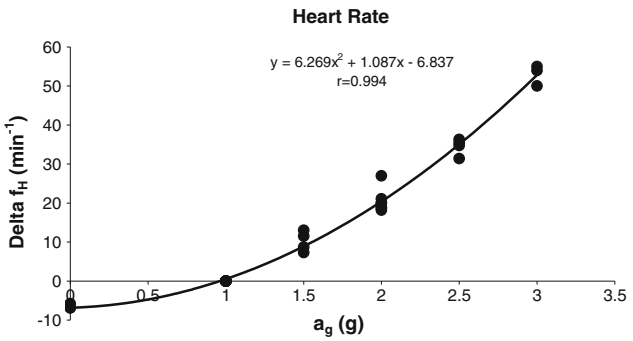

Fig. 2 Heart rate (f_H), expressed as the difference (delta) with respect to the corresponding value observed at 1 *g*, as a function of acceleration in the G_z axis, from the three considered studies. Each point is the mean value from a given study at a given power. The line (quadratic model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

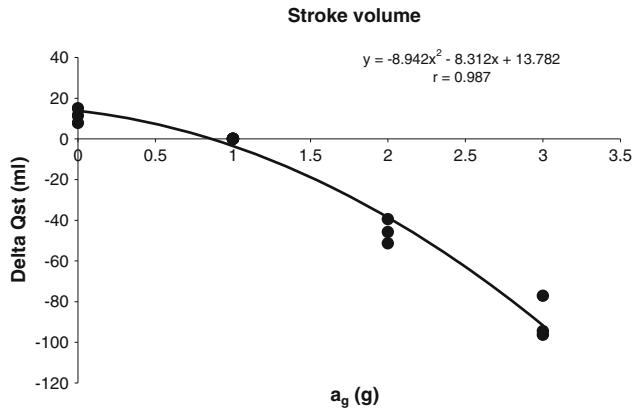

Fig. 3 Stroke volume (Q_{st}), expressed as the difference (delta) with respect to the corresponding value observed at 1 *g*, as a function of acceleration in the G_z axis, from the Euromir and Buffalo studies. Each point is the mean value from a given study at a given power. The line (quadratic model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

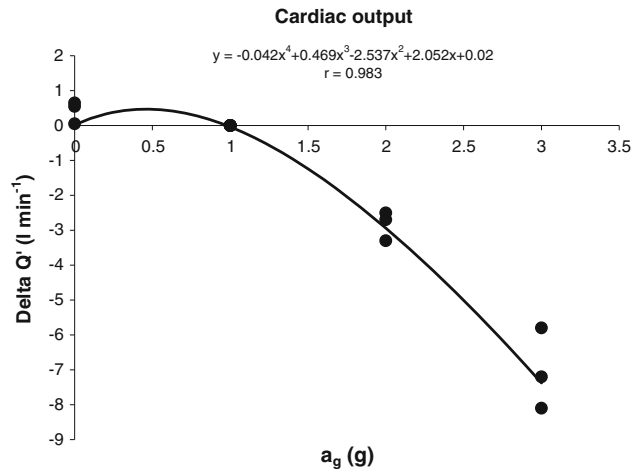

Fig. 4 Cardiac output ($\dot{Q}$), expressed as the difference (delta) with respect to the corresponding value observed at 1 *g*, as a function of acceleration in the G_z axis, from the Euromir and Buffalo studies. Each point is the mean value from a given study at a given power. The line (fourth power model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

at various G levels. The results of this analysis (1) confirmed the linear relation between $\dot{V}_{O_2}$ (and $\dot{V}_{CO_2}$) and a_g, already demonstrated in previous studies (Nunneley and Shindell 1975; Nunneley 1976; Girardis et al. 1999; Bonjour et al. 2010) over the entire a_g range from 0 *g* to 3 *g*; (2) suggested a positive non-linear relation between f_H and a_g, which is at variance with previous reports on data over a narrower a_g range (Bonjour et al. 2010); (3) revealed a negative relationship between Q_{st} and a_g; (4) suggested optimisation of $\dot{Q}$ in the 0.5–1 *g* range; (5) identified the increase in $\bar{P}$ and total peripheral resistance with a_g over the entire investigated a_g range.

The paucity of and different methods of reporting data on the cardiovascular response to exercise in hypergravity or microgravity make a comparison among previous results difficult. In microgravity, the results of Shykoff et al. (1996) were expressed only in relative terms, and it is impossible from that study to reconstruct absolute $\dot{Q}$ values. As far as hypergravity is concerned, the most classical study is the one carried out by Rosenhamer (1967). In that study, very low $\dot{Q}$ values, much lower than in the present study, were obtained at 3 *g*. However, if one considers only the data at 1 *g*, the results of Rosenhamer are very close to the present ones. Similarly, f_H and $\dot{V}_{O_2}$ values close

Table 2 Estimate of cardiac output during centrifugation in Stockholm experiments

a_g (g)	Power (W)	$\dot{Q}$ (l min^{-1})	
		$f_H \times Q_{st}$	Equation
1.5	25	8.15	7.49
1.5	50	9.91	9.53
1.5	75	11.04	10.45
1.5	100	11.43	11.49
2	25	7.45	5.75
2	50	8.69	7.79
2	75	9.45	8.71
2	100	10.03	9.75
2.5	25	6.88	3.68
2.5	50	6.77	5.72
2.5	75	7.53	6.64
2.5	100	7.82	7.68

Concerning cardiac output ($\dot{Q}$), in the first column, measured heart rate (f_H) was multiplied by stroke volume (Q_{st}) estimated after Fig. 3; in the second column, $\dot{Q}$ was estimated using the equation of Fig. 4. a_g acceleration in the G_z axis

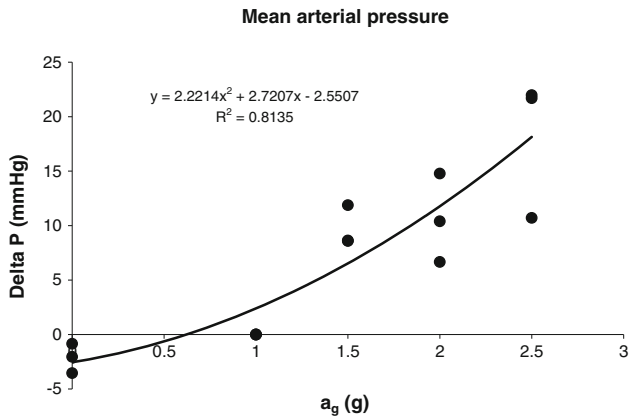

Fig. 5 Mean arterial pressure ($\bar{P}$), expressed as the difference (delta) with respect to the corresponding value observed at 1 g, as a function of acceleration in the G_z axis, from the three considered studies. Each point is the mean value from a given study at a given power. The line (quadratic model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

to the present ones were found by Rosenhamer (1967) at 1 g, but not at 3 g, where again much lower values were found. Thus, the increase in f_H at 3 g, with respect to the value at 1 g, was much less in Rosenhamer's (1967) than in the present studies. In fact, the f_H increase at 3 g observed by Rosenhamer corresponded to what was observed at 2 g in the present study. The same was the case for the f_H values by Linnarsson and Rosenhamer (1968), whose study was carried out with the same ergometer as that by Rosenhamer (1967). The present study is the first one to provide useful data on the cardiovascular response during

Table 3 Mean arterial pressure at heart, carotid, buttocks and feet levels

a_g	Heart	Carotid	Buttocks	Feet
0.0	82	82	82	82
0.5	84	73	99	132
1.0	87	65	117	183
1.5	92	58	136	235
2.0	97	53	156	288
2.5	103	48	177	342
3.0	111	44	199	397

Data at heart level calculated after Fig. 5. The heart–carotid distance was assumed equal to 30 cm; the heart–buttocks distance was assumed equal to 40 cm. The pressure data for the feet are calculated for a standing human (assumed heart–feet distance 130 cm). Note that in the present experiments the subjects pedalled inside the gondola in a semi-recumbent posture, so that blood pressure in the feet was similar to that in the buttocks. Blood pressure values are in mmHg; acceleration in the G_z axis (a_g) values are in g

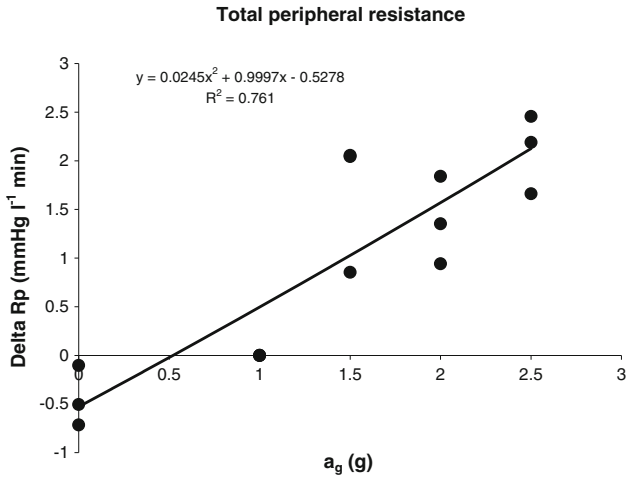

Fig. 6 Total peripheral resistance (R_p), expressed as the difference (delta) with respect to the corresponding value observed at 1 g, as a function of acceleration in the G_z axis, from the three considered studies. Each point is the mean value from a given study at a given power. The line (xxx model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

exercise in microgravity and hypergravity together. The inclusion of both microgravity and hypergravity in the model led us to treat the data with non-linear, rather than with linear equations, considering that the cardiovascular responses in hypergravity were expected to be, and actually were greater than those observed in microgravity. In part, these differences in response might have a methodological origin. In fact, when respiratory methods are used for the determination of $\dot{Q}$, we cannot exclude a progressive underestimate of $\dot{Q}$ as a_g is increased, due to more heterogeneous distribution of ventilation/perfusion ratio, associated with arterial blood hypoxaemia, with a higher

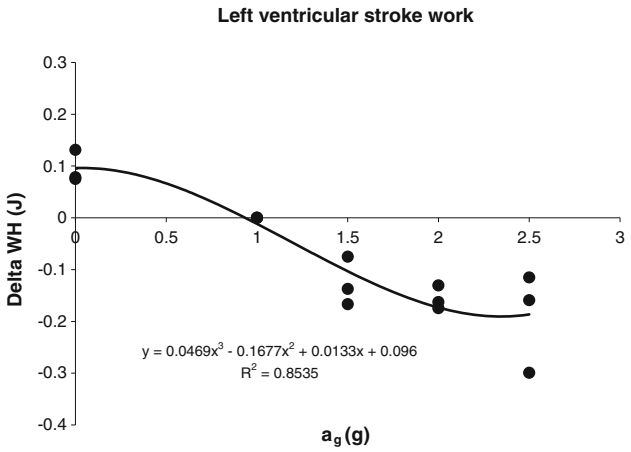

Fig. 7 Left ventricular stroke work (W_H), expressed as the difference (delta) with respect to the corresponding value observed at 1 *g*, as a function of acceleration in the G_z axis, from the three considered studies. Each point is the mean value from a given study at a given power. The line (third power model) is a regression line, calculated through all individual points. The regression equation is reported on the figure

Table 4 Estimate of maximal O_2 consumption at varying gravitational environments

a_g (g)	$\dot{V}O_{2\,max}$ (l min^{-1})	$\dot{w}_{max}$ (W)	$\dot{Q}$ (l min^{-1})	$CaO_2 - C\bar{v}O_2$ (ml l^{-1})
0	3.70	333	28.2	131
1	3.66	315	27.8	132
1.5	3.51	290	25.5	138
2	3.26	258	22.0	148
2.5	2.92	217	17.3	169
3	2.49	167	12.7	196

a_g acceleration in the G_z axis, $\dot{V}O_{2\,max}$ maximal O_2 consumption, $\dot{w}_{max}$ maximal aerobic power, $\dot{Q}$ cardiac output, $CaO_2 - C\bar{v}O_2$ arterovenous blood oxygen difference

fraction of perfused but unventilated lung units (Glaister 1970; Hlastala et al. 1998; Rohdin et al. 2004).

The results of this study are not consistent with the classical notion that the linear $\dot{Q}$ versus $\dot{V}_{O_2}$ relationship during exercise is independent of environmental factors (Blomqvist and Saltin 1983; Cerretelli and di Prampero 1987). That notion was generated by the observation that the linear relationship between $\dot{Q}$ and $\dot{V}_{O_2}$, originally described by Åstrand et al. (1964), was unchanged under most circumstances, except in presence of significant changes in arterial oxygen concentration (Ferretti et al. 1992). However, data reported in microgravity obtained by Shykoff et al. (1996), by the one-step CO_2 rebreathing method (Farhi et al. 1976) demonstrated a deviation from the previously reported relationship between $\dot{Q}$ and $\dot{V}_{O_2}$. Their data also suggest a possible upward displacement of the $\dot{Q}$–$\dot{V}_{O_2}$ relationship at 0 *g*. These data (Shykoff et al. 1996), however, are not directly comparable with the data from the present study, because their subjects exercised at powers corresponding to 30 and 60% of the maximal aerobic mechanical power determined before flight; thus different subjects exercised at different absolute powers.

Despite the decrease in $\dot{Q}$ and in Q_{st}, $\bar{P}$ at the level of the heart increased in hypergravity. As shown in Table 3, such an increase was necessary to maintain pressure in carotid artery at high a_g. It is the result of a complex regulation mechanism, likely mediated by sympathetic activation through stimulation of cardiopulmonary and arterial baroreflexes (Goodman et al. 2000; Strempel et al. 2008), stimulated, respectively, by sudden reduction in central blood volume and carotid artery pressure as a_g is increased, and/or by the vestibular system stimulated by increased otolith acceleration (Voustianiouk et al. 2006).

The blood pressure response includes at least strong peripheral vasoconstriction, as demonstrated by the increase in total peripheral resistance both at rest and during exercise. Total peripheral resistance, however, is only an overall index of peripheral vasoconstriction and does not per se provide information on the sites were vasoconstriction actually occurs. We could not perform local blood flow measurements in these studies. Experiments by others on subjects exposed to lower body negative pressure, which induces haemodynamic responses similar to those observed in hypergravity, showed that there are remarkable differences in regional vascular resistance among various districts (Fischer et al. 2007; Arbeille et al. 2008a, b), which should be taken into account for a deeper understanding of the circulatory changes that may occur in a hypergravity environment. A vasoconstrictor response may also face to the reduction in circulating blood volume related to increased venous blood stowage, especially in the splanchnic district, and to plasma leakage toward interstitial space, especially in the skin (Eichler et al. 2000; Christ et al. 2001; Arbeille et al. 2008b). The blood pressure response was observed also by Bjurstedt et al. (1974), despite the fact that their exercise at 3 *g* was carried out at a higher relative work load than was performed at 1 *g*.

Tachycardia was systematically observed, at any given metabolic level, in virtually all studies in hypergravity, whether at rest (Linnarsson and Rosenhamer 1968; Strempel et al. 2008) or during exercise (Rosenhamer 1967; Bjurstedt et al. 1968, 1974; Linnarsson and Rosenhamer 1968; Pendergast et al. 1987, Bonjour et al. 2010). Similarly, tachycardia was observed also in almost all studies employing lower body negative pressure (see, e.g. in the last couple of years, Fu et al. 2009; Guinet et al. 2009; Lewis et al. 2010; Momen et al. 2010). The increase

in f_H with a_g above 1 g was considered essentially linear up to 7 g at rest (Burton and Smith 1996), where the maximal heart rate was attained. If one excludes the data at $a_g < 1$ g, this would not be contradictory with the present Fig. 2. It rather suggests the practical impossibility of performing exercise at $a_g > 5$ g. The increase in f_H in hypergravity, however, was not such as to compensate for the dramatic decrease in Q_{st}, whence the drastic drop in $\dot{Q}$. By analogy, the combination of a strong reduction in Q_{st} and $\dot{Q}$ with higher $\bar{P}$ values was such as to lead to the reduction in left ventricular stroke work and power, respectively, observed in hypergravity.

The maximal exercise prediction of 5 g is further supported by the estimates of $\dot{V}_{O_2max}$ reported in Table 4, suggesting a significant and large reduction in $\dot{V}_{O_2max}$ as a_g is increased. Extrapolation of the relation between $\dot{V}O_{2max}$ and a_g above 3 g indicates that $\dot{V}O_{2max}$ would be reached around a resting $\dot{V}O_2$ at 4.5 g, confirming the inability to performing exercise at and above those a_g levels. In this study, at each investigated a_g, $\dot{V}O_{2max}$ was calculated from the respective $\dot{V}_{O_2}$ versus f_H relations, after assuming the same maximal f_H. At 1 g, the calculated $\dot{V}_{O_2max}$ (3.66 l min^{-1}) corresponds well to the value actually measured in the Stockholm experiments (3.59 ± 0.17 l min^{-1}, Bonjour et al. 2010), whereas the corresponding calculated $\dot{w}_{max}$ (315 W) is slightly higher than the measured one (279 ± 22 W). Concerning $\dot{Q}$, the mean maximal $\dot{Q}$ value at 1 g obtained from Stockholm experiments was 26.1 ± 3.7 l min^{-1}, a value similar not only to the one estimated by extrapolating the submaximal $\dot{Q}$ versus $\dot{V}_{O_2}$ relation up to the calculated $\dot{V}_{O_2max}$(27.8 l min^{-1}), but also to the one calculated using a linear equation that was previously described (26.5 l min^{-1}, Ferretti et al. 1992) for trained normaemic subjects, in a study in which $\dot{Q}$ was measured with the CO_2 rebreathing method, as in the microgravity and in the Buffalo experiments.

At higher a_g levels, the estimated maximal $\dot{Q}$ would decrease more than the corresponding $\dot{V}_{O_2max}$, because there are two additive phenomena, namely the decrease of $\dot{V}_{O_2max}$ and $\dot{w}_{max}$ with a_g and the downward displacement of the $\dot{Q}$ versus $\dot{V}_{O_2}$ relationship. As a consequence, an increase in the maximal arterial-venous oxygen difference would occur as a_g is increased (Table 3). In microgravity, however, practically no changes in maximal $\dot{Q}$ with respect to the value at 1 g are to be expected.

It is noteworthy that the results from this study in hypergravity were obtained during acute exposure, so they are unaffected by possible adaptation processes. By contrast, the data in microgravity in the present study were obtained during prolonged sojourns, where the effects of adaptation processes might influence the results. For instance, prolonged sojourns in microgravity, leading to muscle atrophy (di Prampero and Narici 2003; Narici and de Boer 2011), would imply slight reductions of $\dot{V}_{O_2max}$. Yet bed rest studies demonstrated that the time constant of the slow component of the $\dot{V}_{O_2max}$ decay in microgravity, associated with the development of muscle atrophy, was such that its effects on $\dot{V}_{O_2max}$ can be considered negligible within 2 months in bed or in flight (Capelli et al. 2006). In any case, changes in $\dot{V}_{O_2max}$ did not occur during space flight at least up to 17 days (Levine et al. 1996).

Concerning outer planets, it would be of some practical interest to predict the cardiovascular response to exercise on a cycle ergometer on the Moon and on Mars, in view of possible future space flights, as it appears after the present analysis. These predictions are shown in Table 5, considering only the effects of a_g and neglecting the effects of muscle atrophy. It is noteworthy that both on the Moon and on Mars $\dot{V}_{O_2max}$, and thus the capacity of performing work on them, would not be substantially different from that on Earth.

The results and conclusions of this study represent a conjecture that will need future systematic testing, perhaps

Table 5 Prediction of the cardiovascular response to exercise on the Moon and on Mars

		Power (W)		
		50	75	100
$\dot{V}O_2$ (l min^{-1})	On Earth	0.87	1.12	1.42
	On Moon	0.74	0.99	1.29
	On Mars	0.78	1.03	1.33
f_H (min^{-1})	On Earth	93	102	112
	On Moon	87	96	105
	On Mars	88	97	106
$\dot{Q}$ (l min^{-1})	On Earth	11.3	12.4	14.5
	On Moon	11.6	12.7	14.8
	On Mars	11.8	12.9	14.9
Q_{st} (ml)	On Earth	121	122	130
	On Moon	133	134	142
	On Mars	130	131	139
$\bar{P}$ (mmHg)	On Earth	87	93	94
	On Moon	84	91	91
	On Mars	85	92	92
R_p (mmHg l^{-1} min)	On Earth	8.4	7.8	7.0
	On Moon	8.0	7.5	6.6
	On Mars	8.3	7.7	6.8

The values on Earth represent the overall mean at 1 g from the three experiments, weighted for subject number

$\dot{V}O_2$ oxygen consumption, f_H heart rate, $\dot{Q}$ cardiac output, Q_{st} stroke volume, $\bar{P}$ mean arterial pressure, R_p total peripheral resistance

over wider ranges of a_g and powers. In particular, performance of further, more systematic measurements of $\dot{Q}$ at elevated a_g levels during submaximal steady-state exercise is a key experiment to be carried out in the future to improve our understanding of gravitational effects on the cardiovascular system in humans, and thus exercise performance in these environments.

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