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DOI 10.1055/s-0035-1559774
Int J Sports Med 2016; 37: 785–791

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Rüdigerstraße 14
70469 Stuttgart
ISSN 0172-4622

Sildenafil does not Improve Exercise Capacity under Acute Hypoxia Exposure

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Key words
- sildenafil
- doping
- altitude
- performance

Abstract

The increase in pulmonary arterial pressure (PAP) due to hypoxic pulmonary vasoconstriction (HPV) could be a limiting factor for physical performance during hypoxic exposure. Sildenafil has been shown to reduce PAP in situations of moderate or severe hypoxia, and consequently its role as an ergogenic aid and even a possible doping substance must be considered. We performed a double-blind crossover study to determine the effects of sildenafil on cardiovascular, respiratory and metabolic parameters in normoxia and during acute exposure to hypobaric hypoxia (4000 m) at rest and during maximal and submaximal (60% VO_2 max) exercise tests. One hour before testing started, sildenafil (100 mg) or a placebo was orally administered to 11 volunteers. In normoxic conditions, sildenafil did not affect performance. Similarly, no significant differences were found in cardiovascular and respiratory parameters in hypoxic conditions at rest or during exercise. The use of sildenafil to improve physical performance in non-acclimatized subjects is not supported by our data.

Introduction

Acute exposure to hypoxia reduces maximal aerobic capacity, which directly affects exercise performance [14,29,39]. The maximum oxygen uptake (VO_2 max) tends to decrease in direct proportion to the decrease in arterial oxygen content (CaO_2) that occurs as altitude increases [6,20]. The main factors involved are a drop in alveolar oxygen pressure, which reduces the diffusion of oxygen in the lungs and thus decreases the transport of oxygen to other tissues, and an increase in pulmonary arterial pressure (PAP) due to hypoxic pulmonary vasoconstriction (HPV), which overloads the right ventricle, affecting right ventricular afterload and cardiac output [37,38]. Moreover, during exercise in acute hypoxia, blood lactate levels are higher than at sea level [8,10], which is probably due to increased sympathetic activity [15]. However, these values decrease in chronic hypoxia [3] as a consequence of acclimation; a phenomenon known as the "lactate paradox" [9,25] and to enhanced lactate utilization during exercise [18]. Exercise in hypoxia also exacerbates the reduction in oxygen arterial saturation, which reduces arterial oxygen content due to higher extraction at peripheral level and lower uptake during the exchange in the lungs [16,28], and increases the risk of pulmonary edema [2,30], especially in people with higher susceptibility to acute mountain sickness [13].

Sildenafil use was originally prescribed for the treatment of erectile dysfunction [12,26,33]. Its mechanism of action is based in its properties as a selective inhibitor of phosphodiesterase (PDE5), which increases the concentration of cyclic guanosine monophosphate (GMPc), thus causing relaxation of the smooth muscles in the arterial wall of vascular territories where this enzyme is especially abundant, such as corpora cavernosa and the lungs [21].

Because of its vasodilating effects, sildenafil has been used to decrease pulmonary vascular resistance. It has mainly been used in some disorders in which pulmonary hypertension is an associated disease, such as chronic heart failure [1,17] or lung pathologies such as chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis [4,5,42]. Vasodilation promotes alveolar oxygen uptake, increases CaO_2 and has even improved exercise performance in these diseases. For this reason, sildenafil is being investigated as a pharmacological strategy for the

accepted after revision
August 05, 2015

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DOI http://dx.doi.org/10.1055/s-0035-1559774
Published online: July 14, 2016
Int J Sports Med 2016; 37: 785–791 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0172-4622

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reduction of pulmonary arterial hypertension (PAH) in mild or severe hypoxia in healthy people.

Previous research has shown that sildenafil diminishes pulmonary arterial hypertension during medium or high altitude exposure and under similar experimental hypoxic conditions [31,41], and may improve exercise performance [14,16]. Furthermore, it has been shown that sildenafil can improve oxygen saturation during several days of exposure to high altitude [32]. However, other studies have reported no major improvements with the use of sildenafil during exercise in conditions of acute [22,23] or chronic hypoxia [14]. Since an increase in pulmonary arterial pressure could be a limiting factor for physical performance under hypoxic conditions [27], sildenafil could be considered an ergogenic aid for physical activity in such conditions, and even a possible doping substance in case of significant improvements in athletic performance in competitive events at moderate altitude, and mountain activities ranging from tourist trekking to top level alpine expeditions to the higher summits. Although there is a lack of indisputable scientific evidence, in recent years sildenafil use has risen and it has become popular among some mountaineers.

The purpose of this study was to determine the effects of sildenafil administration on several parameters related to cardiovascular, respiratory and metabolic functions in normoxia and during acute exposure to hypobaric hypoxia (4000 m) at rest and during exercise on 2 physical tests at different intensities. Our work plan was designed to check for possible changes in physiological and metabolic parameters, and to look for evidence of improvement in physical performance. Our hypothesis was that sildenafil does not induce sufficient changes in physical capacity to consider it an ergogenic aid, and much less a doping agent at altitude.

Material and Methods

Subjects

11 healthy young volunteers were enrolled for the study: 6 men and 5 women who normally live at sea level and have no previous record of pulmonary hypertension or acute mountain sickness (age 26.8 ± 4.2 years; body weight 66 ± 7.3 kg, and height 173 ± 7 cm). The study was performed in accordance with the IJSM's ethical standards and the ethical guidelines set forth in the Helsinki Declaration, and all subjects signed an informed consent form [19]. Approval was obtained from the *Comisión de Bioética de la Universitat de Barcelona* (Institutional Review Board #IRB00003099).

Experimental design

The double-blind crossover study was carried out during 4 consecutive weeks, at the same hour and on the same day of the week for each subject. The combination of the 2 study factors, environmental oxygen availability and sildenafil administration, was randomly applied to avoid a possible training effect during the 4 successive trials. Subjects underwent the tests at sea level on 2 days (one day for the placebo and the other for sildenafil), and at a simulated altitude of 4000 m in a hypobaric chamber on the other 2 days. Each individual was randomly administered on 2 days with 100 mg of sildenafil and on the other 2 days with 100 mg of methylcellulose as a placebo, taking the opposite capsule in the other 2 sessions corresponding to normoxia and hypoxia conditions. Capsules were prepared by external pharmaceutical personnel and marked blindly. One hour elapsed between the ingestion of the capsule and the measurements in all sessions. 3 subjects were not able to finish the 4 trials and all their data were excluded from the analysis.

Exercise tests

Each individual exercise test was composed of 2 phases at 2 different intensities to assess the individual physical fitness in each session. All tests were performed on an ergometer bike (Excalibur, Lode, Groningen, Netherlands). The first phase (maximal incremental test) started from 20 watts, and 20 watts were added per minute until exhaustion. The second phase was a submaximal intensity test, which lasted for 6 min at 60 % of the maximum workload reached in the first phase. The break between each of the 2 phases was about 30 min, until basal heart rate was recovered. To simulate an altitude of 4000 m, we used

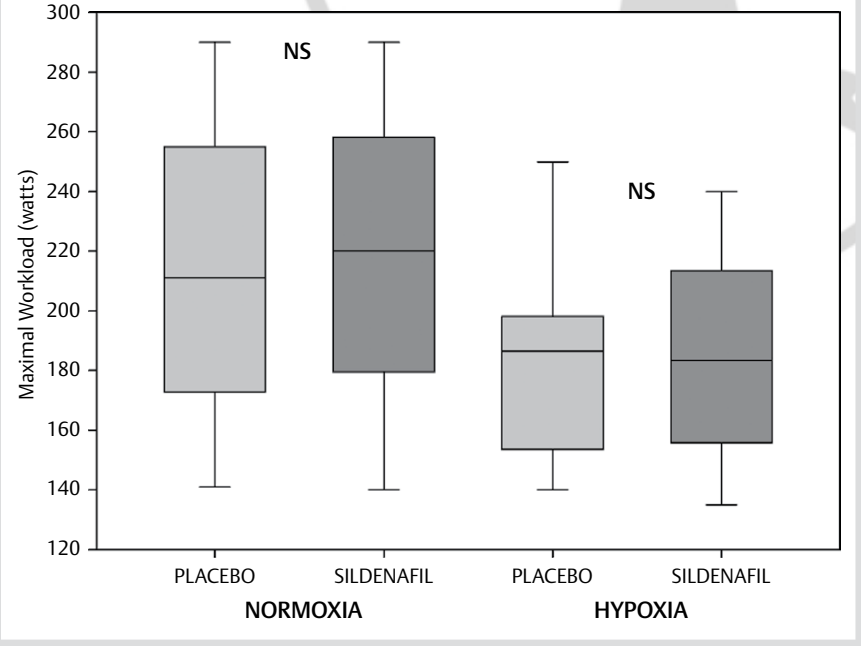

Fig. 1 Maximal workload reached at the different maximal trials after administration of placebo (light grey) or sildenafil (dark grey) at normoxic (at left) and 4000 m above sea level of simulated altitude in the hypobaric chamber (at right).

the hypobaric chamber (CHEx-1, Moelco, Spain) at the Bellvitge Campus of the University of Barcelona. The atmospheric pressure inside the chamber during tests was 462 mmHg (616 hPa), which is equivalent to an inspired pO_2 (tracheal air) of approximately 90 mmHg. Exercise tests at sea level were also performed inside the hypobaric chamber with the same equipment and set-up.

Respiratory parameters

Gas exchange analysis was carried out using a 2-way mask (Hans Rudolph, Kansas, USA) through the exchange system of respiratory gases "breath to breath", with a Metasys TR-Plus automatic gas analyzer (Brainware SA, France) equipped with a pneumotachograph.

Cardiovascular parameters

Hemodynamic parameters were determined by means of non-invasive, finger cuff technology (Nexfin, BMEYE, Amsterdam, Netherlands), using the middle finger of the left hand. The following variables were measured: systolic blood pressure (Sys, mmHg), diastolic blood pressure (Dia, mmHg), mean arterial pressure (MAP, mmHg), systolic volume (SV, $ml \cdot beat^{-1}$), peripheral vascular resistance (SVR, $dyn \cdot sec \cdot cm^{-5}$), contractility (dP/dt, $mmHg\,s^{-1}$), cardiac output (CO, $L\,min^{-1}$), cardiac index (CI, $L \cdot min^{-1} \cdot m^{-2}$), stroke index (SI, $ml \cdot beat^{-1}\,m^{-2}$), systemic vascular resistance index (SVRI, $dyn \cdot sec \cdot cm^{-5} \cdot m^{-2}$) and pulse pressure (PP, mmHg). Heart rate (HR, $beats \cdot min^{-1}$) was monitored throughout the test using a pulsometer (Polar Acurex Plus, Polar Electro OY, Finland).

Lactate and oxygen saturation

Blood lactate concentration (LA, mmol/L) was analyzed using a micro method system (Reflotron, Boehringer Mannheim GmbH, Mannheim, Germany). Oxygen saturation (SaO_2) was obtained using a pulse oximeter (Onyx II 9550, Nonin Medical Inc., Plymouth, MN). For the maximum effort phase, maximal blood lactate concentration was obtained at the end of the exercise burst; for the submaximal phase, oxygen saturation was registered every minute, whereas lactic acid was only measured at the end.

Statistical analysis

The differences between sildenafil and the placebo for the 2 environmental conditions were compared using 2-way ANOVA and a paired Student's t test. The Wilcoxon test was applied in the case of non-normal distribution (Shapiro-Wilk test) of samples. A SigmaPlot 12 (SYSTAT Software, USA) software package was used for data treatment, graphical representation and statistical analysis. Values are expressed as mean values ± standard deviation (SD). Significance was considered for a P-value < 0.05.

Results

Maximal exercise capacity in hypobaric hypoxia and normoxia with sildenafil and a placebo

Fig. 1 shows the maximum workload (W_{peak}) reached under hypobaric hypoxia and normoxia after sildenafil or placebo administration. As expected, hypobaric hypoxia clearly reduced

Table 1 Respiratory and cardiovascular parameters at rest before starting the maximal exercise test in 2 environmental conditions (normoxia and hypoxia) using a placebo and sildenafil.

		Rest Normoxia			Rest Hypoxia		
	Variable	Placebo	Sildenafil	p-value	Placebo	Sildenafil	p-value
Respiratory Parameters	RR ($breaths \cdot min^{-1}$)	17.4 ± 1.9	18.1 ± 3.5	0.576	17.0 ± 3.5	17.1 ± 2.2	0.931
	VE(BTPS) ($L \cdot min^{-1}$)	10.32 ± 1.54	10.23 ± 1.76	0.906	11.95 ± 0.86	12.35 ± 2.09	0.661
	VT (L)	0.54 ± 0.12	0.52 ± 0.09	0.630	0.72 ± 0.12	0.72 ± 0.10	0.992
	VO_2/kg ($ml \cdot kg \cdot min^{-1}$)	5.27 ± 0.92	5.49 ± 1.21	0.722	5.91 ± 0.93	5.42 ± 1.14	0.237
	VO_2 ($L \cdot min^{-1}$)	0.34 ± 0.05	0.37 ± 0.07	0.574	0.39 ± 0.07	0.36 ± 0.08	0.262
	RER	0.82 ± 0.06	0.80 ± 0.08	0.454	0.80 ± 0.50	0.81 ± 0.04	0.875
	VCO_2 ($L \cdot min^{-1}$)	0.27 ± 0.04	0.29 ± 0.08	0.664	0.32 ± 0.04	0.29 ± 0.07	0.148
	FeO_2 (%)	16.97 ± 0.28	16.79 ± 0.51	0.420	14.36 ± 0.59	14.93 ± 1.21	0.148
	$FeCO_2$ (%)	3.24 ± 0.37	3.36 ± 0.43	0.496	5.54 ± 0.62	4.95 ± 0.98	0.065
	VE/VO_2 (L)	32.34 ± 3.17	29.86 ± 3.76	0.217	31.18 ± 2.93	35.40 ± 5.53	0.059
	VE/VCO_2 (L)	39.29 ± 4.71	37.60 ± 4.85	0.484	37.88 ± 3.86	43.26 ± 7.67	0.059
	O_2 Pulse	4.21 ± 1.11	4.39 ± 1.40	0.712	4.33 ± 0.86	3.98 ± 1.03	0.241
	$PETO_2$ (mmHg)	106.25 ± 2.71	105.75 ± 2.76	0.729	48.28 ± 2.54	50.12 ± 3.33	0.133
	$PETCO_2$ (mmHg)	34.50 ± 2.88	35.25 ± 3.20	0.559	33.19 ± 2.99	30.85 ± 3.52	0.108
Cardiovascular Parameters	Sys (mmHg)	116.8 ± 8.2	119.3 ± 10.0	0.521	124.0 ± 12.9	116.0 ± 17.7	0.324
	Dia (mmHg)	75.3 ± 5.8	79.4 ± 7.8	0.290	79.8 ± 8.4	75.3 ± 10.2	0.358
	MAP (mmHg)	91.4 ± 5.9	95.4 ± 8.0	0.318	96.6 ± 9.4	90.8 ± 12.5	0.302
	SV ($ml \cdot beat^{-1}$)	83.8 ± 8.0	82.6 ± 13.2	0.768	85.3 ± 16.5	82.6 ± 11.4	0.715
	SVR ($dyn \cdot sec \cdot cm^{-5}$)	1168 ± 148	1285 ± 286	0.346	1119 ± 271	997 ± 194	0.159
	dP/dt ($mmHg \cdot s^{-1}$)	759 ± 167	785 ± 306	0.834	938 ± 302	899 ± 235	0.762
	CO ($L \cdot min^{-1}$)	6.4 ± 0.7	6.4 ± 1.3	0.902	7.4 ± 2.0	7.5 ± 1.1	0.907
	CI ($L \cdot min^{-1}\,m^{-2}$)	3.6 ± 0.4	3.6 ± 0.7	0.954	4.2 ± 1.2	4.2 ± 0.6	0.934
	SI ($ml \cdot beat^{-1} \cdot m^{-2}$)	46.6 ± 3.3	45.9 ± 6.4	0.729	48.0 ± 10.0	46.0 ± 4.6	0.628
	SVRI ($dyn \cdot sec \cdot cm^{-5} \cdot m^{-2}$)	2084 ± 301	2282 ± 494	0.378	2005 ± 532	1773 ± 336	0.147
	PP (mmHg)	41.1 ± 4.6	39.6 ± 8.6	0.600	44.1 ± 8.8	40.3 ± 9.1	0.422
	HR ($beats \cdot min^{-1}$)	84.1 ± 16.1	84.9 ± 12.6	0.920	91.6 ± 16.9	91.8 ± 19.5	0.984

Values are means ± SD. RR, respiratory rate; VE(BTPS) volume of expired air (at body temperature and water saturated pressure); VT, tidal volume; VO_2/kg, oxygen consumption according to body weight; VO_2, Oxygen consumption; RER, respiratory exchange ratio; VCO_2, production of carbon dioxide; FeO_2, fractional exhaled oxygen; $FeCO_2$, fractional exhaled carbon dioxide; VE/VO_2, respiratory equivalent for oxygen; VE/VCO_2, respiratory equivalent for carbon dioxide; O_2 Pulse, oxygen pulse; $PETO_2$, end-tidal oxygen tension; $PETCO_2$, end-tidal carbon dioxide tension; Sys, systolic blood pressure; Dia, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SVR, systemic vascular resistance; dP/dt, contractility; CO, cardiac output; CI, cardiac index; SI, systolic index; SVRI, systemic vascular resistance index; PP, pulse pressure; HR, heart rate

the maximum workload compared to normoxia by 13.1% with the placebo ($p=0.009$) and by 15.1% using sildenafil ($p=0.001$). The difference between normoxia and hypoxia was significant for both pills. At sea level, W_{peak} was slightly higher (+2.8%) after administration of sildenafil than the placebo, but this difference was not significant ($p=0.29$). In hypoxia, sildenafil had a negligible increase (+0.5%) compared to the placebo ($p=0.81$).

Respiratory and cardiovascular parameters at rest and maximal exercise

Basal data for several respiratory and cardiovascular parameters at rest in the 4 different experimental conditions are presented in **Table 1**. The same parameters at the end of maximal exercise are presented in **Table 2**. No statistically significant differences due to sildenafil administration were identified for any of the respiratory and cardiovascular parameters when the 2 factors, normoxia and hypoxia, were compared at rest or during exercise.

Respiratory and cardiovascular parameters during submaximal exercise

Selected respiratory and cardiovascular parameters are presented in **Table 3**. In normoxia, fractional exhaled oxygen (FeO_2) and end tidal oxygen partial pressure ($PETO_2$) were the only respiratory parameters that had significantly greater differences ($p<0.05$) with sildenafil than with the placebo. In hypoxia, no significant differences were detected for any respiratory parameter. Regarding cardiovascular parameters, only diastolic blood pressure (Dia) showed a significantly ($p<0.05$) lower value for sildenafil than for the placebo. SVR and SVRI in hypoxia were lower with sildenafil.

Lactate (LA) and oxygen saturation (SaO_2) for incremental and submaximal test

Blood lactate levels (**Table 4**) tended to be slightly higher (around 5%) after sildenafil administration, although no statistically significant differences were detected between sildenafil and the placebo in the 2 exercise challenges and in both environmental conditions. No differences in SaO_2 (**Table 4**) were detected at the end or throughout the submaximal or incremental phases in any environmental condition. This test thus also failed to reveal any significant effect of sildenafil administration during exercise.

Discussion

The main finding of this research was that during acute exposure to hypoxia in non-acclimatized subjects, no evidence was found to suggest that sildenafil improves performance to the extent that it could be considered a doping substance either at altitude or at sea level, due to the lack of significant differences in the cardiovascular, respiratory and metabolic parameters assessed in both exercise phases.

Table 2 Respiratory and cardiovascular parameters at the end of maximal test in 2 environmental conditions (normoxia and hypoxia) using a placebo and sildenafil on exercise.

		Exercise Normoxia			Exercise Hypoxia		
	Variable	**Placebo**	**Sildenafil**	**p-value**	**Placebo**	**Sildenafil**	**p-value**
Respiratory Parameters	RR (breaths·min^{-1})	49.5±11.0	50.0±10.4	0.852	51.8±8.4	49.3±8.7	0.323
	VE(BTPS) (L·min^{-1})	101.86±30.33	106.20±31.20	0.218	109.46±25.70	108.27±29.50	0.822
	VT (L)	1.82±0.22	1.92±0.40	0.342	2.11±0.32	2.19±0.36	0.417
	VO_2/kg (ml·kg·min^{-1})	41.96±9.39	43.27±5.95	0.545	34.11±4.05	34.24±6.22	0.937
	VO_2 (L·min^{-1})	2.79±0.79	2.87±0.61	0.579	2.27±0.49	2.27±0.52	0.985
	RER	1.19±0.16	1.16±0.10	0.335	1.27±0.09	1.25±0.10	0.647
	VCO_2 (L·min^{-1})	3.25±0.70	3.32±0.69	0.567	2.87±0.62	2.84±0.67	0.808
	FeO_2 (%)	17.29±0.70	17.36±0.62	0.516	16.25±0.63	16.18±0.64	0.554
	$FeCO_2$ (%)	4.06±0.59	3.88±0.49	0.149	5.50±0.73	5.50±0.57	1.00
	VE/VO_2 (L)	36.64±8.46	36.86±6.72	0.242	48.61±7.73	47.85±7.28	0.592
	VE/VCO_2 (L)	30.54±4.08	31.56±3.74	0.886	38.44±5.87	38.09±3.73	0.829
	O_2 Pulse	16.86±6.37	16.29±3.65	0.687	13.11±2.69	13.24±3.14	0.828
	$PETO_2$ (mmHg)	116.00±6.87	116.50±6.48	0.529	63.31±3.20	62.50±3.67	0.309
	$PETCO_2$ (mmHg)	36.50±6.80	35.13±5.79	0.196	27.54±3.24	27.92±3.34	0.710
Cardiovascular Parameters	Sys (mmHg)	181.8±13.5	175.0±12.2	0.145	169.3±17.7	160.4±21.1	0.129
	Dia (mmHg)	103.3±11.7	102.0±8.7	0.730	98.6±16.4	94.0±10.9	0.317
	MAP (mmHg)	137.0±10.9	132.5±6.9	0.205	125.9±17.8	120.1±13.1	0.216
	SV (ml·beat^{-1})	109.5±21.6	108.1±24.3	0.839	104.9±24.7	107.3±12.4	0.816
	SVR (dyn·sec·cm^{-5})	628±189	598±143	0.610	633±220	543±71	0.241
	dP/dt (mmHg·s^{-1})	2130±588	2072±632	0.813	1904±454	1789±472	0.619
	CO (L·min^{-1})	18.9±4.5	18.7±4.0	0.893	17.4±4.2	18.0±2.0	0.573
	CI (L·min^{-1} m^{-2})	10.5±2.2	10.4±1.9	0.922	9.7±2.3	10.1±0.9	0.550
	SI (ml·beat^{-1}·m^{-2})	60.9±10.9	60.0±12.1	0.821	58.6±14.0	59.9±4.5	0.825
	SVRI (dyn·sec·cm^{-5}·m^{-2})	1111±295	1059±222	0.619	1127±398	966±118	0.243
	PP (mmHg)	77.9±11.9	72.6±14.9	0.340	70.3±9.8	66.0±14.1	0.454
	HR (beats·min^{-1})	171.0±20.0	177.0±16.1	0.417	173.4±12.5	172.9±18.9	0.872

Values are means±SD. RR, respiratory rate; VE(BTPS) volume of expired air (at body temperature and water saturated pressure); VT, tidal volume; VO_2/kg, oxygen consumption according to body weight; VO_2, Oxygen consumption; RER, respiratory exchange ratio; VCO_2, production of carbon dioxide; FeO_2, fractional exhaled oxygen; $FeCO_2$, fractional exhaled carbon dioxide; VE/VO_2, respiratory equivalent for oxygen; VE/VCO_2, respiratory equivalent for carbon dioxide; O_2 Pulse, oxygen pulse; $PETO_2$, end-tidal oxygen tension; $PETCO_2$, end-tidal carbon dioxide tension; Sys, systolic blood pressure; Dia, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SVR, systemic vascular resistance; dP/dt, contractility; CO, cardiac output; CI, cardiac index; SI, systolic index; SVRI, systemic vascular resistance index; PP, pulse pressure; HR, heart rate

Table 3 Respiratory and cardiovascular parameters in submaximal test in 2 environmental condition (normoxia and hypoxia) using a placebo and sildenafil on exercise.

		Exercise Normoxia			Exercise Hypoxia		
	Variable	**Placebo**	**Sildenafil**	**p-value**	**Placebo**	**Sildenafil**	**p-value**
Respiratory Parameters	RR (breaths · min^{-1})	32.8 ± 3.7	34.9 ± 5.8	0.139	39.4 ± 7.1	38.1 ± 5.2	0.496
	VE(BTPS) (L · min^{-1})	65.21 ± 13.61	68.84 ± 15.73	0.052	86.09 ± 13.34	83.42 ± 14.03	0.171
	VT (L)	1.80 ± 0.29	1.80 ± 0.38	0.986	2.23 ± 0.41	2.21 ± 0.40	0.817
	VO_2/kg (ml · kg · min^{-1})	33.45 ± 5.12	33.64 ± 5.71	0.856	31.11 ± 3.81	31.49 ± 2.73	0.593
	VO_2 (L · min^{-1})	2.23 ± 0.53	2.24 ± 0.55	0.901	2.05 ± 0.36	2.08 ± 0.30	0.635
	RER	0.99± 0.11	1.01 ± 0.09	0.379	1.06 ± 0.07	1.03 ± 0.06	0.193
	VCO_2 (L · min^{-1})	2.18 ± 0.43	2.24 ± 0.48	0.318	2.16 ± 0.35	2.14 ± 0.31	0.521
	FeO_2 (%)	**16.66 ± 0.70**	**† 16.88 ± 0.60**	**0.046**	15.78 ± 0.62	15.58 ± 0.62	0.234
	$FeCO_2$ (%)	4.11 ± 0.56	3.99 ± 0.52	0.129	5.25 ± 0.67	5.36 ± 0.53	0.309
	VE/VO_2 (L)	30.05 ± 7.60	31.31 ± 6.44	0.139	42.33 ± 6.07	40.30 ± 5.41	0.148
	VE/VCO_2 (L)	30.08 ± 4.89	30.90 ± 4.93	0.182	40.11 ± 4.97	39.06 ± 3.87	0.187
	O_2 Pulse	13.46 ± 3.57	13.45 ± 3.83	0.975	12.16 ± 2.25	12.71 ± 2.77	0.073
	$PETO_2$ (mmHg)	**109.25 ± 6.63**	**† 110.63 ± 6.30**	**0.020**	34.93 ± 1.93	34.25 ± 2.02	0.134
	$PETCO_2$ (mmHg)	38.25 ± 5.15	37.50 ± 5.61	0.111	15.91 ± 2.16	16.38 ± 1.90	0.204
Cardiovascular Parameters	Sys (mmHg)	156.0 ± 7.9	164.1 ± 18.7	0.190	161.0 ± 20.1	152.9 ± 20.9	0.260
	Dia (mmHg)	92.0 ± 7.0	94.5 ± 8.4	0.520	**94.9 ± 12.7**	**† 85.8 ± 10.7**	**0.016**
	MAP (mmHg)	119.5 ± 5.6	123.3 ± 10.3	0.367	120.0 ± 14.9	111.6 ± 13.0	0.059
	SV (ml · beat^{-1})	108.6 ± 20.1	111.5 ± 23.3	0.720	107.1 ± 23.5	113.1 ± 19.0	0.351
	SVR (dyn · sec · cm^{-5})	557 ± 128	556 ± 146	0.990	598 ± 213	499 ± 131	0.059
	dP/dt (mmHg · s^{-1})	1 685 ± 277	1 976 ± 598	0.172	1 832 ± 488	1 829 ± 533	0.989
	CO (L · min^{-1})	18.1 ± 3.6	18.8 ± 4.3	0.595	18.3 ± 4.9	18.8 ± 3.7	0.706
	CI (L · min^{-1} m^{-2})	10.1 ± 1.8	10.4 ± 2.1	0.629	10.1 ± 2.5	10.5 ± 1.9	0.609
	SI (ml · beat^{-1} · m^{-2})	60.4 ± 8.9	62.0 ± 10.5	0.725	59.3 ± 11.3	63.0 ± 7.9	0.316
	SVRI (dyn · sec · cm^{-5} · m^{-2})	987 ± 204	983 ± 224	0.969	1 063 ± 338	883 ± 188	0.051
	PP (mmHg)	63.8 ± 7.7	69.1 ± 12.3	0.270	66.0 ± 12.3	66.9 ± 14.5	0.870
	HR (beats · min^{-1})	166.7 ± 11.0	168.2 ± 13.8	0.488	169.9 ± 15.8	166.2 ± 18.2	0.236

Values are means ± SD. † Significant differences for sildenafil vs. placebo. RR, respiratory rate; VE(BTPS) volume of expired air (at body temperature and water saturated pressure); VT, tidal volume; VO_2/kg, oxygen consumption according to body weight; VO_2, Oxygen consumption; RER, respiratory exchange ratio; VCO_2, production of carbon dioxide; FeO_2, fractional exhaled oxygen; $FeCO_2$, fractional exhaled carbon dioxide; VE/VO_2, respiratory equivalent for oxygen; VE/VCO_2, respiratory equivalent for carbon dioxide; O_2 Pulse, oxygen pulse; $PETO_2$, end-tidal oxygen tension; $PETCO_2$, end-tidal carbon dioxide tension; Sys, systolic blood pressure; Dia, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SVR, systemic vascular resistance; dP/dt, contractility; CO, cardiac output; CI, cardiac index; SI, systolic index; SVRI, systemic vascular resistance index; PP, pulse pressure; HR, heart rate

Table 4 Blood lactate concentration and arterial oxygen saturation in maximal and submaximal tests under 2 environmental conditions (normoxia and hypoxia) using a placebo and sildenafil.

	Maximal phase							
	Normoxia				**Hypoxia**			
	Placebo	**Sildenafil**	**Δ (%)**	**p-value**	**Placebo**	**Sildenafil**	**Δ (%)**	**p-value**
Blood lactate (mmol · L^{-1})	8.3 ± 1.8	8.5 ± 1.6	2.8	0.79	8.2 ± 2.1	8.7 ± 1.6	5.2	0.64
SaO_2 (%)	95.4 ± 4.0	96.5 ± 2.1	1.1	0.70	75.3 ± 4.8	77.6 ± 3.6	3.0	0.08
	Submaximal phase							
	Normoxia				**Hypoxia**			
	Placebo	**Sildenafil**	**Δ (%)**	**p-value**	**Placebo**	**Sildenafil**	**Δ (%)**	**p-value**
Blood lactate (mmol · L^{-1})	7.9 ± 1.8	8.4 ± 2.2	5.8	0.68	8.6 ± 1.9	9.1 ± 2.4	5.9	0.63
SaO_2 (%)	96.0 ± 1.7	96.4 ± 2.6	0.4	0.66	77.1 ± 6.8	76.5 ± 6.4	−0.8	0.43

The W_{peak} values obtained in hypoxia were around 13.1% (placebo) and 15.6% (sildenafil) lower than the values obtained under normoxic conditions. Our results differ greatly from the values obtained in other studies, which showed a 25% [20] or 23% [22] decrease in W_{peak}. These studies were conducted under similar environmental conditions (12.8% FiO_2 – 3900 m) although normobaric hypoxia and a half dose (50 mg) of sildenafil were used in the incremental test. Other investigations conducted between 4350 m and 5245 m [14,16,32] presented an even greater decrease of W_{peak} (33–39%). In our research, the use of sildenafil under hypoxia in the maximal test led to a small improvement compared to the placebo of around 0.9% in the W_{peak}. However, the differences were not statistically significant. Similar results were obtained in other studies [14,22,23,29].

As expected, SaO_2 in the incremental and submaximal test, in which normoxia was compared with hypoxia, decreased by 20% to 21% (in a similar way for treatments with sildenafil and placebo, p-value 0.000), which is similar to the values described in previous studies with a decrease of 26% [20] and 24% [22]. In accordance with previous studies [22,24,29,36,41], our data

failed to detect an improvement in SaO_2 when sildenafil was administered in hypoxia. However, other studies showed a positive effect of sildenafil, which improved SaO_2 at altitude. For example, Ghofrani et al [14] reported improved arterial oxygen saturation in acclimatized subjects at Everest Base camp after sildenafil administration, a finding that was corroborated by Hsu et al [20], who found an improvement in arterial oxygen saturation in trained subjects after sildenafil administration during acute hypoxia exposure, and Faoro et al. [12], who found that sildenafil increased SaO_2 during acute hypoxia but not in chronic hypoxia. One possible explanation for this discrepancy is that our study assessed SaO_2 in maximal and submaximal intensity, unlike other studies in which it was measured only at maximum intensity. Another probable explanation for these differences may be due to the methodology used in the study by Hsu et al [20], in which 2 doses of 50 and 100 mg of sildenafil were administered (although no difference between both dosages was detected) and which was conducted at a similar altitude (3 900 m) to our research but by applying normobaric hypoxia to trained subjects, with SaO_2 evaluated in the submaximal test with a varying duration in normoxia (55 % W_{peak} * 60 min + 10 time trial (TT)) in comparison to hypoxia (55 % W_{peak} * 30 min + 6 TT), whereas in our study, the submaximal test duration was 6 min at 60 % of W_{peak}. Because the test has a longer duration, we could allow for a stabilization of the cardiorespiratory system, thus maintaining CaO_2 in a way that in 6 min we possibly could not have done. Furthermore, in the study by Faoro et al. [14] SaO_2 was evaluated only in a maximal test, with untrained subjects, breathing hypoxic gas (11 % O_2 equivalent to 5 000 m), and a later evaluation in chronic hypoxia was carried out after spending 10 days at 5 000 m in the Chimborazo volcano, using a dose of 50 mg of sildenafil. It is important to consider the type of hypoxia applied to the subjects, given that in comparison to hypobaric hypoxia, normobaric systems can lead to less hypoxemia, hypercapnia, lower respiratory alkalosis and higher blood SaO_2. These physiological differences may be the result of decreased dead space ventilation, probably related to the lack of reduced barometric pressure [11, 34]. However, all these studies confirmed that the reduction in SaO_2, which is proportional to hypoxia or altitude, contributes to the decrease of total arterial oxygen content. This is one of the main reasons for the well-known VO_2 max decline due to altitude exposure [6].

Several studies, some with an invasive assessment of intra-arterial blood pressure, have shown that the arterial pressure is reduced at rest and during exercise in acute hypoxia [6, 7]. In our study, we did not find noticeable changes due to sildenafil administration in systemic blood pressure during acute hypoxia, which is in agreement with previous studies [14, 22, 23]. The effect of sildenafil on systemic blood pressure was unclear, although the limiting capacities of Nexfin method under our experimental conditions, with probable extreme vasomotor changes, must be kept in mind [35]. In hypoxia, both at rest and during exercise, arterial pressure was consistently lower after sildenafil administration than after the placebo. These differences were marginally significant. In contrast, systemic blood pressure showed non-statistically significant, slightly higher levels with sildenafil during rest in normoxia. The effect of sildenafil was also reflected in a tendency for a minor decrease in systemic vascular resistance to occur during exercise (SVR, SVRI), especially in hypoxia. In agreement with our findings, a recent meta-analysis on the effects of sildenafil, based on several studies, reported no changes in heart rate [40].

Under normoxia conditions, our results were similar to those obtained in previous studies in which the effects of sildenafil on cardiovascular and pulmonary parameters were transient and non-significant, both at rest and during exercise [14, 17, 20, 21, 31]. However, we observed remarkable differences in comparison with previous reported effects of sildenafil on physical performance. Most of the previous performance improvements after sildenafil administration were found in acclimatized subjects at altitudes usually reserved for mountaineering activities [16, 17]. However, most sports competitions are held at much lower altitudes. According to our results, under acute altitude exposure in non-acclimatized subjects, the use of sildenafil to achieve a possible performance improvement would not be supported. This should be taken into consideration, especially in the case of teams or individual athletes competing at altitude locations a short time after arrival. However, some data obtained at the normobaric hypoxia equivalent to 3 900 m [20] leaves the question open about the possible beneficial effect of sildenafil administration at altitudes below 4 000 m to individuals with an elevated response to this substance.

We conclude that under our experimental conditions in normoxia (sea level) and hypoxia (at a simulated altitude of 4 000 m), acute sildenafil administration to subjects non-acclimatized to altitude does not cause remarkable changes in respiratory or cardiovascular parameters during maximal or submaximal exercise bursts. Our data does not support the use of sildenafil in order to improve the gas exchange (assessed indirectly) and did not improve physical fitness capacity (SaO_2, VO_2max or W_{peak}) during acute exposure to hypoxia in non-acclimatized subjects. Further research is needed into the effects of PDE-5 inhibitors, in order to clarify remaining doubts about the following issues: the altitude and intensity of exercise at which sildenafil could have a really advantageous effect on performance, the adverse effects of sildenafil and its possible prophylactic use for acute mountain sickness, its possible beneficial use in chronic hypoxia, and the existence of positive responders to sildenafil, as previously proposed [20].

Acknowledgements

We thank the subjects who voluntarily agreed to participate in this study. The authors are also grateful to X. Ortega and J.C. Checa from Pfizer in Spain for their collaboration, and to Mr. Cristopher Evans at the Languages Advisory Service from the University of Barcelona for helping to edit the manuscript.

Conflict of interest: The authors have no conflict of interest to declare.

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