Efficacy of Sildenafil on healthy humans in high-altitude hypoxia at rest and during exercise: A meta-analysis

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Abstract. The current meta-analysis aimed to fully evaluate the efficacy of Sildenafil in healthy humans at different altitudes, focusing on echocardiographic and hemodynamic parameters. Relevant studies were retrieved from the Cochrane, Embase and PubMed databases. Odds ratios (OR) were determined for dichotomous data and weighted mean differences with 95% confidence intervals (CIs) for continuous data. A total of 16 RCTs were included in the current meta-analysis. Short-term treatment with Sildenafil significantly elevated resting heart rate (P<0.01) at altitudes <4,000 meters. No significant differences in heart rate were observed between the Sildenafil and placebo groups at rest and during exercise at an altitude of >4,000 meters (P>0.05). Sildenafil improved resting cardiac output at an altitude of >5,000 meters (P<0.01) and exercising arterial oxygen saturation at <4,000 meters (P<0.01). Sildenafil reduced resting pulmonary artery systolic pressure (PASP) at altitudes >4,000 meters (P<0.01) and exercising PASP at altitudes >5,000 meters (P<0.01). Therefore, Sildenafil efficacy in healthy humans with high-altitude hypoxia is related to altitude and rest or exercise.

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Abbreviations: PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; SaO_2, oxygen saturation; CaO_2, oxygen content; PASP, pulmonary artery systolic pressure

Key words: meta-analysis, Sildenafil, hypoxia, high-altitude, healthy humans

Introduction

Exposure to high altitude or normobaric hypoxia is a characteristic reason behind pulmonary vasoconstriction and pulmonary hypertension (1-6). Initially, pulmonary vasoconstriction is a physiological adaptation to maintain the ventilation/perfusion ratio as a response to hypoxia. This leads to a decline in arterial oxygen saturation (SaO_2), causing pulmonary vasoconstriction and enhanced pulmonary artery systolic pressure (PASP). This can be observed after exposure to hypoxia for only 2 h (7), despite being more pronounced for several days or weeks (5). One of the response mechanisms is the reduction of nitric oxide (NO) production in pulmonary artery smooth muscle cells (8). cGMP is a potent vasodilator synthesized by NO-activated soluble guanylate cyclase.

Sildenafil, a phosphodiesterase type-5 (PDE-5) inhibitor, induces vasodilation by inhibiting the hydrolytic breakdown of cGMP (9) with approved indications as pulmonary arterial hypertension treatment (10). Indeed, a recent meta-analysis revealed that PDE-5 inhibitors effectively attenuated high-altitude pulmonary hypertension (11).

Studies have been conducted on the clinical efficacy of Sildenafil during altitude-induced hypoxemia (2,12,13). Short-term Sildenafil treatment can attenuate the altitude-induced high pulmonary systolic arterial pressure without significant beneficial effects on arterial oxygen saturation, heart rate and acute mountain sickness (14). However, there are conflicting views (2,15,16). Several meta-analyses have assessed the efficacy of Sildenafil in treating high altitude-induced hypoxia (11,14). However, the effects of Sildenafil on hypoxia have been inconsistent during rest and exercise. Some studies of Sildenafil on endurance performance in hypoxia show beneficial effects (2,3), while others show no significant effect (17). The degree and duration of hypoxia affect associated parameters, such as pulmonary artery pressure (PAP), SaO_2 and arterial oxygen content (CaO_2) (18-20). Whether different altitudes influence the outcomes significantly remains to be elucidated. The efficacy of Sildenafil may be different at varying altitudes for most of the population (16). Therefore, the present study aimed to review systematically the efficacy of Sildenafil on hypoxia-related parameters and

Table I. Study characteristics.

First author, year	N	M/F	Median age	Median weight, kg	Altitude or simulated altitude	Sildenafil dose, mg	(Ref.)
Ghofrani *et al*, 2004	14	12/2	36.5	72.3	Mount Everest (altitude: 5,245 m)	50	(2)
Ricart *et al*, 2005	14	14/0	33.1±7.2	76.3±7.2	Hypobaric chamber: P_B=405 mmHg, P_{O2}=85 mmHg, (simulated altitude: 5,000 m)	100	(4)
Richalet *et al*, 2004	12	12/0	29±6	79±11	Observatoire Vallot Altitude (altitude: 4.350 m)	40	(5)
Hsu *et al*, 2006	10	10/0	31±4	76.83±9.5	Breathing hypoxic gas (12.8% oxygen simulated altitude: 3,874 m)	50, 100	(3)
Faoro *et al*, 2007	14	8/6	36	67±10	Mount Chimborazo (altitude: 5,000 m)	50	(17)
Reichenberger *et al*, 2007	14	12/12	37	-	Inspiration of gas containing 10% O_2 (simulated altitude: 4,500 m); Himalaya region (altitude: 3,440 m) Mount Everest (altitude: 5,245 m)	50	(20)
Snyder *et al*, 2008	14	13	33±11	85±14	Low-oxygen tent, 12.5% O_2 (simulated altitude: 4,300 m)	100	(25)
Lalande *et al*, 2009	15	7/8	34.8±2.4	73.8±3.7	Low-oxygen tent, 12.5% O_2 (simulated altitude: 4,300 m)	40	(26)
Rodway *et al*, 2016	12	8/4	66.5	67.2	Hypobaric chamber (simulated altitude: 2,750 m)	50	(41)
Bates *et al*, 2011	62	36/26	21	SI: 65.1±7.5 pla: 69.5±11.8	Chacaltaya laboratory (altitude: 5,200 m)	50	(42)
Zhao *et al*, 2001	10	10/0	-	-	Breathing 11% O_2 (simulated altitude: 5,350 m)	100	(15)
Cornolo *et al*, 2004	12	12/0	29±6	79±11	Observatoire Vallot Altitude in France (altitude: 4,350 m)	40	(30)
Toro-Salinas *et al*, 2016	11	6/5	26.8±4.2	66±7.3	Hypobaric chamber (simulated altitude: 4,000 m)	100	(28)
Olfert *et al*, 2011	16	8/8	SI: 25±3 BS: 28±7	175±7	Hypoxic chamber, 11% O_2 (simulated altitude: 5,350 m)	50	(27)
Kressler *et al*, 2011	21	11/10	M: 25±2 F: 27±2	M: 72.1±1.2 F: 60.8±2.1	Breathed hypoxic gas (12.8% FiO_2; simulated altitude: 3,900 m)	50	(16)
Jacobs *et al*, 2011	35		M: 26.3±1.2 F: 25.5±1.4	M: 176.8±1.4 F: 166.8±1.4	Breathed hypoxic gas (12.8% FiO_2; simulated altitude: 3,900 m)	50	(29)

SI, Sildenafil group; BS, Bosentan group; pla, Placebo; M, male.

endurance performance in healthy humans based on the exercise state and different altitudes using meta-analysis.

Materials and methods

Inclusion Criteria. Eligible articles were independently identified with the following inclusion criteria: i) The target population was healthy unacclimatized lowlanders; ii) studies were randomized controlled trials (RCT) in which the experimental group was treated with Sildenafil and the control group was given a placebo or other drugs; iii) hypoxia was induced in either simulated high altitude or natural high altitude environments; iv) the principal evaluation indicator included at least one parameter of echocardiography or hemodynamics. The exclusion criteria were: i) Subjects with pre-existing high-altitude cerebral edema and/or high-altitude pulmonary edema; ii) Studies related to Sildenafil usage combined with the treatment; and iii) incomplete, unavailable or inaccessible data.

Literature search. A systematic search for clinical trials of sildenafil was performed using the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com) and Cochrane (https://www.cochrane.org/) to databases. The following terms: 'Sildenafil OR Sildenafil citrate OR phosphodi-esterase type 5 inhibitor OR PDE-5 inhibitor' AND 'high altitude OR hypoxia OR plateau' with applicable filter limit to 'randomized controlled clinical trials (RCTs)' were searched. The period of searching the online databases was between 1998 and Dec 2022.

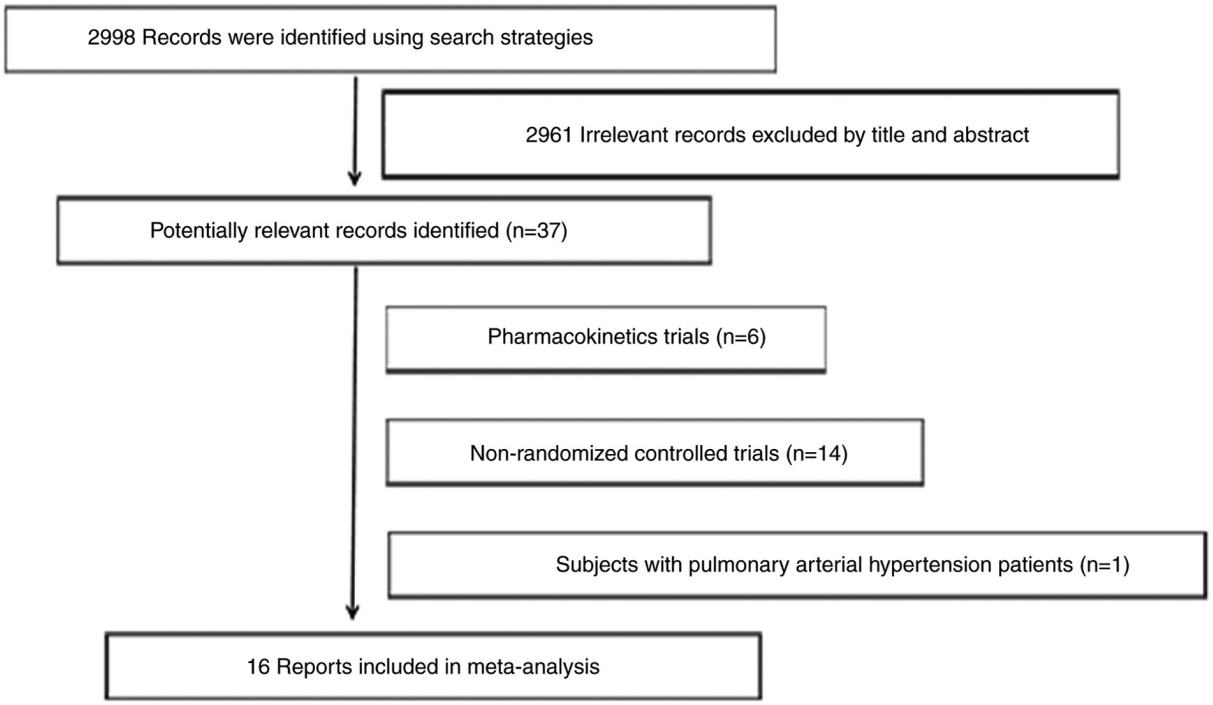

Figure 1. Flow diagram for the studies included in the meta-analysis concerning the therapy effect of Sildenafil to counter high altitude hypoxia in healthy humans.

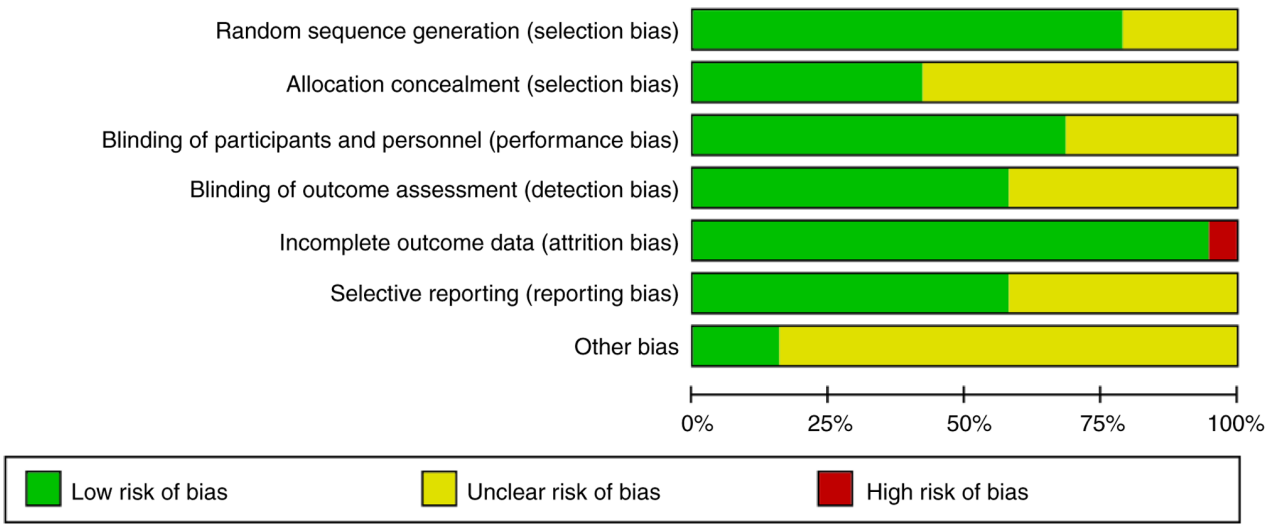

Figure 2. Risk of bias graph. Risk of bias for each included RCT, representing low risk of bias (+), high risk of bias (-) and unclear risk of bias (?). RCT, randomized controlled trial.

Quality assessment. The selected studies were assessed for quality by estimating the risk of bias, using the Cochrane risk of bias assessment tool (21), which tests for randomization, blinding, reporting of withdrawal, generation of random numbers and allocation concealment.

Data extraction. The data was extracted from the studies included in the review by two reviewers independently. The following information was collected: Year of publication, number of included participants, demographic characteristics, the duration of follow-up, the altitude or simulated altitude and dose of Sildenafil.

Statistical analysis. Data were analyzed using RevMan 5.4 (The Cochrane Collaboration) and Stata15 software (version 15.0; Stata Corp LP). Variability between studies in a systematic review may be termed heterogeneity, commonly evaluated using a chi-squared test (χ^2) in which an I^2 statistic >50% or P<0.10 are considered indicators (22). A fixed effects model helped analyze the data where no significant heterogeneity was observed between studies (P>0.10; $I^2 \leq 50\%$). Conversely, a random effects model was used where heterogeneity was identified. Standard deviation is calculated by the simple formula: SD=SEx$\sqrt{}$sample size (23). Means and standard variance from the median were derived using range and sample size (24).

For graphical data, the authors were contacted for statistical values. If the authors did not respond, the data were estimated from the graphs.

Results

Study characteristics. A total of 2,998 articles were identified using the pre-defined search strategy. Among these studies, 37 satisfied the primary inclusion criteria after reading titles and abstracts. After carefully reading the full text, 20 studies were excluded due to pharmacokinetics trials in healthy volunteers (n=6), non-randomized controlled studies (n=14) and pulmonary arterial hypertension (n=1). One randomized controlled trial (RCT) was reported twice (13,25) and the data were extracted from a study by Snyder *et al* (25). Eventually, 16 RCTs were included in the current meta-analysis (Fig. 1).

The key characteristics of the 16 trials are demonstrated in Table I. A total of 314 healthy volunteers were enrolled in the 16 RCTs, of which 150 were in the Sildenafil treatment group and 164 in the placebo group. A total of six studies evaluated participants at a naturally high altitude, and 10 studies investigated hypoxia by the simulation of high altitude in laboratory conditions. The participants in the study performed by Lalande *et al* (26) were randomly receiving Sildenafil and acetazolamide or a placebo. The data was extracted from Sildenafil and placebo groups. The participants in the study performed by Olfert *et al* (27) randomly received Sildenafil or bosentan group. Thus, data was extracted from the bosentan group as the control group.

Data quality. The selected studies were also assessed using Cochrane's recommended tool to assess the risk of bias. There was a low risk of bias in >50% of studies in terms of random sequence generation, blinding of the participants and trial personnel, incomplete outcome data and selective reporting. (Fig. 2). All the studies except for Hsu *et al* (3), Toro-Salinas *et al* (28) and Lalande *et al* (26) described the randomization process (Fig. 3).

A total of 14 studies reported the mean resting heart rate while 12 studies reported the exercising heart rate. Only two of the 14 studies indicated a statistically significant elevation in resting heart rate (16,29). Meta-analysis of the data indicated that Sildenafil increased heart rate, without significance, except at altitude <4,000 meters. The mean increase in the resting heart rate of participants allocated to the Sildenafil treatment group was 5.24 (95% CI 1.59-8.90; P<0.01; Fig. 4A) compared with the control group at <4,000 meters, without significant heterogeneity (I^2=0%; P>0.1). There was also no significant difference in the resting heart rate between both groups above 4,000 meters, with no heterogeneity evidence (I^2≤50%). During exercise, no change in heart rate was associated with Sildenafil treatment across different altitudes (P>0.05; Fig. 4B). I^2 value of heterogeneity was 50% among studies above 5,000 meters, natural hypoxia and simulated hypoxia were used for subgroup analysis. A total of three studies (4,15,27) simulated hypoxia and others simulated natural hypoxia. Subgroup analysis results show that no significant difference in heart rate was observed between the two groups whether at naturally high altitude or simulation of high altitude ($P_{simulated}$=0.77, $P_{natural}$=0.12), with no evidence of heterogeneity (I^2=0%). Moreover, the results of performing a leave-one-out sensitivity analysis remained consistent with those of the overall analysis (Fig. 5A). Publication bias using Egger's test showed no publication bias (P>0.05; Fig. 5B)

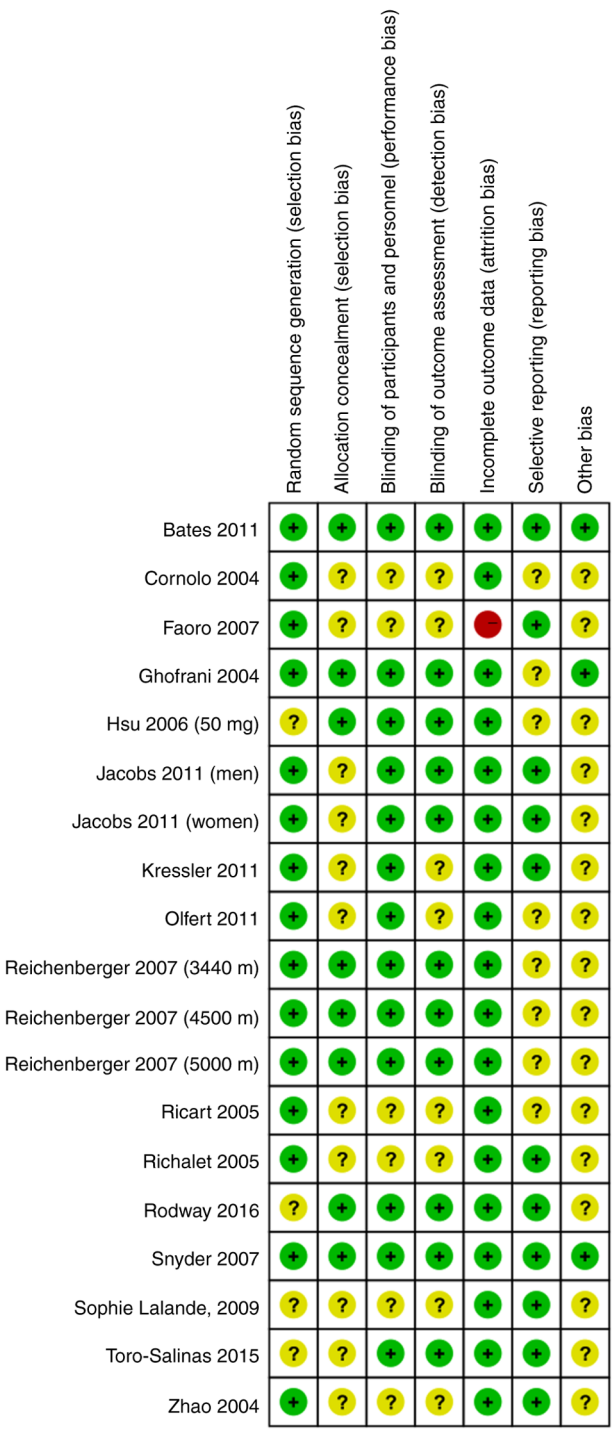

Figure 3. Risk of bias summary. Bar chart comparing percentage risk of bias for each included RCT. Green, low risk of bias; Red, high risk of bias; Yellow, unclear risk of bias; RCT, randomized controlled trial.

A total of nine studies reported data on cardiac output at rest (2,3,5,16,17,25,28-30). Meta-analysis of the data indicated that Sildenafil did not elevate cardiac output below 5,000 meters. However, cardiac output did increase at rest compared with the placebo group when exposed to altitudes above 5,000 meters (MD, 1.14; 95% CI, 0.44, 1.84; P<0.01;

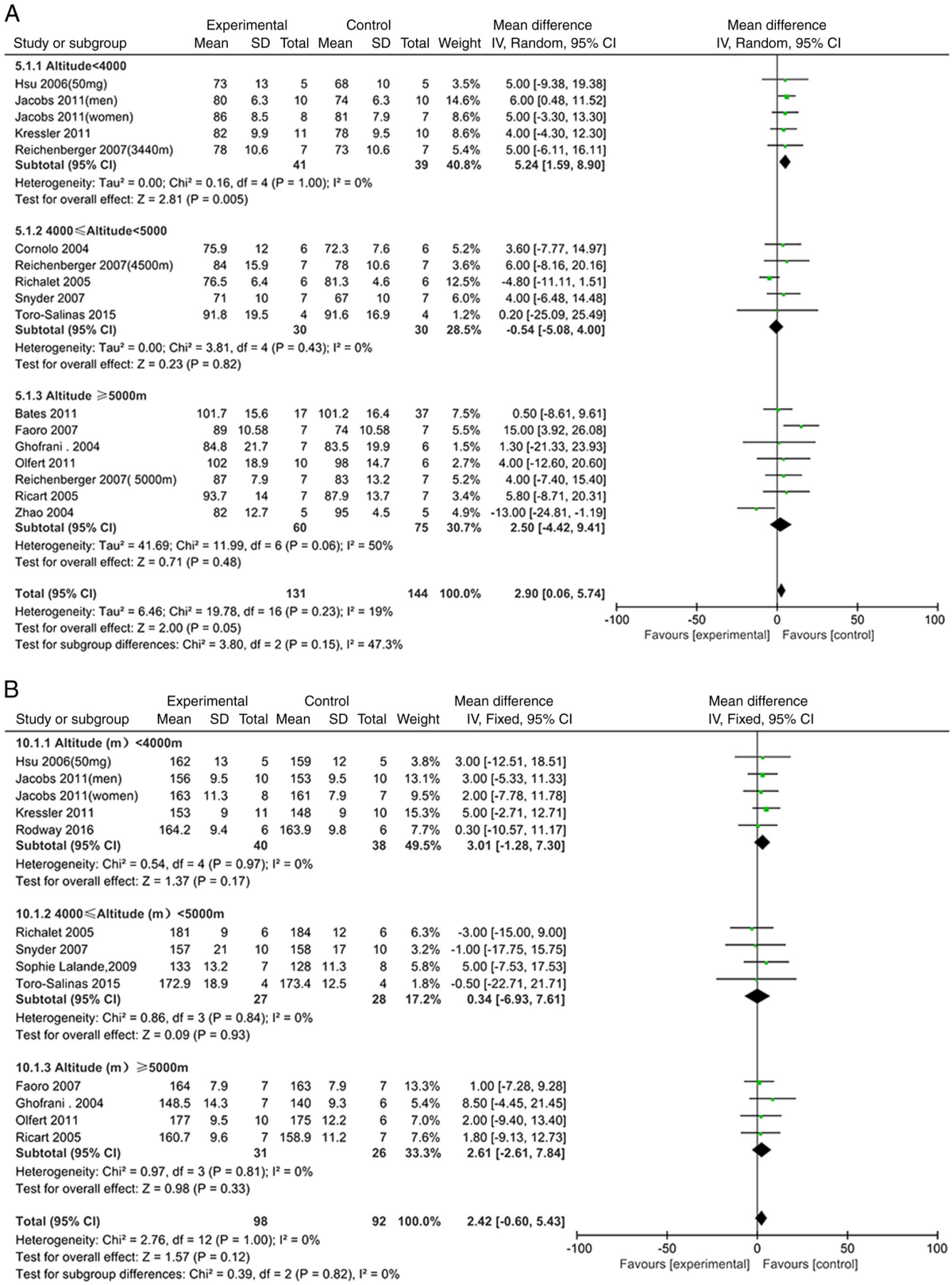

Figure 4. Forest plot of heart rate at rest and during exercise after treatment with Sildenafil vs. placebo control at high altitude. (A) Heart rate at rest. (B) Heart rate during exercise. The mean increase in resting heart rate of participants allocated to the Sildenafil treatment group was 5.24 (P<0.01) vs. the control group at <4,000 meters, without significant heterogeneity (I2=0%; P>0.1). There was no change in heart rate during exercise associated with therapeutic of Sildenafil at different altitudes (P>0.05). CI, confidence interval.

Fig. 6A). Although there was a trend of increased cardiac output during exercise at different altitudes, the difference was not significant (P>0.05; Fig. 6B).

A total of 13 studies reported data at rest and nine during exercise for SaO_2. Meta-analysis indicated that the administration of Sildenafil did not increase SaO_2 at rest after exposure

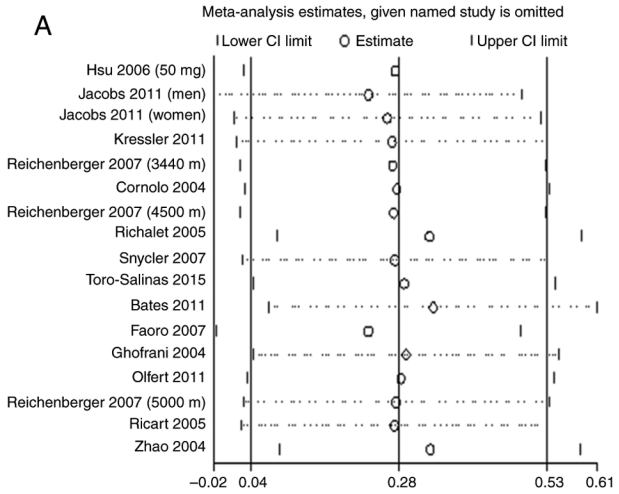

Figure 5. Sensitivity analysis of (A) heart rate and (B) Egger's test bias. CI, confidence interval.

to high altitudes (P>0.05) with no apparent heterogeneity (I^2=0%; P>0.1) detected among studies (Fig. 7A). SaO_2 of the treatment group was significantly higher during exercise than the control group below 4,000 meters (MD=1.72; 95% CI: 1.16, 2.28; P<0.0001), with no significant heterogeneity observed (I^2=0%; P>0.1). No significant difference and heterogeneity were observed between the Sildenafil and placebo groups (P>0.05) above 4,000 meters (I^2=0%) (Fig. 7B).

A total of seven studies reported PASP at rest and five studies revealed that Sildenafil significantly attenuated PASP. According to the meta-analysis, a significant PASP reduction was observed due to treatment with Sildenafil by a mean of 4.07 mmHg (95% CI: -7.36, -0.78; P=0.02) at an altitude of 4,000-5,000 meters and 5.67 mmHg (95% CI: -7.32, -4.01; P<0.0001) above 5,000 meters, without significant heterogeneity (I^2<50%; P>0.1) (Fig. 8A). Two studies reported PASP during exercise at an altitude of 5,000 meters. Compared with the placebo group, the mean reduction was 6.10 mmHg (95% CI: -8.34, -3.86; P<0.0001) in the Sildenafil group (Fig. 8B).

A total of two studies reported minute ventilation (V_E) at rest and five during exercise. No differences were identified for V_E either rest or during exercise (P>0.05) in Sildenafil group compared with the control group after exposure to high altitudes (Fig. 9).

Discussion

High altitudes are among the most inhospitable locations on earth. The atmospheric pressure decreases gradually as altitude increases. Research in a hypobaric hypoxic environment indicates that altitude differences and the rate of increase affect humans physiologically (31-34). However, to the best of our knowledge, almost no hypoxic effects below 2,500 meters have been reported (31). Humans can be affected by hypoxia at an altitude of >3,000 meters (31). Individuals unaccustomed to high altitudes will be affected at >4,000 meters without environmental adaptation (31). High altitude hypoxia leads to altitude sickness, due to decreased barometric pressure when ascending from low to high altitudes, thereby reducing the pressure of inspired oxygen (35,36). Sildenafil helped to reduce pulmonary vascular resistance in different forms of precapillary pulmonary hypertension (37-39) and mimicked the features of a selective pulmonary vasodilator. However, a threshold altitude may limit the usefulness of Sildenafil at lower altitudes while providing greater benefits above the threshold (16). The hypoxic pulmonary vasoconstriction (HPV) response does not elevate cardiac output sufficiently for Sildenafil to impart a recognizable improvement below 3,000 meters (16). Researchers have also considered several other factors modulating the effectiveness of Sildenafil (16,29,40). This includes the possibility of responders and non-responders, the influence of central regulation on exercise and sex difference.

Encouraged by the previous research, the present study considered the effect of sildenafil on healthy humans in plateau environment according to different altitude and exercise state. Unlike previous meta-analyses involving the impact of Sildenafil on high altitude hypoxia and its complications, the present meta-analysis focused on the potential clinical efficacy of Sildenafil at different high altitudes among healthy individuals while exercising and resting.

The present study revealed that Sildenafil therapy increases resting heart rate at <4,000 meters and decreases PASP at other altitudes. Cardiac output could be significantly elevated above 5,000 meters. During exercise, Sildenafil increased SaO_2 <4,000 meters and reduced PASP above 5,000 meters.

The meta-analysis data revealed that the resting heart rate was significantly elevated after Sildenafil treatment below 4,000 meters, inconsistent with previous research. A total of two studies found an increase in resting heart rate at above 5,000 meters due to Sildenafil (4,27), but it was found to decrease in the present review (15). There are possible adverse effects of Sildenafil treatment at altitudes <4,000 meters in individuals with an elevated response to this drug (28). These data suggest that treating healthy individuals with Sildenafil is not likely to be beneficial for every person. An explanation for this differential response is worthy of further research. Sildenafil has a moderate effect on increasing SaO_2 during exercise (40), but another study provided non-significant benefits (11). The present meta-analysis showed that Sildenafil considerably increased SaO_2 during exercise, but only at altitudes <4,000 meters. The beneficial effect was not apparent at other altitudes, either during exercise or at rest. Therefore, the beneficial impact of Sildenafil on SaO_2 is associated with altitude, rest, or exercise.

Sildenafil reduces PASP at rest and during exercise and the effect was observed at any altitude. The effect of Sildenafil on PAP leads to increased cardiac output, mostly above 5,000 meters. The pooled data analysis revealed that the effect on PAP moderately increases cardiac output at rest.

The aforementioned results in the present study demonstrated that the efficacy of Sildenafil in healthy humans with high-altitude hypoxia was associated with altitude and rest or exercise.

Throughout the current analysis, two studies depicted an elevated effect of Sildenafil on heart rate without any significant methodological heterogeneity (16,29). When the study by Jacobs *et al* was removed, the effect on heart rate decreased (29).

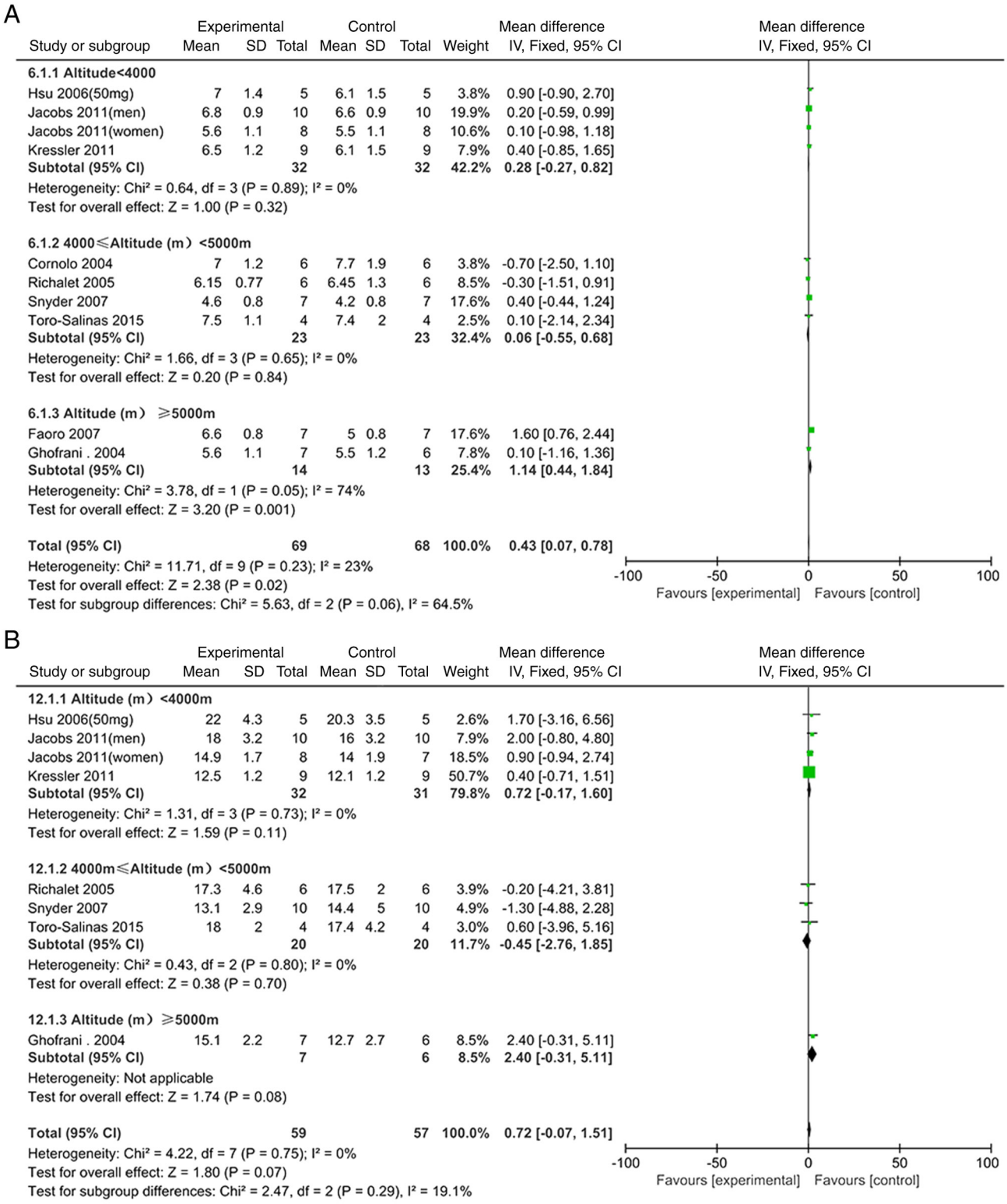

Figure 6. Forest plot of cardiac output at rest and during exercise after treatment with Sildenafil vs. placebo control at high altitude. (A) Cardiac output at rest; (B) cardiac output during exercise. Cardiac output at rest did increase vs. the placebo group when exposed to altitudes >5,000 meters (P<0.01); CI, confidence interval.

This study stratified the effects of Sildenafil in men and women and is an outlying data point and its effect on the outcome requires careful consideration. The possible lack of published negative research will bias the aggregate effect towards the positive effect of Sildenafil. This will significantly affect the rational guidance of medication for people rushing into the plateau or altitude hypoxia, in sports medicine, or altitude acclimatization and combat ability of officers and men at altitude.

There were several limitations to the present study. In recognition of the differences between hypoxia simulated at high altitudes in laboratory conditions and natural high altitudes, subgroup analysis would have enhanced the findings of the

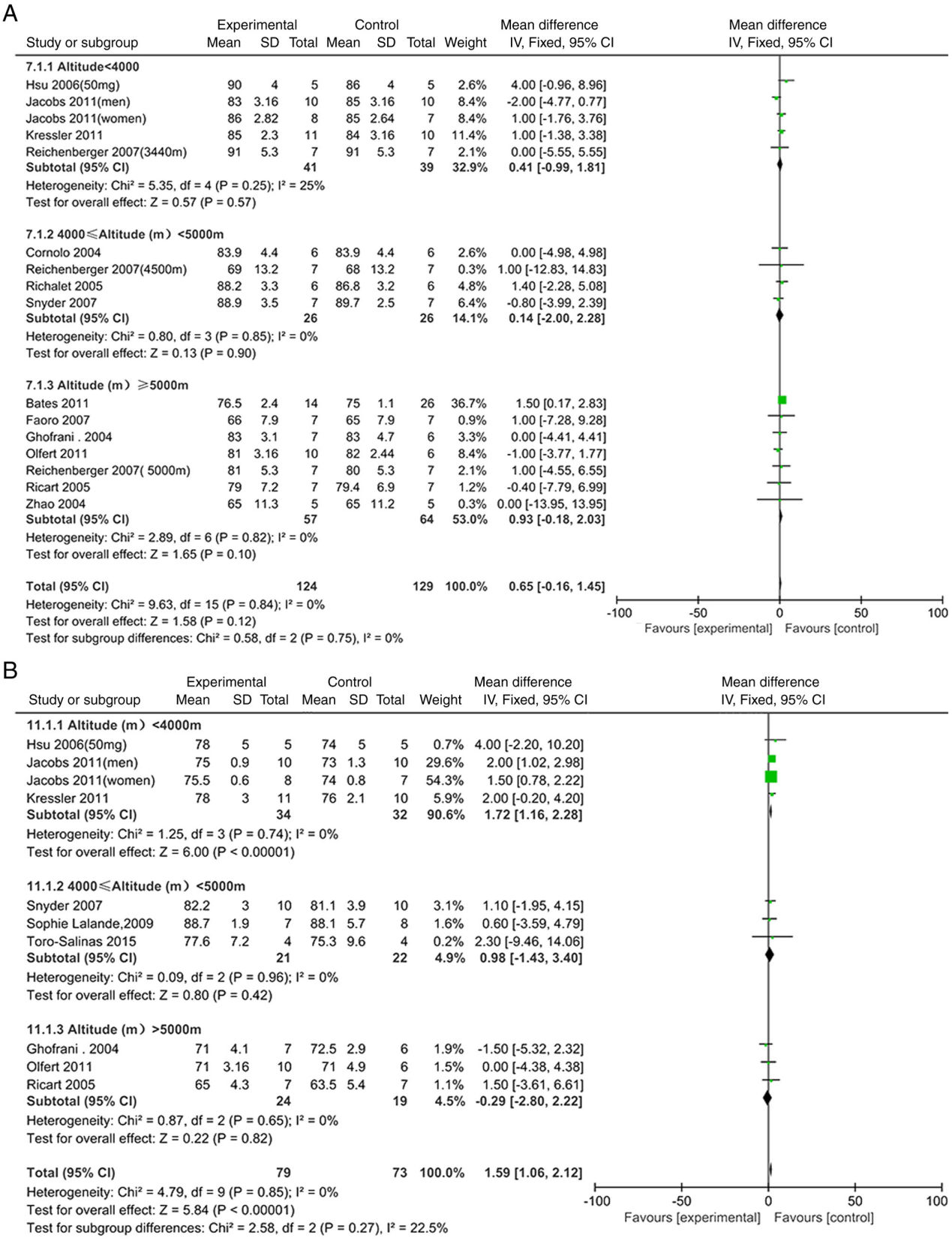

Figure 7. Forest plot of SaO_2 at rest and during exercise after treatment with Sildenafil vs. placebo control at high altitude. (A) SaO_2 at rest; (B) SaO_2 during exercise. At <4,000 meters, SaO_2 of the treatment group was significantly higher during exercise vs. the control group (P<0.0001). No significant difference was observed between the Sildenafil and placebo groups (P>0.05) at >4,000 meters. SaO_2, arterial oxygen saturation; CI, confidence interval.

present review. However, the lack of available studies prevented such an analysis. There were different designs of experiments. A total of six included studies were cross-over trials, all with small sample sizes. Although the research was conducted based on altitude, other outcomes, such as exercise intensity and different dose, were not classified due to a lack of data.

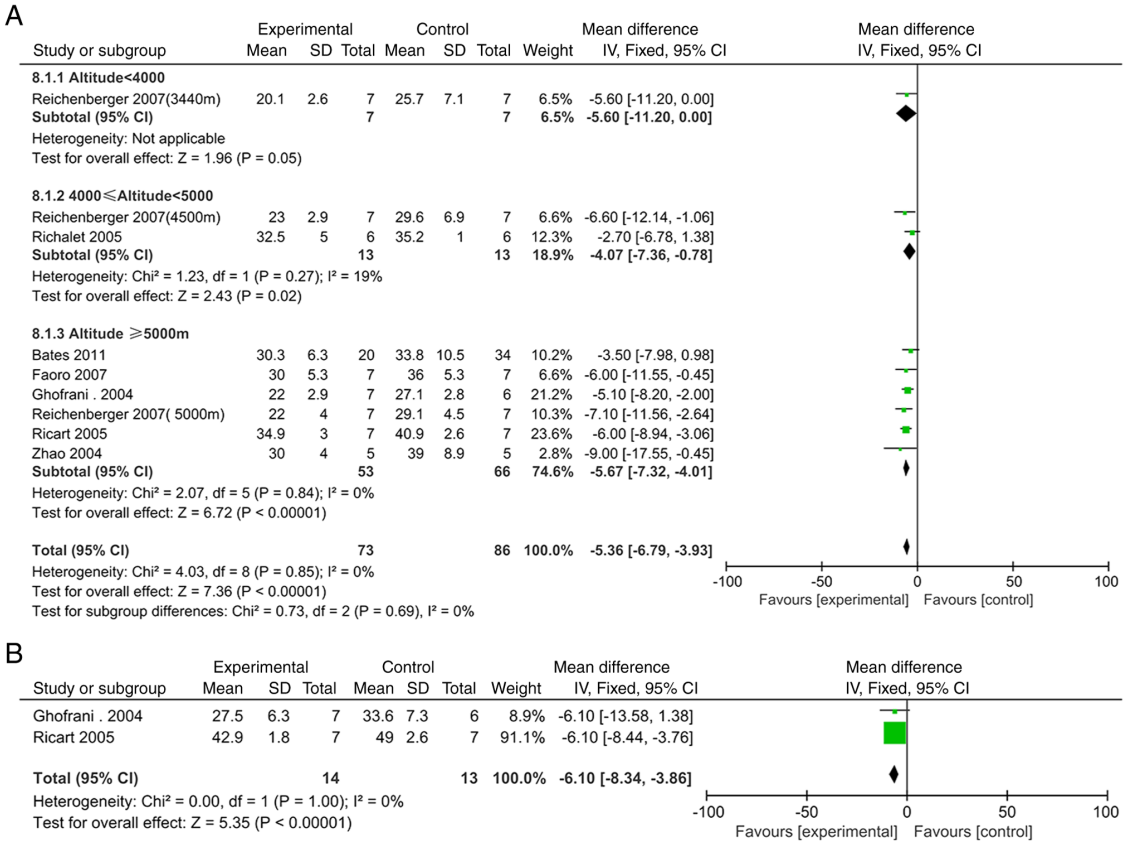

Figure 8. Forest plot of PASP at rest and during exercise after treatment with Sildenafil vs. placebo control at high altitude. (A) PASP at rest; (B) PASP during exercise. There was a significant reduction in PASP due to treatment with Sildenafil at >4,000 meters at rest (P<0.05) and during exercise at an altitude of 5,000 meters (P<0.0001). PASP, pulmonary artery systolic pressure; CI, confidence interval.

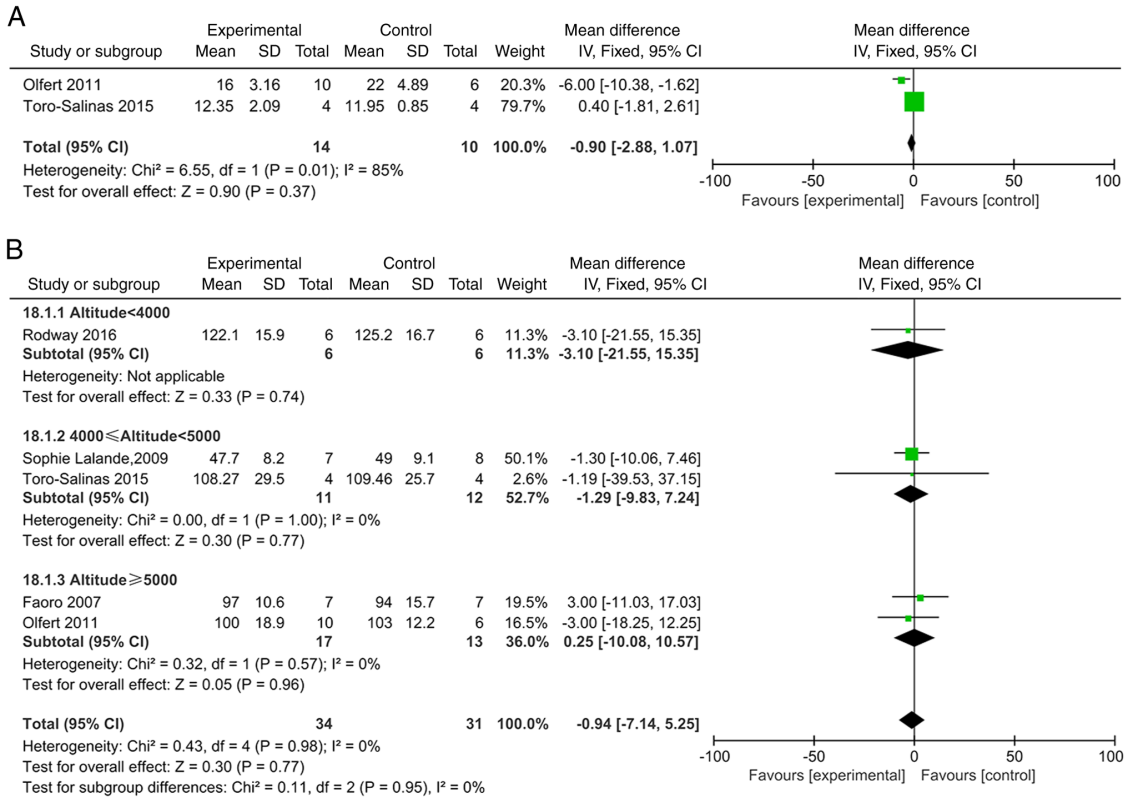

Figure 9. Forest plot of minute ventilation (V_E) at rest and during exercise after treatment with Sildenafil vs. placebo control at high altitude. (A) V_E at rest; (B) V_E during exercise. No differences were observed for V_E either rest or during exercise in Sildenafil group vs. the control group after exposure to high altitudes (P>0.05). V_E, minute ventilation; CI, confidence interval.

Therefore, the present review provided novel insights while interpreting the efficacy of Sildenafil on echocardiographic and hemodynamic parameters in healthy humans in high-altitude hypoxia. The efficacy depended on whether the subject is exercising or at rest but also on altitude.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com) and Cochrane (https://www.cochrane.org/) website. The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZCD and ZZZ contributed to study conception and design, drafted the submitted manuscript and revised it critically for important intellectual content. ZQY and GMD independently appraised the study quality of the included trials and contributed to the analysis and interpretation of data. LDJ processed and beautified the pictures in the manuscript. ZCD and ZZZ contributed to acquisition, analysis and interpretation of data and drafted the manuscript. ZCD and ZQY contributed to the literature search and extracted data. SL contributed to sensitivity analyses and publication bias. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rubin LJ: Primary pulmonary hypertension. N Engl J Med 336: 111-117, 1997.
2. Ghofrani HA, Reichenberger F, Kohstall MG, Mrosek EH, Seeger T, Olschewski H, Seeger W and Grimminger F: Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: A randomized, double-blind, placebo-controlled crossover trial. Ann Intern Med 141: 169-177, 2004.
3. Hsu AR, Barnholt KE, Grundmann NK, Lin JH, McCallum SW and Friedlander AL: Sildenafil improves cardiac output and exercise performance during acute hypoxia, but not normoxia. J Appl Physiol (1985) 100: 2031-2040, 2006.
4. Ricart A, Maristany J, Fort N, Leal C, Pagés T and Viscor G: Effects of sildenafil on the human response to acute hypoxia and exercise. High Alt Med Biol 6: 43-49, 2005.
5. Richalet JP, Gratadour P, Robach P, Pham I, Déchaux M, Joncquiert-Latarjet A, Mollard P, Brugniaux J and Cornolo J: Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. Am J Respir Crit Care Med 171: 275-281, 2005.
6. Weitzenblum E: Chronic cor pulmonale. Heart 89: 225-230, 2003.
7. Dorrington KL, Clar C, Young JD, Jonas M, Tansley JG and Robbins PA: Time course of the human pulmonary vascular response to 8 hours of isocapnic hypoxia. Am J Physiol 273: H1126-H1134, 1997.
8. Scherrer U, Allemann Y, Rexhaj E, Rimoldi SF and Sartori C: Mechanisms and drug therapy of pulmonary hypertension at high altitude. High Alt Med Biol 14: 126-133, 2013.
9. Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, Christman BW, Weir EK, Eickelberg O, Voelkel NF and Rabinovitch M: Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol 43(12 Suppl S) 43: S13-S24, 2004.
10. Andersson KE: PDE5 inhibitors-pharmacology and clinical applications 20 years after sildenafil discovery. Br J Pharmacol 175: 2554-2565, 2018.
11. Jin B, Luo XP, Ni HC and Shi HM: Phosphodiesterase type 5 inhibitors for high-altitude pulmonary hypertension: A meta-analysis. Clin Drug Investig 30: 259-265, 2010.
12. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, Sastry BK, Pulido T, Layton GR, Serdarevic-Pehar M and Wessel DL: A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation 125: 324-334, 2012.
13. Kjaergaard J, Snyder EM, Hassager C, Olson TP, Oh JK, Johnson BD and Frantz RP: Right ventricular function with hypoxic exercise: Effects of sildenafil. Eur J Appl Physiol 102: 87-95, 2007.
14. Xu Y, Liu Y, Liu J and Qian G: Meta-analysis of clinical efficacy of sildenafil, a phosphodiesterase type-5 inhibitor on high altitude hypoxia and its complications. High Alt Med Biol 15: 46-51, 2014.
15. Zhao L, Mason NA, Morrell NW, Kojonazarov B, Sadykov A, Maripov A, Mirrakhimov MM, Aldashev A and Wilkins MR: Sildenafil inhibits hypoxia-induced pulmonary hypertension. Circulation 104: 424-428, 2001.
16. Kressler J, Stoutenberg M, Roos BA, Friedlander AL, Perry AC, Signorile JF and Jacobs KA: Sildenafil does not improve steady state cardiovascular hemodynamics, peak power, or 15-km time trial cycling performance at simulated moderate or high altitudes in men and women. Eur J Appl Physiol 111: 3031-3040, 2011.
17. Faoro V, Lamotte M, Deboeck G, Pavelescu A, Huez S, Guenard H, Martinot JB and Naeije R: Effects of sildenafil on exercise capacity in hypoxic normal subjects. High Alt Med Biol 8: 155-163, 2007.
18. Calbet JA, Boushel R, Rådegran G, Søndergaard H, Wagner PD and Saltin B: Determinants of maximal oxygen uptake in severe acute hypoxia. Am J Physiol Regul Integr Comp Physio 284: R291-R303, 2003.
19. Fulco CS, Rock PB and Cymerman A: Maximal and submaximal exercise performance at altitude. Aviat Space Environ Med 69: 793-801, 1998.
20. Reichenberger F, Kohstall MG, Seeger T, Olschewski H, Grimminger F, Seeger W and Ghofrani HA: Effect of sildenafil on hypoxia-induced changes in pulmonary circulation and right ventricular function. Respir Physiol Neurobiol 159: 196-201, 2007.
21. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P and Klassen TP: Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 352: 609-613, 1998.
22. Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ 327: 557-560, 2003.
23. Altman DG and Bland JM: Standard deviations and standard errors. BMJ 331: 903, 2005.

24. Hozo SP, Djulbegovic B and Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5: 13, 2005.
25. Snyder EM, Olson TP, Johnson BD and Frantz RP: Influence of sildenafil on lung diffusion during exposure to acute hypoxia at rest and during exercise in healthy humans. Eur J Appl Physiol 103: 421-430, 2008.
26. Lalande S, Snyder EM, Olson TP, Hulsebus ML, Orban M, Somers VK, Johnson BD and Frantz RP: The effects of sildenafil and acetazolamide on breathing efficiency and ventilatory control during hypoxic exercise. Eur J Appl Physiol 106: 509-515, 2009.
27. Olfert IM, Loeckinger A, Treml B, Faulhaber M, Flatz M, Burtscher M, Truebsbach S and Kleinsasser A: Sildenafil and bosentan improve arterial oxygenation during acute hypoxic exercise: A controlled laboratory trial. Wilderness Environ Med 22: 211-221, 2011.
28. Toro-Salinas AH, Fort N, Torrella JR, Pagès T, Javierre C and Viscor G: Sildenafil does not improve exercise capacity under acute hypoxia exposure. Int J Sports Med 37: 785-791, 2016.
29. Jacobs KA, Kressler J, Stoutenberg M, Roos BA and Friedlander AL: Sildenafil has little influence on cardiovascular hemodynamics or 6-km time trial performance in trained men and women at simulated high altitude. High Alt Med Biol 12: 215-222, 2011.
30. Cornolo J, Mollard P, Brugniaux JV, Robach P and Richalet JP: Autonomic control of the cardiovascular system during acclimatization to high altitude: Effects of sildenafil. J Appl Physiol 97: 935-940, 2004.
31. Hainsworth R, Drinkhill MJ and Rivera-Chira M: The autonomic nervous system at high altitude. Clin Auton Res 17: 13-19, 2007.
32. Vogel JA, Hansen JE and Harris CW: Cardiovascular responses in man during exhaustive work at sea level and high altitude. J Appl Physiol 23: 531-539, 1967.
33. Vogel JA and Harris CW: Cardiopulmonary responses of resting man during early exposure to high altitude. J Appl Physiol 22: 1124-1128, 1967.
34. Coppel J, Hennis P, Gilbert-Kawai E and Grocott MP: The physiological effects of hypobaric hypoxia versus normobaric hypoxia: A systematic review of crossover trials. Extrem Physiol Med 4: 2, 2015.
35. Netzer N, Strohl K, Faulhaber M, Gatterer H and Burtscher M: Hypoxia-related altitude illnesses. J Travel Med 20: 247-255, 2013.
36. Swenson ER: Hypoxic pulmonary vasoconstriction. High Alt Med Biol 14: 101-110, 2013.
37. Ghofrani HA, Wiedemann R, Rose F, Olschewski H, Schermuly RT, Weissmann N, Seeger W and Grimminger F: Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med 136: 515-522, 2002.
38. Wilkens H, Guth A, König J, Forestier N, Cremers B, Hennen B, Böhm M and Sybrecht GW: Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. Circulation 104: 1218-1222, 2001.
39. Sastry BK, Narasimhan C, Reddy NK, Anand B, Prakash GS, Raju PR and Kumar DN: A study of clinical efficacy of sildenafil in patients with primary pulmonary hypertension. Indian Heart J 54: 410-414, 2002.
40. Carter EA, Lohse K, Sheel W and Koehle M: Sildenafil does not reliably improve exercise performance in hypoxia: A systematic review. BMJ Open Sport Exerc Med 5: e000526, 2019.
41. Rodway GW, Lovelace AJ, Lanspa MJ, McIntosh SE, Bell J, Briggs B, Weaver LK, Yanowitz F and Grissom CK: Sildenafil and exercise capacity in the elderly at moderate altitude. Wilderness Environ Med 27: 307-315, 2016.
42. Bates MG, Thompson AA, Baillie JK, Sutherland AI, Irving JB, Hirani N and Webb DJ: Sildenafil citrate for the prevention of high altitude hypoxic pulmonary hypertension: double blind, randomized, placebo-controlled trial. High Alt Med Biol 12: 207-214, 2011.