Apunts Med Esport. 2016;51(189):27–35

apunts
MEDICINA DE L'ESPORT
www.apunts/org

REVIEW

Can sildenafil improve physical performance at altitude? Current scientific evidence

Andrés Toro-Salinas[a], Joan Ramon Torrella[a], Teresa Pagès[a], Casimiro Javierre[b], Ginés Viscor[a,*]

[a] Departament de Fisiologia i Immunologia, Facultat de Biologia, Universitat de Barcelona, Spain
[b] Departament de Ciències Fisiològiques II, Facultat de Medicina, Universitat de Barcelona, Spain

Received 2 October 2015; accepted 8 November 2015
Available online 12 January 2016

KEYWORDS
Sildenafil;
High altitude;
PDE-5 inhibitor;
Exercise;
Hypoxia;
Normobaric;
Hypobaric

Abstract Sildenafil has proven to efficiently reduce the increase in pulmonary artery pressure provoked by hypoxic pulmonary vasoconstriction. However, its role as a possible factor in increasing exercise performance under hypoxic conditions remains to be demonstrated. The use of sildenafil has increased among mountaineers, not as a high altitude pulmonary edema preventive drug, but as a means that could help to improve performance. Several studies have attempted to address this issue, with conflicting results. Currently, despite the inconclusive data at simulated or real altitude, and with the clear evidence that, in normoxia, sildenafil does not improve performance, this drug is being used (and sometimes overused) by people who climb high peaks. However, such potential performance improvement would depend on the degree of hypoxemia (altitude) and the individual responsiveness to this drug. This paper reviews the current knowledge on this matter.

PALABRAS CLAVE
Sildenafilo;
Gran altitud;
Inhibidor de PDE-5;
Ejercicio;
Hipoxia;
Normobárico;
Hipobárico

¿Afecta sidenafilo a la capacidad física en altitud? Evidencias científicas en la actualidad

Resumen Sildenafilo ha demostrado eficacia reduciendo la hipertensión pulmonar provocada por la vasoconstricción pulmonar hipóxica. Su papel como posible factor para aumentar el rendimiento en el ejercicio en condiciones de hipoxia está por demostrar, pero el uso de sildenafilo ha aumentado entre los montañeros, no como un fármaco preventivo del edema pulmonar de gran altitud, sino en la creencia de que podría ayudar a mejorar el rendimiento físico a gran altura geográfica. Varios estudios han tratado de abordar este tema, con resultados

* Corresponding author.
E-mail address: gviscor@ub.edu (G. Viscor).

http://dx.doi.org/10.1016/j.apunts.2015.11.001

contradictorios. Actualmente, a pesar de que no hay datos concluyentes, ni en altitud simulada ni real, y con la clara evidencia de que en normoxia el sildenafilo no mejora el rendimiento físico, se continúa utilizando esta sustancia (a veces en exceso) por personas que suben a altas cumbres. Tal potencial mejora de rendimiento dependería del grado de hipoxemia (altitud) y de la capacidad de respuesta individual a este medicamento. El presente artículo revisa el conocimiento actual sobre este tema.

Mechanism of sildenafil action

Since the work of Ghofrani et al.[1] about the improvement of physical capacity during exercise in hypoxia conditions due to the use of sildenafil,[1] several studies have attempted to reproduce their findings. However, to date, there is still controversy over whether phosphodiesterase type 5 (PDE-5) inhibitor is a substance that can actually improve performance under hypoxic conditions. Sildenafil has been used to treat erectile dysfunction[2] through inhibition of PDE-5 activity which, in turn, increases the cyclic guanosine monophosphate (cGMP) local concentration, thus causing vasodilatation by inducing relaxation of arterial wall smooth muscle fibers, especially in the corpus cavernosum and lungs.[3] In the lungs, its effect is focused on the treatment of pulmonary arterial hypertension (PAH)[4,5] caused by the general hypoxic vasoconstriction: the vasodilation response induced by sildenafil decreases pulmonary vascular resistance, thus favoring the uptake of oxygen and increasing the arterial oxygen content (CaO_2). Sildenafil has also been used in patients suffering from diseases associated with PAH such as chronic heart failure,[6,7] chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis.[8–10] In all these cases, sildenafil was able to decrease pulmonary artery pressure (PAP) and improve the patients exercise performance.

Apart from these medical considerations, the effect of sildenafil in PAH and hypoxic pulmonary vasoconstriction (PHV) in situations of moderate or severe hypoxia in healthy people has also attracted researchers' interest. The acute exposure to normobaric or hypobaric hypoxia produces a pulmonary vasoconstriction due to the decrease in alveolar oxygen tension (PAO_2), thus causing a reduction in oxygen diffusion from alveoli to capillaries and a consequent decrease in the oxygen transport to other tissues.[11] Moreover, increased pulmonary artery pressure causes overload in the right ventricle, affecting afterload and cardiac output (CO).[12,13]

Hypoxia and exercise

Exposure to acute hypoxia (AH) causes the reduction of the maximum aerobic capacity, directly affecting the exercise performance.[14–16] VO_{2max} tends to diminish in direct proportion to the decrease in CaO_2, which occurs as hypoxia increases.[17,18] Exercise exacerbates CaO_2 reduction due to the lower uptake of O_2 during gas exchanging in the lungs,[1,19] which may increase the risk of pulmonary edema,[11,20] especially in people predisposed to suffer this complications associated to rapid ascent.[21] Considering that the increase in PAP could be an important factor limiting performance during exercise in hypoxia,[22] sildenafil has been proposed as a potential ergogenic aid for physical activity in hypoxic conditions due to its possible benefits for athletic performance, and has been widely used.[23–27] This could be of especial interest in some countries, such as Andean or central Asia plateaus, where many professional athletes and football and other collective sport teams have to perform or play in locations higher than 2500 m. Finally, sildenafil use has also been promoted under the name of ''Vitamin V'' in some Internet forums because it supposedly improves muscle hypertrophy in bodybuilders and fitness enthusiasts.[28]

Sildenafil effects during exercise and hypoxia

Research conducted on healthy people, combining the effects of exercise and hypoxia after sildenafil administration, has yielded contrasting results. Studies on this subject present a wide range of designs and methodologies leaving many questions still unanswered about the possible benefits of the sildenafil administration under hypoxic conditions. The following paragraphs present a review of the most relevant studies on sildenafil administration and exercise in hypoxia. All the studies had a randomized double blind, placebo controlled and crossover design, except for Olfert et al.,[15] which was single-blind designed and did not use placebo. Table 1 summarizes the main methodological characteristics of the included studies.

The first published study concerning the relationship between sildenafil, exercise and hypoxia was that of Ghofrani et al.[1] These authors studied a group of 14 people (12 men and 2 women) who had previous experience in altitude exposure. Data from the participants were recorded at rest and during maximum incremental exercise tests (W_{peak}) in two different situations: (1) at an altitude of 171 m breathing through a mask of a hypoxic gas mixture with 10% fraction of oxygen for 2 h and (2) at an altitude of 5245 m after 8 days of ascent until Everest base camp. Under a random-controlled environment and 2 h before evaluating the participants, one dose of 50 mg of sildenafil or one dose of placebo were administered to each group. Their results showed that sildenafil reduced the PAH at