Effects of sildenafil on pulmonary artery pressure and gas exchange at high altitude.
A double-blind placebo-controlled study

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Transfer of fluids within the lung in hypoxia

- Capillary
- Alveolus
- Endothelial cell
- P II
- Lymphatics

Hyperpressure
Increased permeability
Reduced reabsorption
Available treatments of hypoxic pulmonary hypertension (PHT) are not satisfactory:

- systemic hypotensive effects,
- difficulty to handle in the field

Phosphodiesterase type 5 is an enzyme localized in corpus cavernosum and in pulmonary vessels (distal muscularized pulmonary arteries)

Inhibition of PDE5 prolongs the vasodilating effects of NO and ANP by blocking the hydrolysis of cGMP

Sildenafil (PDE5 inhibitor) could be useful in reducing altitude hypoxia-induced PHT
Subjects

12 healthy male volunteers
Double blind placebo - controlled study
PLA, n=6       SIL, n=6

Treatment

Sildenafil : 3 x 40 mg / day (08:00 – 12:00 – 20:00)
Methods

B.S.: blood sampling for cGMP,  \textit{maxVO}_2: maximal exercise test (cycloergometer)  
Echo: echocardiography (Cypress, Acuson/Siemens, Germany)
Methods (cont’d)

Lake Louise AMS Score

Heart rate, SaO₂, systemic blood pressure

Cardiac output and intra-thoracic fluid by trans-thoracic impedancemetry

(Physioflow, Manatec, France)
* P<0.05 vs Sea-level PRE,  # P<0.05 SIL vs PLA,  + P<0.05 SIL vs PLA pooled D2-D3 D5-D6,
§: P<0.05 D1 vs Sea-level PRE, pooled SIL + PLA
Cardiac output

* P<0.05 vs Sea-level PRE, §: P<0.05  D1 vs Sea-level PRE, pooled SIL + PLA
Pulmonary vascular resistance index

* P<0.05 vs Sea-level PRE,  # P<0.05 SIL vs PLA,  ++ P<0.01 SIL vs PLA pooled D2-D3 D5-D6,
§: P<0.05  D1 vs Sea-level PRE, pooled SIL + PLA
cGMP

* P<0.05 vs Sea-level PRE,  # P<0.05 SIL vs PLA,  + P<0.05 SIL vs PLA pooled D3-D6,
§§: P<0.01  D1 vs Sea-level PRE, pooled SIL + PLA
Systemic arterial pressure

* P<0.05 vs Sea-level PRE, §§: P<0.05  D1 vs Sea-level PRE, pooled SIL + PLA
**SaO₂**

![Graph showing SaO₂ levels over time at sea level and high altitude.](image)

* P<0.05 vs Sea-level PRE,  
# P<0.05 SIL vs PLA,  
## P<0.01 SIL vs PLA,  
 §§: P<0.01 D1 vs Sea-level PRE, pooled SIL + PLA,  
+++ P<0.001 SIL vs PLA pooled D2-D6
**PET-PaO₂ rest**

* P<0.05 vs Sea-level PRE,
# P<0.05 SIL vs PLA,
+++ P<0.001 SIL vs PLA pooled D2-D5
Δ Intra-thoracic fluid index, %

* P<0.05 vs Sea-level PRE,    # P<0.05 SIL vs PLA,
§§: P<0.01  D1 vs Sea-level PRE, pooled SIL + PLA
Decrease in maxVO$_2$

* P<0.05 vs Sea-level PRE,  # P<0.05 SIL vs PLA,
++ P<0.01 SIL vs PLA pooled D2-D5
Summary

Sildenafil decreased systolic PAP
  decreased pulmonary vascular resistance

Sildenafil had no effect on
  cardiac output and
  systemic blood pressures

Sildenafil facilitated the oxygen transfer within the lungs and
  reduced the level of hypoxemia

Sildenafil limited the HA-induced decrease in VO$_2$max

Sildenafil had no effect on Acute Mountain Sickness and
  acclimatization to HA.
Hypotheses of mechanisms of action of sildenafil at high altitude

- **Sildenafil**
  - Increase in PAP
  - Decrease in VO₂max

- **GMPc**
  - Positive effect
  - Negative effect on vasoconstriction

- **Hypoxia**
  - Decrease in PaO₂
  - Increase in PA-Pa O₂ gradient

- **Decrease in PaO₂**
  - Decrease in VO₂max

- **Vasoconstriction**

- **Capillary leak**

- **Interstitial edema**

- **Alveolar edema**

- **Increase in PAP**
Conclusions

Sildenafil protects against the development of HA-induced PHT and ameliorates gas exchange, thus limiting the altitude-induced hypoxemia and decrease in exercise performance.

Sildenafil could be used to treat HAPE, or to prevent HAPE in highly susceptible subjects instead of calcium blockers.

Sildenafil should not be used to prevent AMS.