

# The effect of bosentan on exercise capacity in acute hypoxia



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# High altitude

Aerobic exercise capacity at high altitude is decreased because:

- ↓ O<sub>2</sub> delivery to tissue
- ↓ arterial oxygenation
- ↓ maximum cardiac output

# Up to 5000m

- Decreased arterial O<sub>2</sub> saturation is being compensated
- Exercise capacity remains decreased  
→ related to a decrease in maximum cardiac output



# Possible explanation:

Limitation in right ventricular flow output by hypoxic pulmonary vasoconstriction

# Hypothesis:

Pulmonary vascular resistance (PVR) decreases exercise capacity in hypoxic healthy subjects.

# Bosentan

- Therapy of pulmonary hypertension
- ETA/ETb receptor blocker
- Decreases pulmonary arterial pressure
- NO effect on syst. blood pressure, ventilation or arterial oxygenation
  - Investigate the decrease of pulmonary vascular resistance on exercise in acute hypoxia.

# Methods

## Subjects

- 11 healthy volunteers
- 2 women and 9 men
- Age 29 years (mean)
- Height  $178 \pm 10$  cm (mean  $\pm$  SD)
- Weight  $70 \pm 11$  kg (mean  $\pm$  SD)

# Double-blind randomized placebo-controlled cross-over design

- Normoxia placebo
- Normoxia bosentan
- Hypoxia placebo
- Hypoxia bosentan

Normoxia:  $FIO_2$ : 0,21

Hypoxia:  $FIO_2$ : 0,12



# Experimental design

Day 1: 62,5mg bosentan 2dd

Day 2-3: 125 mg bosentan 2dd

Day 4: Tests

Day 5-7: Rest

Tests:

- Echocardiogram at rest
- Echocardiogram at different levels of exercise
- Cycle ergometer cardio-pulmonary exercise test (CPET)

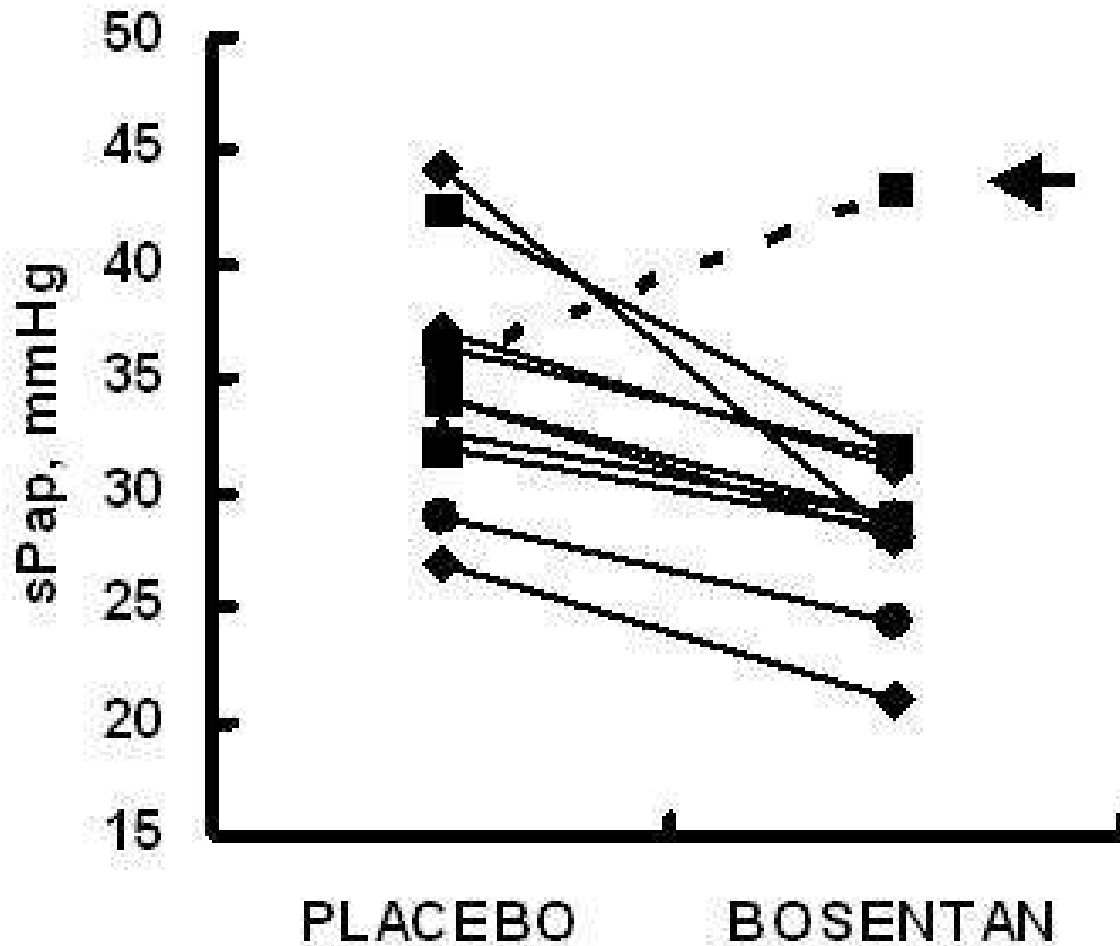


# Effects on hemodynamics and O<sub>2</sub> saturation at rest

Variables	Normoxia		Acute hypoxia	
	Placebo	Bosentan	Placebo	Bosentan
HR, beats/min	68 ± 5	71 ± 4	78 ± 5*	78 ± 4
SpO <sub>2</sub> , %	99 ± 1	98 ± 1	73 ± 3***	74 ± 3
Psa, mmHg	87 ± 3	87 ± 2	85 ± 3	88 ± 3
Q, L/min/m <sup>2</sup>	2.9 ± 0.2	3.3 ± 0.2	3.4 ± 0.2*	3.7 ± 0.2
sPap, mmHg	24 ± 1	25 ± 1	35 ± 2**	30 ± 2§§
PVR, mmHg/L/min/m <sup>2</sup>	5.7 ± 0.3	5.2 ± 0.5	7.1 ± 0.5*	5.5 ± 0.3§§

\* = effect of hypoxia, § = effect of bosentan

# Effect of bosentan on pulmonary artery pressure (sPap) in hypoxia



# Effects of hypoxia on cardiopulmonary exercise variables

Variables	Normoxia	Hypoxia
Workload max, W	275 ± 16	200 ± 14***
VO <sub>2</sub> max, ml/kg/min	47 ± 2	35 ± 2***
V <sub>E</sub> max, L/min	125 ± 8	108 ± 8*
HR max, beats/min	189 ± 3	179 ± 2*
O <sub>2</sub> pulse, ml/beat	17 ± 1	13 ± 1***
Exercise SpO <sub>2</sub> , %	92 ± 1	73 ± 2***

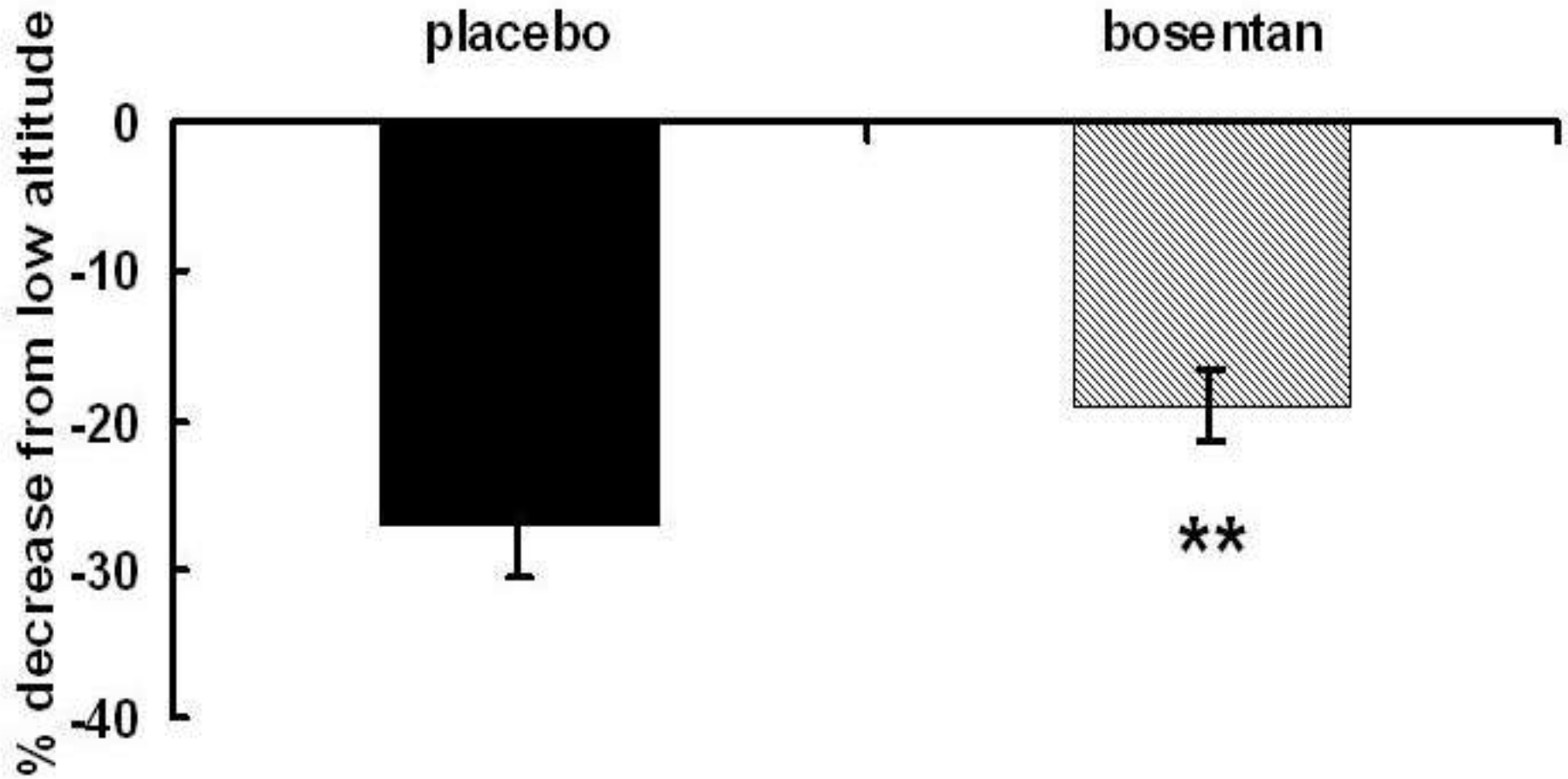
\* = effect of hypoxia, § =effect of bosentan

# Effects of bosentan on cardiopulmonary exercise variables

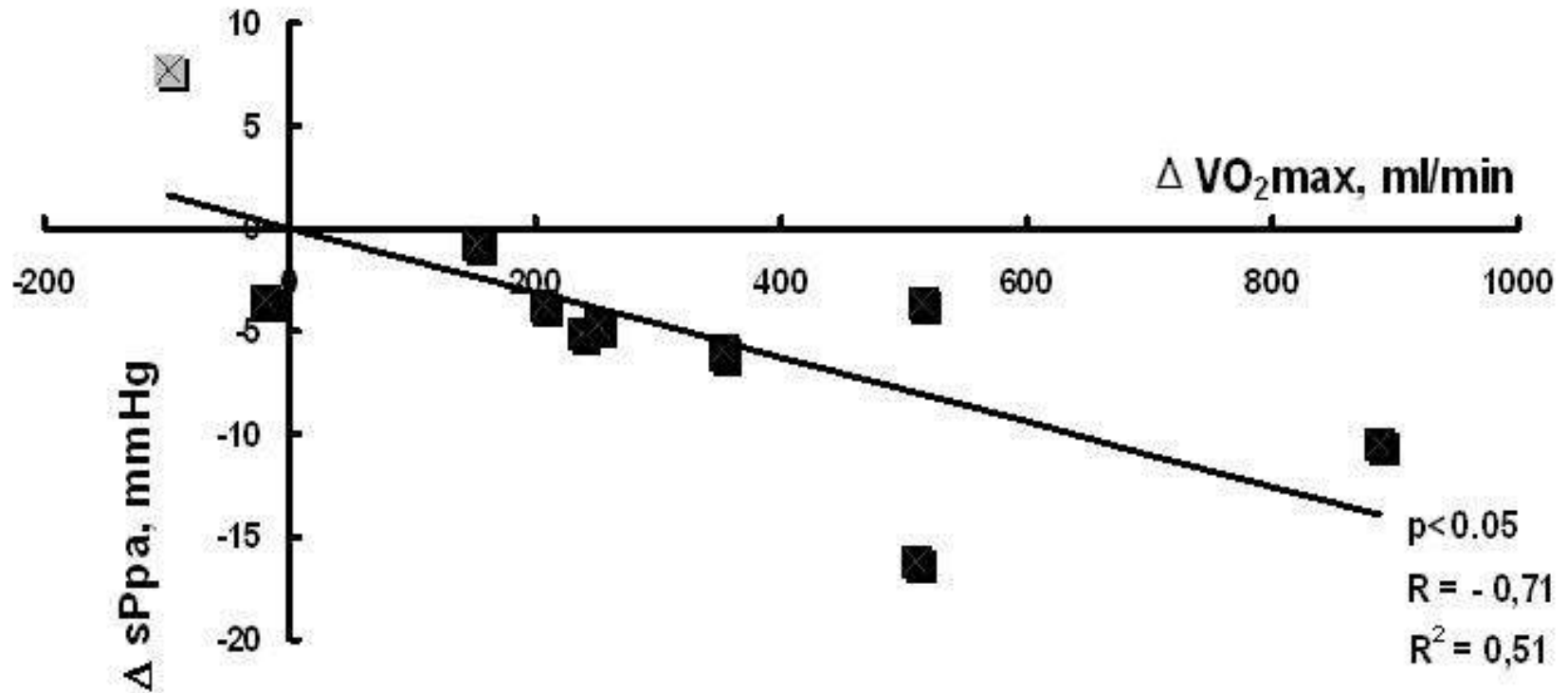
Variables	Hypoxia placebo	Hypoxia bosentan
Workload max, W	200 ± 14***	211 ± 14§
VO <sub>2</sub> max, ml/kg/min	35 ± 2***	39 ± 2§§
O <sub>2</sub> pulse, ml/beat	13 ± 1***	15 ± 1§
VE/VCO <sub>2</sub> at AT	31 ± 1***	30 ± 1

\* = effect of hypoxia, § = effect of bosentan

# VO<sub>2</sub>max



# Systolic pulmonary artery pressure vs. maximum O<sub>2</sub> uptake in acute hypoxia





# Conclusion

These results show that intake of bosentan improves aerobic exercise capacity in relation to the inhibition of hypoxic pulmonary vasoconstriction.


This suggests that mild pulmonary hypertension limits aerobic exercise capacity, probably through a limitation of right ventricular flow output.

This can be prevented by bosentan therapy.

# References

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ALTITUDE KILLS

धिटो गए लेक लाउध।

GO SLOWLY

जसले ज्यान लिन्ध।

AVOID ALTITUDE SICKNESS

विरुतारै जानुस्।

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