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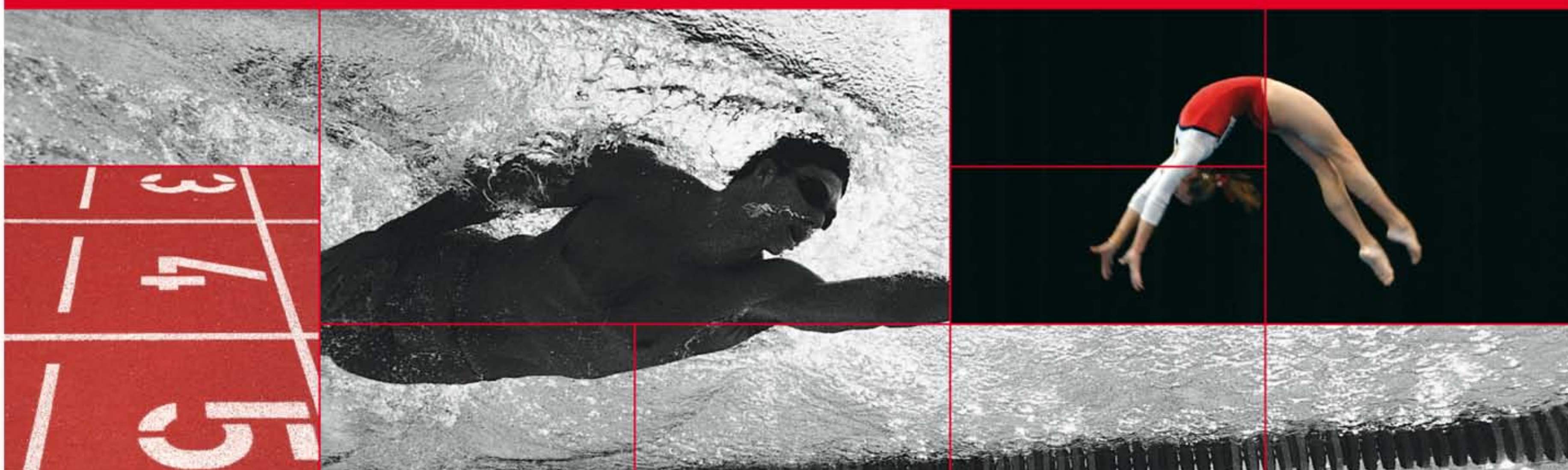
Flinders University South Australia

Australian Government
Australian Sports Commission

Hypoxic conditions and performance enhancement

Christopher J Gore



WADA/JADA Symposium on Blood-Doping, November 2009

Overview

- Types of hypoxia
- Effects of hypoxia – EPO & blood variables
- Worthwhile changes in performance
- Effects of hypoxia on performance
- Conclusions

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Background

- Altitude training used by endurance athletes for past 40+ yr
  - Balke et al. *JAMA 194 (6):176-179, 1965.*
  - Saltin. *Symposium proceedings. RF Goddard (Ed), Chicago: The Athletic Institute, 1967, p. 97-102*
  - Dill & Adams. *J.Appl.Physiol. 30 (6):854-59, 1971.*
- Widespread acceptance that altitude training improves performance at altitude and at sea-level
  - Dick FW. *Int.J.Sports Med. 13 (Suppl 1):S203-S206, 1992.*
- Scientific evidence more equivocal

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Types of Hypoxia

- Classical altitude training
  - Live and train at moderate natural alti
    (2000-3000m) for 2-6wk (multiple tim
- Live h

- Intern
  - 4 wk
- Intern
  - 4 wk
  - moderate to high altitude equivalent

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Effects of hypoxia:
- Erythropoietic changes

- Prevailing paradigm

~4 wk at moderate altitude (~2000-3000 m)

⇨ ↑serum EPO

⇨ ↑red cell volume (RCV)/Hb_{mass}

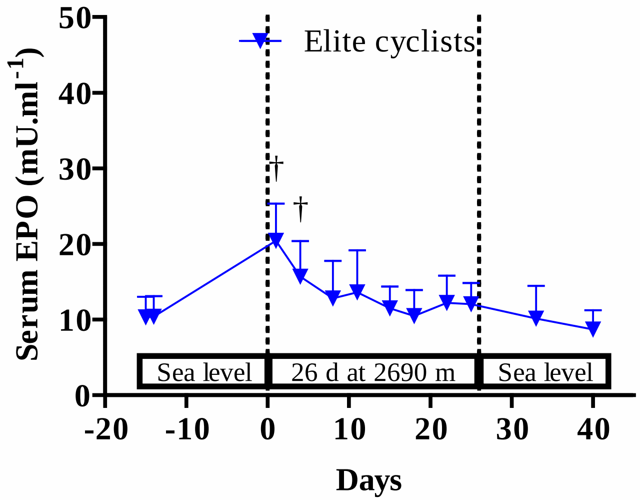
⇨ ↑VO_{2max}

⇨ ↑performance

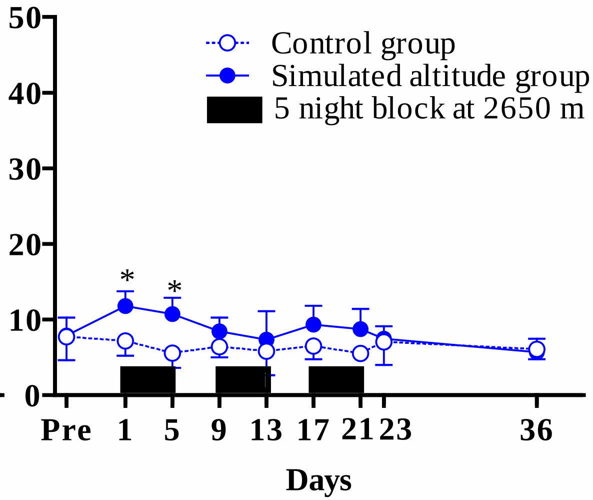
(e.g. Levine & Stray-Gundersen *J Appl Physiol* 83:101-12, 1997
Levine, Chapman & Stray-Gundersen *J Appl Physiol* 91:1113-20, 2001
Levine & Stray-Gundersen *Adv Exp Med & Biol* 502:75-88, 2001
Levine & Stray-Gundersen *Adv Exp Med & Biol* 588:233-47, 2006
Stray-Gundersen & Levine *Scand J Med Sci Sports* 18 Suppl 1:21-8, 2008)

Effects of hypoxia:
- Erythropoietic changes

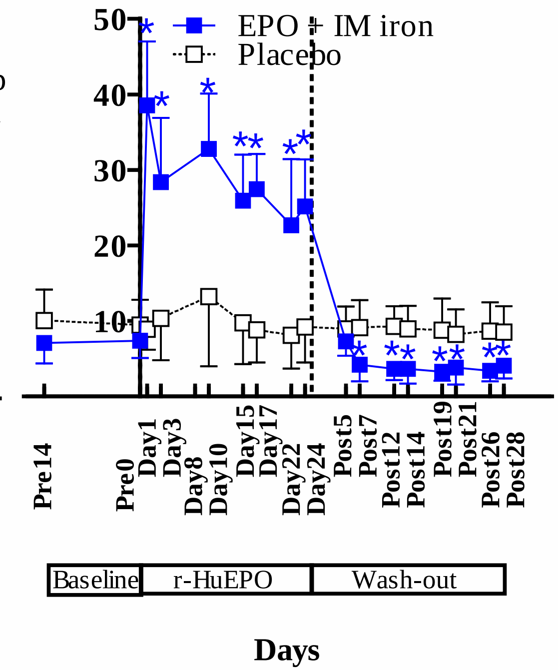
- EPO secretion



Classical altitude training



Simulated LHTL



r-HuEPO

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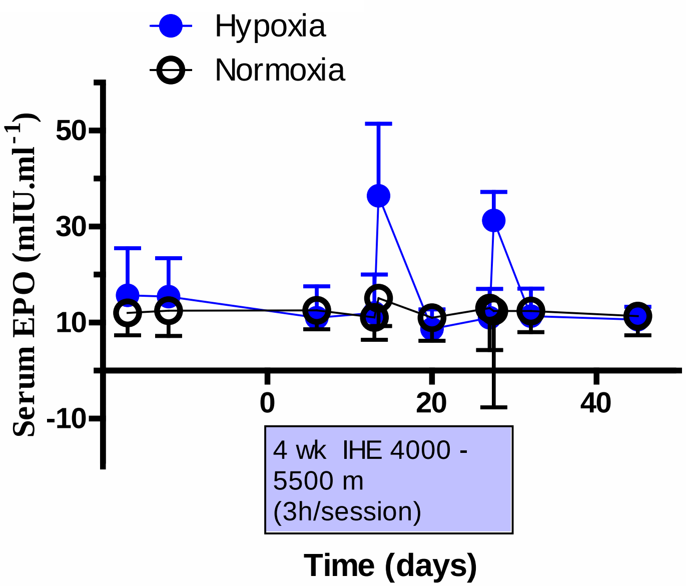
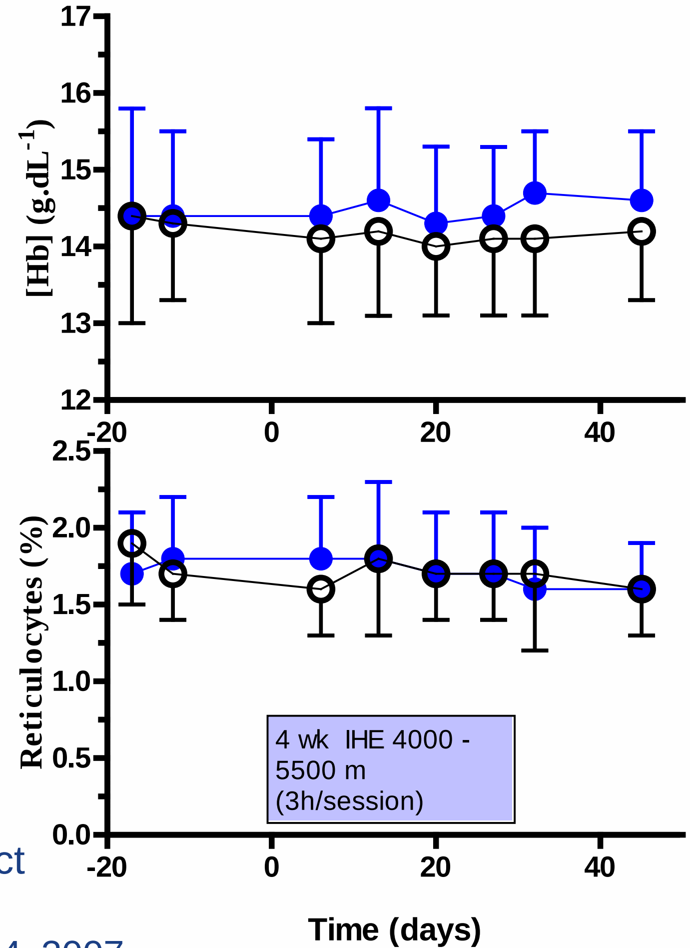
Effects of hypoxia:
- Erythropoietic changes

- EPO secretion





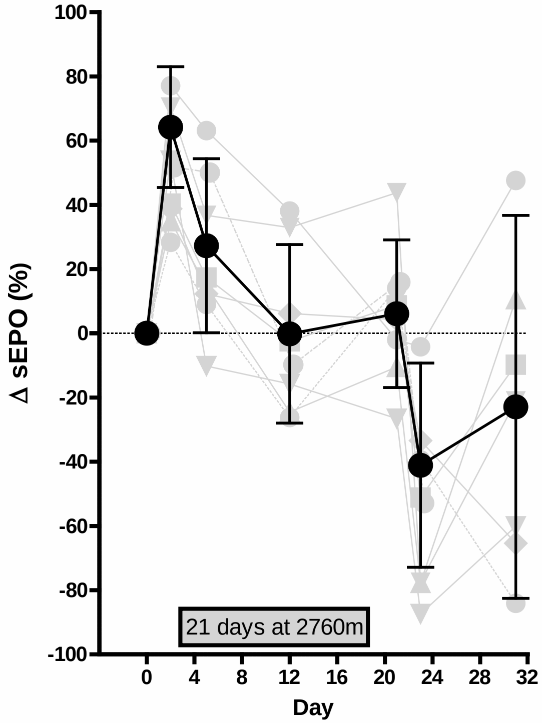
Intermittent Hypoxic Exposure

Similarly, no change sEPO, #RBC, [Hb] or Hct compared with control group.
Tadibi et al. *Med.Sci.Sports Exerc.* 39 (5):858-64, 2007

Gore et al. *J Appl Physiol.* 101:1386-93, 2006

Effects of hypoxia:
- Erythropoietic changes

- EPO secretion – individual variability
  Ge et al. *J.Appl.Physiol.* 92 (6):2361-2367, 2002.

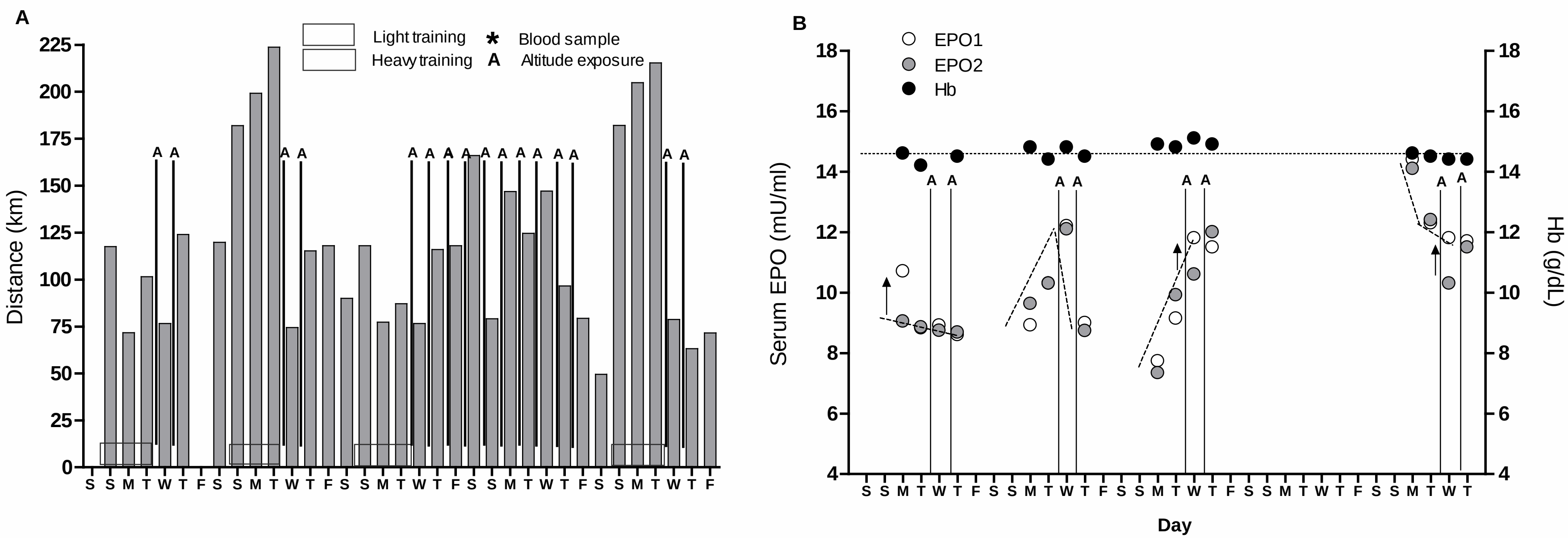


Classical altitude training

Effects of hypoxia:
- Erythropoietic changes

- EPO secretion – individual variability

Ge et al. *J.Appl.Physiol.* 92 (6):2361-2367, 2002.

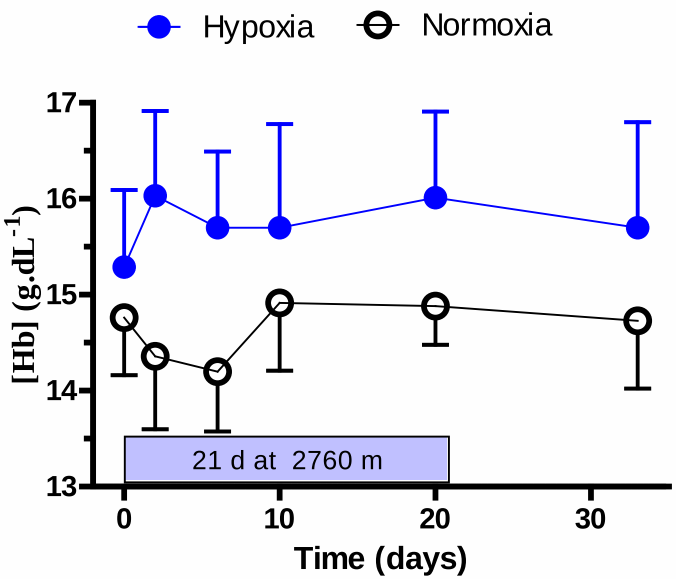


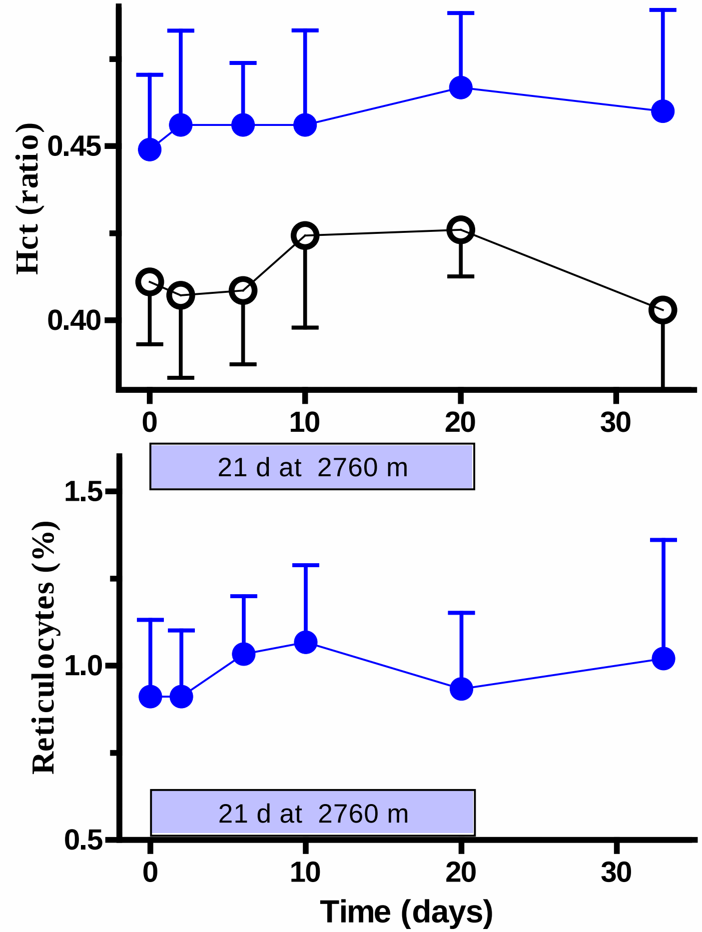
Simulated LHTL 2800 m, 8h/night

Garvican, et al. *Scand J Med Sci Sports* ***In Revision***, Nov 2009.
Garvican, et al. *Int J Sports Physiol Performance*, 2:327-31, 2007

Effects of hypoxia:
- Erythropoietic changes

- Haematology





Classical altitude training

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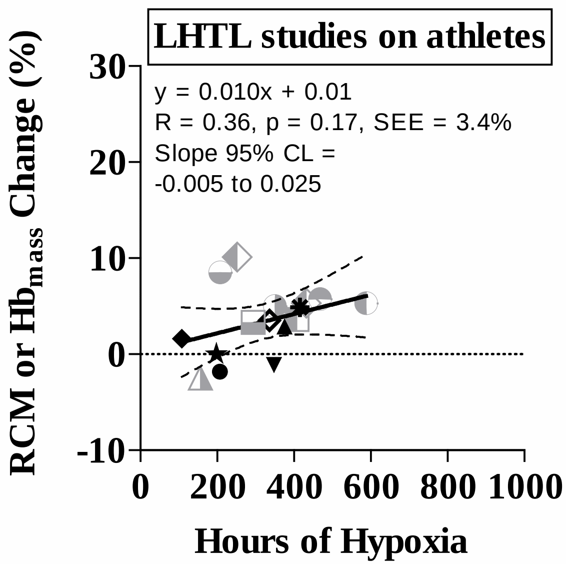
Sufficient dose of hypoxia - Live High Train Low

- Sufficient dose = >2000m for >12h/day for 3-4 weeks.
  - Rusko et al. *Curr. Sports Med. Rep.* 2 (4):233-238, 2003.
  - Levine &Stray-Gundersen *Adv. Exp. Med. Biol.* 588:233-47, 2006.



≤12 h/day
- ● Ashenden 1999 (3000m 9/d)
- ◆ Ashenden1999 (2650m 9h/d)
- ▲ Muir 2003 (2800m 9h/d)
- ✱ Saunders 2007 (2860m 9h/d)
- ★ Robach 2006 (3000m 11h/d)
- ▼ Neya 2007 (3000m 11h/d)
- ◇ Piehl-Aulin 1999 (2700m 12h/d)

>12 h/day
- Denhert 2002 (1956m13 h/d)
- Rusko 1999 (2500m 14h/d)
- Brugniaux 2006 (2500m 14h/d)
- Clark 2009 (3000m 14h/d)
- Robach 2006 (2750 16h/d)
- Laitinen 1995 (2500m 17h/d)
- Wehrlin 2006 (2500m 18h/d)
- Wehrlin 2006 (n=2) (2456m 18h/d)
- Levine 1997 (2500 21 h/d)

>2000m for >12 h/day

3 weeks @ 14 h/d = 294 h
4 weeks @ 20 h/d = 560 h

Clark et al, Eur J Appl Physiol. 106(3):399-406, 2009

Molecular mechanisms of hypoxia

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- **Hypoxia Inducible Factor (HIF)**
  a ubiquitous transcription factor
  - Stabilised in hypoxia (also stimulated by insulin and IGFs)

- HIF target genes (>100) include those for:
- **Oxygen transport: erythropoiesis and iron metabolism**
  - EPO -erythropoiesis; Transferrin -iron transport;
    Transferrin receptor -iron uptake; Ceruloplasmin -iron oxidation
- **Oxygen transport: vascular regulation**
  - VEGF, EG-VEGF, PAI 1-angiogenisis; Flt 1-VEGF-receptor 1; Endothelin 1; Atrial Natriuretic Peptide, Adrenomedullin; alpha-1B adrenergic receptor -vascular tone; iNOS -NO production; Heme oxygenase 1-CO production
- **Anaerobic energy: glucose uptake and glycolysis**
  - Glucose transporters 1&3- glucose uptake;
    Hexokinase, Phosphofrutco kinase L, aldolase, enolase 1, Lactate dehydrogenase, phosphoglycerate kinase 1 -glycolysis
- **Other**
  - Carbonic anhydrase -pH regulation, IGFBP-1 -growth factor
  - Transglutaminase 2, Asparagine synthase -amino acid metabolism
- EPO increase of “responders” to hypoxia may be co-incident with, but not solely causative of, possible performance benefits

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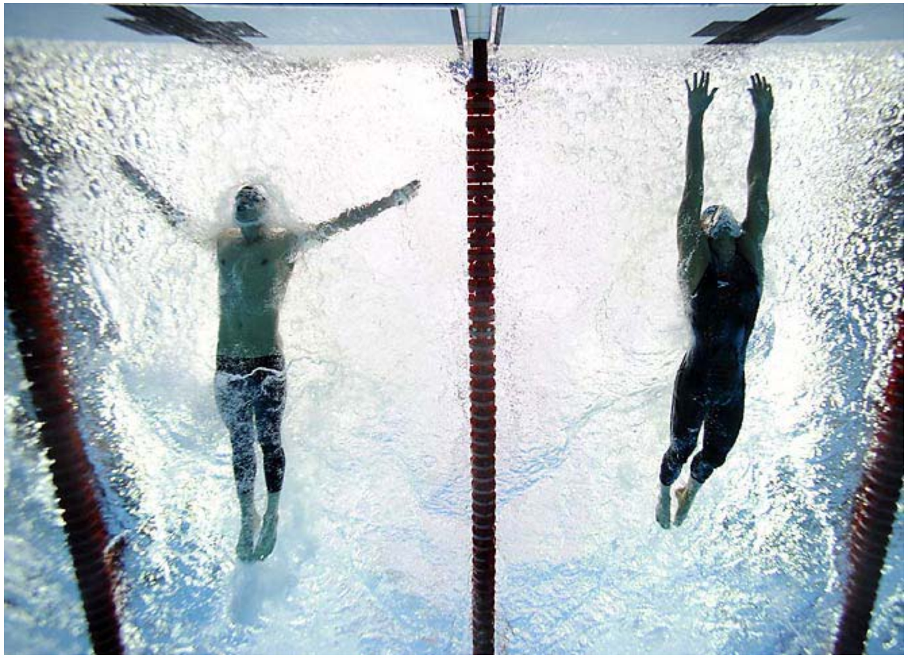
Performance benefits of hypoxia for elite athletes

- What is a *worthwhile change* in performance?
- How reliable are performances of *elite* athletes?

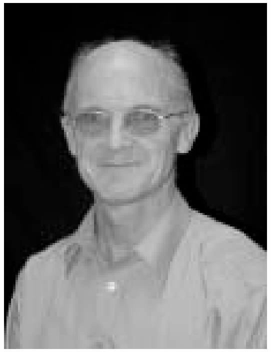


Reliability of elite athlete performance

- 676 official race times of 26 US and 25 Australian Olympic **swimmers** 1 yr before 2000 Olympic Games.
- The coefficient of variation in performance time was:
  0.6% (95% CL 0.56 to 0.65%) **within** a competition
  0.8% (95%CL 0.73 to 0.86%) **between** competitions.
- An enhancement of ~ 0.4%
  (half of the between-competition variability)
  substantially increases chances of a medal

Pyne, et al. *J Sports Sci.* 22 (7):613-620, 2004

Worthwhile improvement



- At elite level, smallest worthwhile change in performance is about half (0.5) the typical variation in an athlete's performance from competition to competition, or ~1%
  or (0.5 x 1.0 = 0.5%)

  (Hopkins, *Sportscience* 8: 1-7, 2004)

- One third (0.3) x the typical variation in athlete's performance from competition to competition,
  or (0.3 x 1.0 = 0.3%)

  Hopkins et al. *MSSE* 41:3-12, 2009
- Conventional stats / sample sizes inadequate

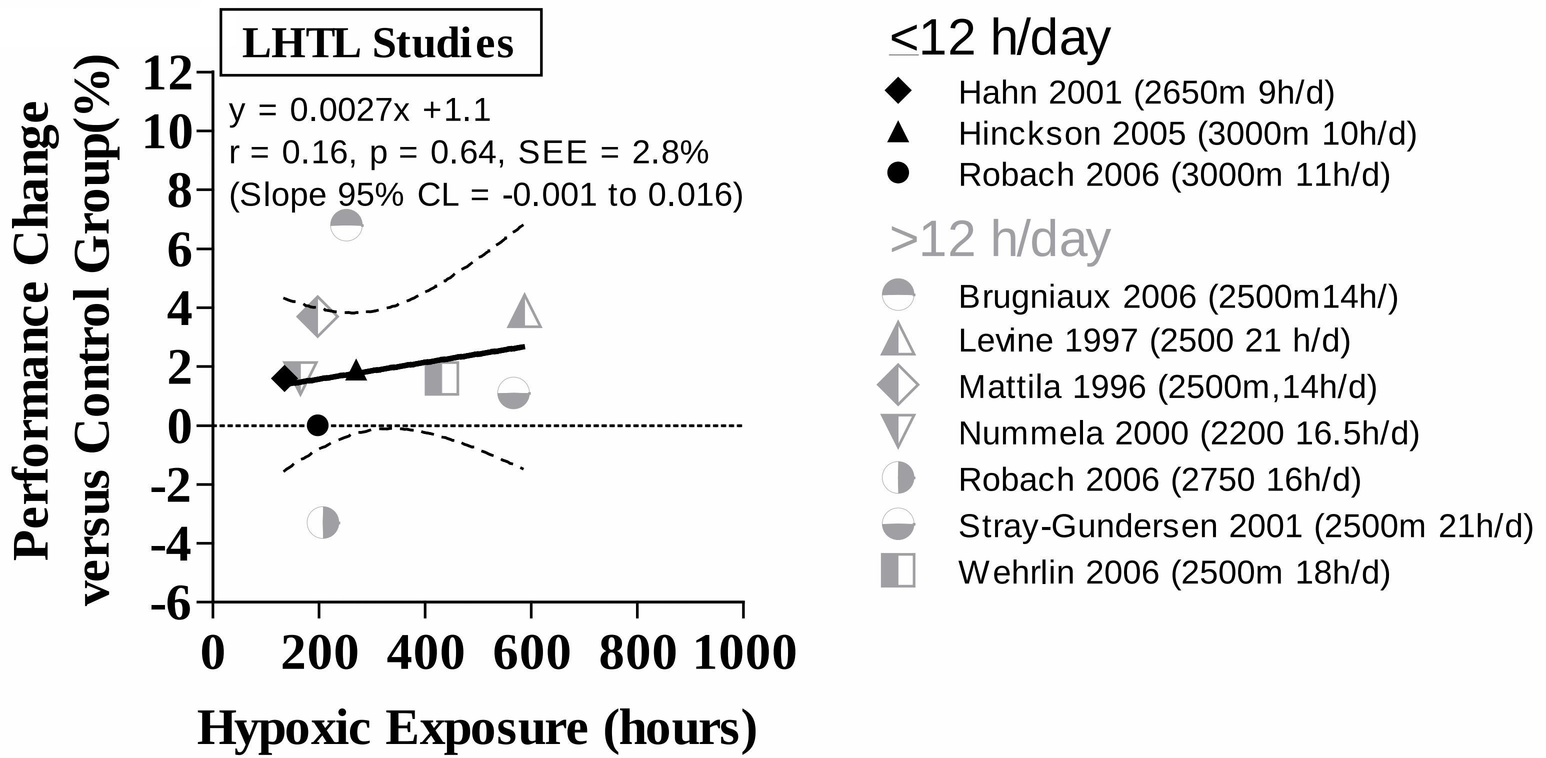
Sea level performance benefits of **Classical Altitude Training** in elite athletes

- Bonetti & Hopkins, Meta-analysis of sea level performance following adaptation to hypoxia. *Sports Medicine* 39: 107-27, 2009

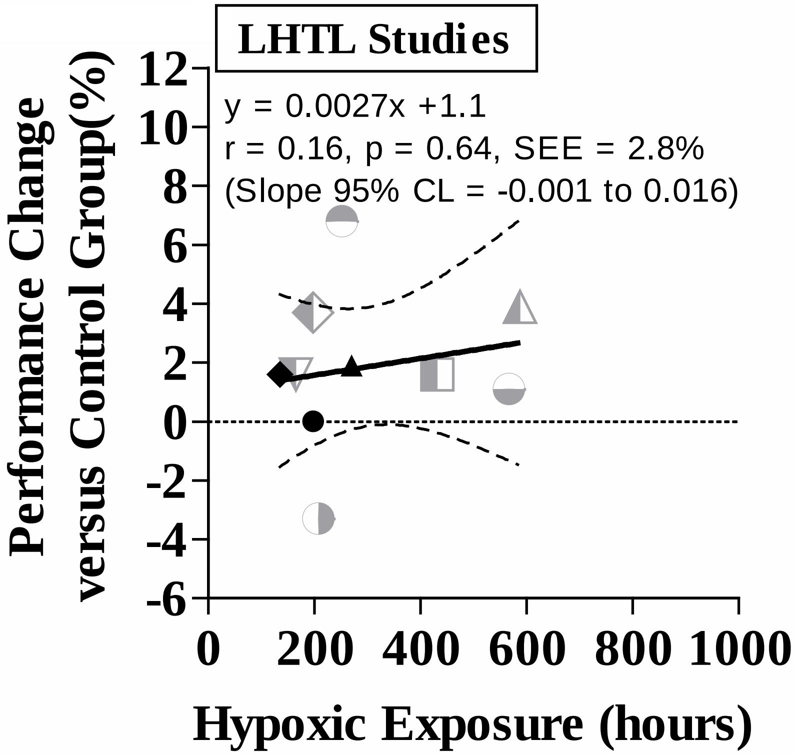
1.9 ± 1.5% (mean ± SD)
all studies
>50% likely beneficial (vs 1% SWC)

1.6 ± 1.6%
controlled studies
>50 % likely trivial benefit
Placebo is problematic

Performance benefits of LHTL in elite athletes



Performance benefits of LHTL in <u>elite</u> athletes



Bonetti & Hopkins, *Sports Medicine* 39: 107-27, 2009

1.6± 1.1%

(mean ± SD) **all studies**

4.0 ± 2.3% controlled studies

Saunders et al *High Alt Med Biol 10 (2):* 135-48, 2009

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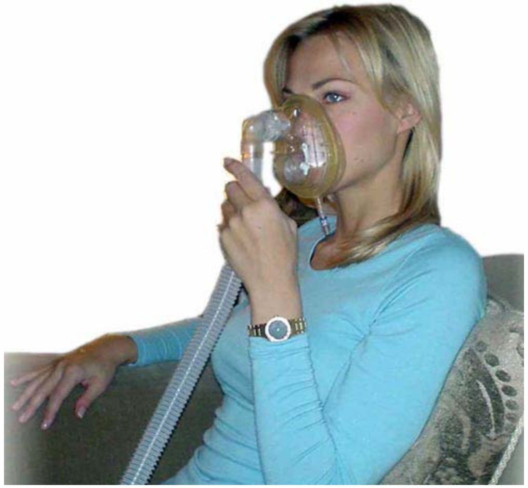
Sea level performance benefits of IHE for elite athletes

- **1.2 ± 1.5% (mean ± SD) all studies**

  >50 % likely trivial benefit

- 3.6 ± 1.3% (mean ± SD) *sub-elite*

  >50 % likely beneficial



Bonetti & Hopkins *Sports Med* 39: 107-27, 2009

Sea level performance benefits of IHT for elite athletes

- **No suitable studies on elite athletes**
- 6.8 ± 3.0% (mean ± SD) sub-elite

  >50 % likely beneficial

Sub-section summary

- Performance benefits of "Altitude Training" ~1-2%,
  - but at the elite level very small improvements (~0.3-0.5%) are worthwhile for race performance
- No studies of performance benefits for events >17 min, e.g. 10,000m, triathlon, marathon or for repeated efforts over days.
- Double-blind placebo studies of performance after classical altitude training & LHTL are lacking
- Since performance benefits (if any) of classical and LHTL are small, is high likelihood of false negatives when searching for mechanisms

Reproducible LHTL?

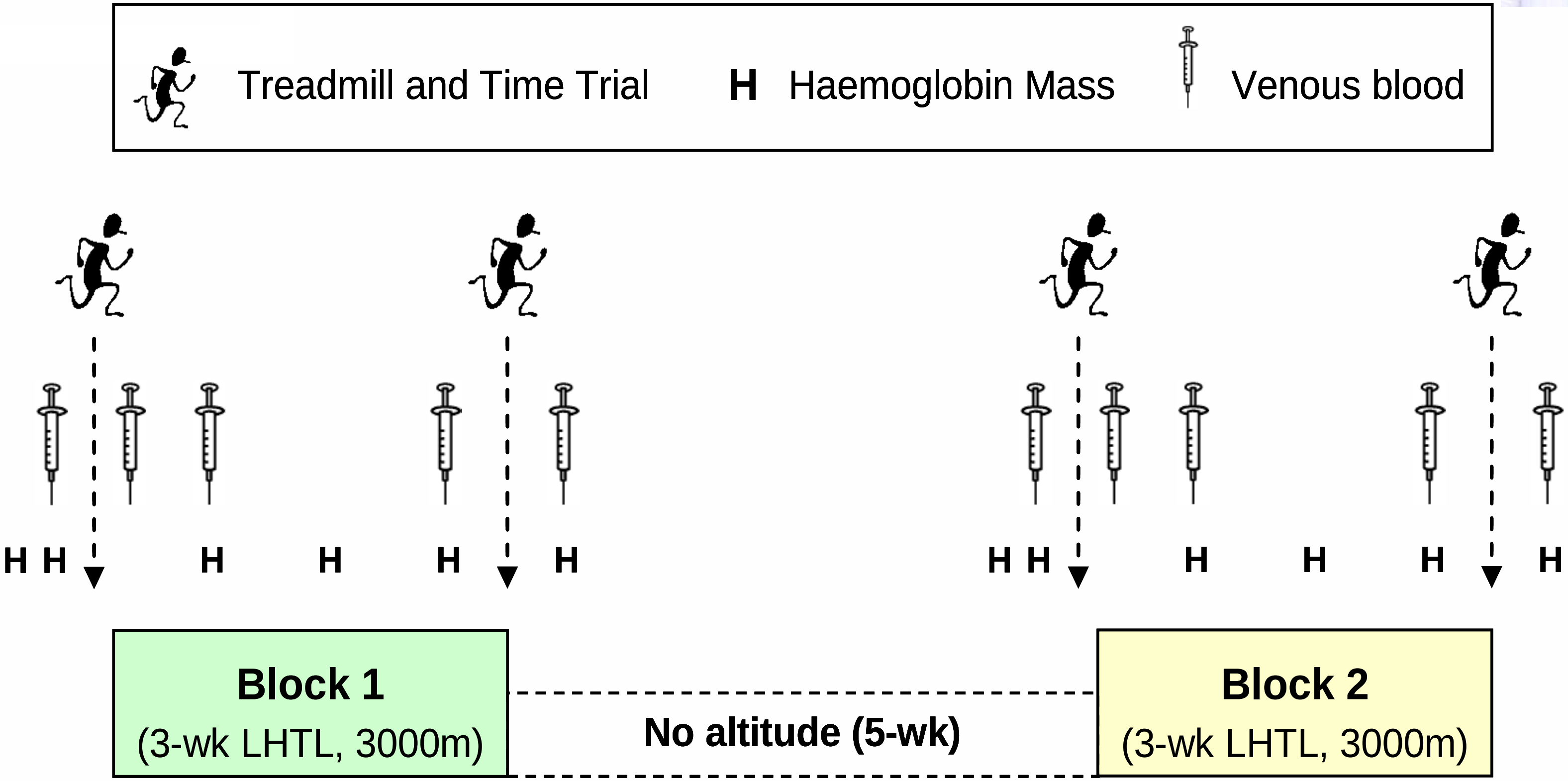


Figure 1. Experimental design, 2 x 3-wk Live High/Train Low (LHTL)

Robertson et al, *MSSE* In Press. 42(Feb), 2010

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Reproducible LHTL?

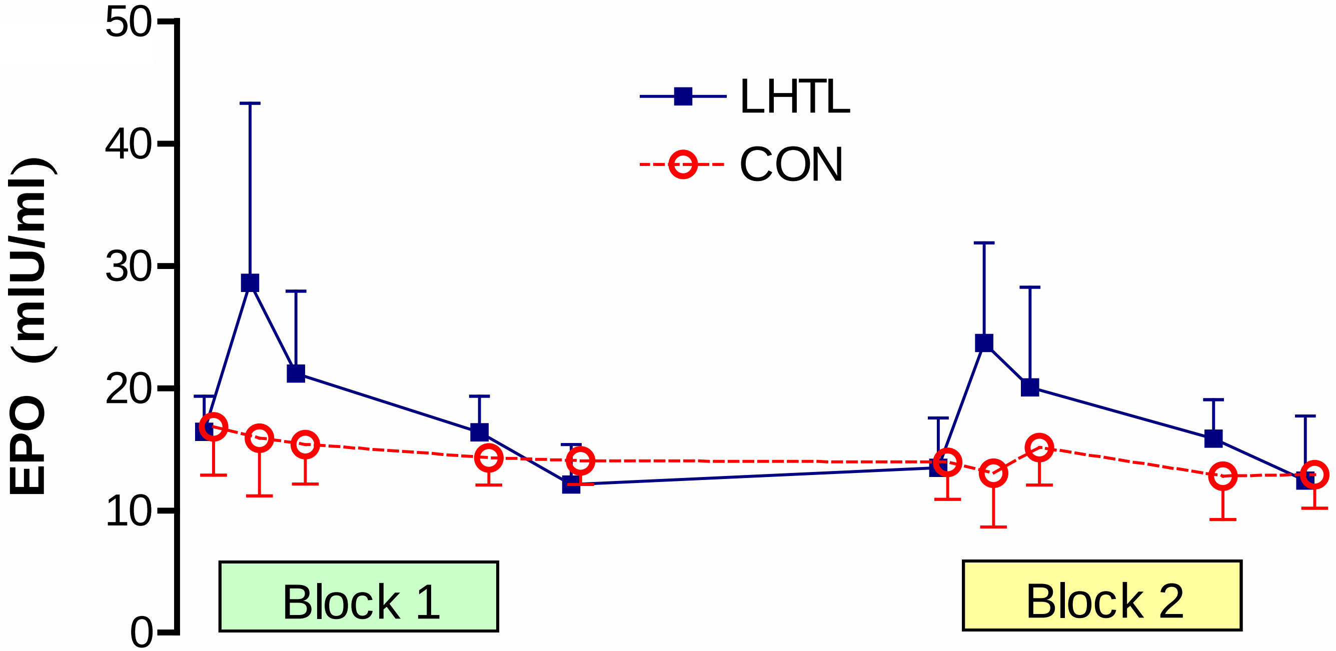
- N = 16 runners, LHTL & Control
- performance = 4.5 km time trial
- Serum EPO and Hb_{mass}

Table 1. Subject Characteristics (mean ± SD)

			Age (y)	Mass (kg)	VO_{2max} ($ml.kg^{-1}.min^{-1}$)
LHTL	(n=8)	6 Male, 2 Female	29.5 ± 4.3	61.8 ± 6.8	72.4 ± 4.5
CON	(n=8)	5 Male, 3 Female	31.8 ± 4.8	59.4 ± 7.8	68.4 ± 6.7

Robertson et al, *MSSE* In Press. 42(Feb), 2010

Reproducible LHTL?



- Block 1 elevated at d2 (70.0; ±29.8%), d6 (36.8; ±28.7%) & d20 (16.2; ±21.1%)
- Block 2 elevated at d2 (90.4; ±23.5%), d6 (33.6; ±27.9%) & d20 (32.2; ±27.6%)

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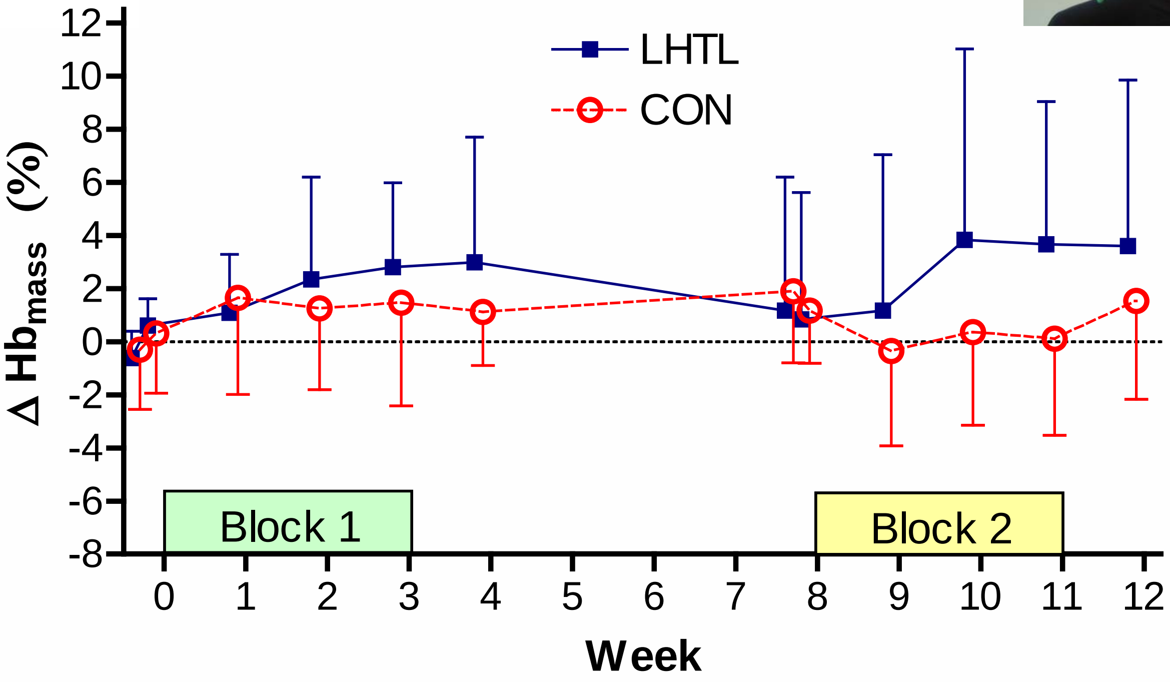
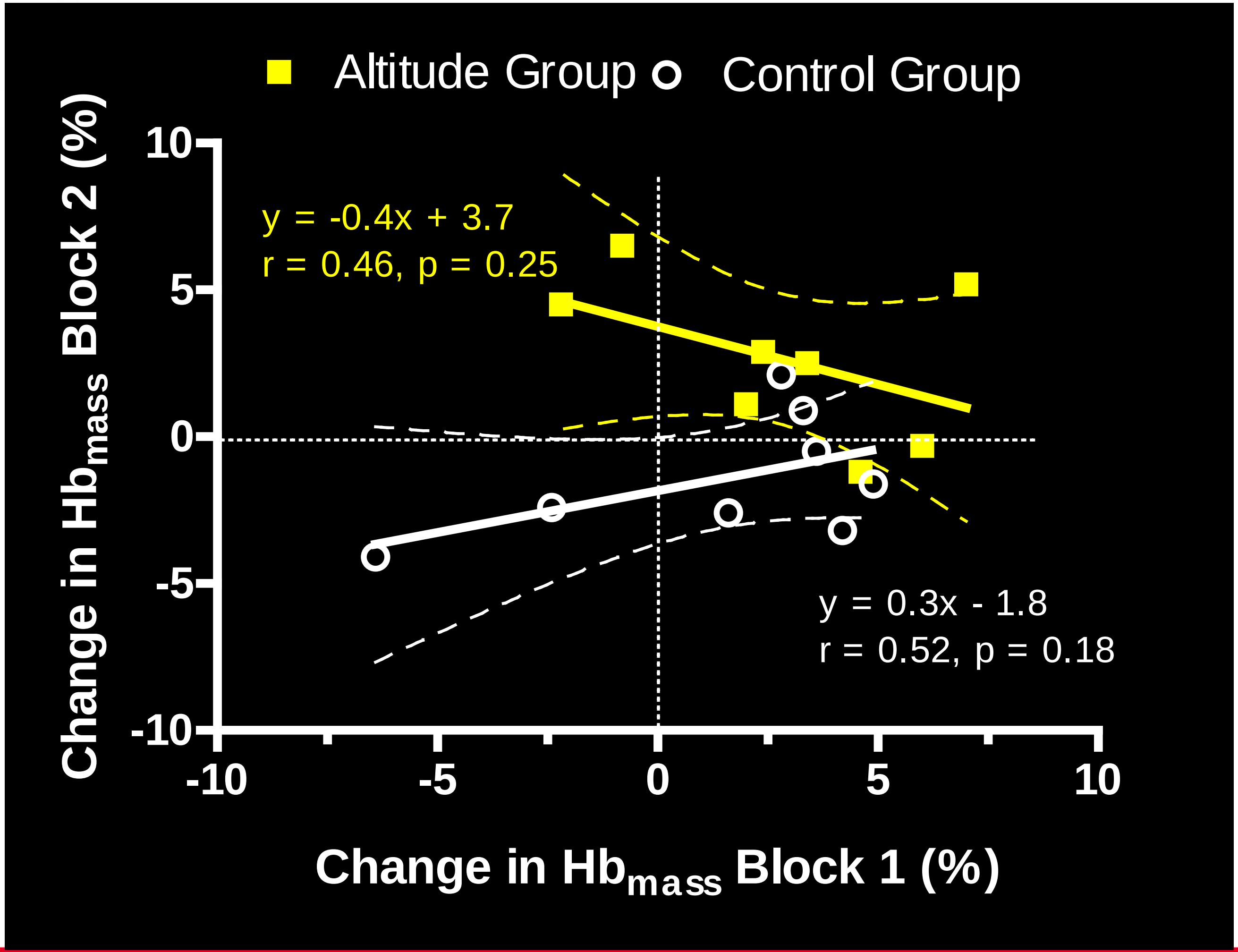
Reproducible LHTL?



Compared with the control group, the altitude group:

- increased their Hb_{mass} after Block 2 (4.2; ±2.1%) mean; ±90% CL),

Reproducibility of Hb_{mass} to LHTL



Robertson et al, *MSSE* In Press. 42(Feb), 2010

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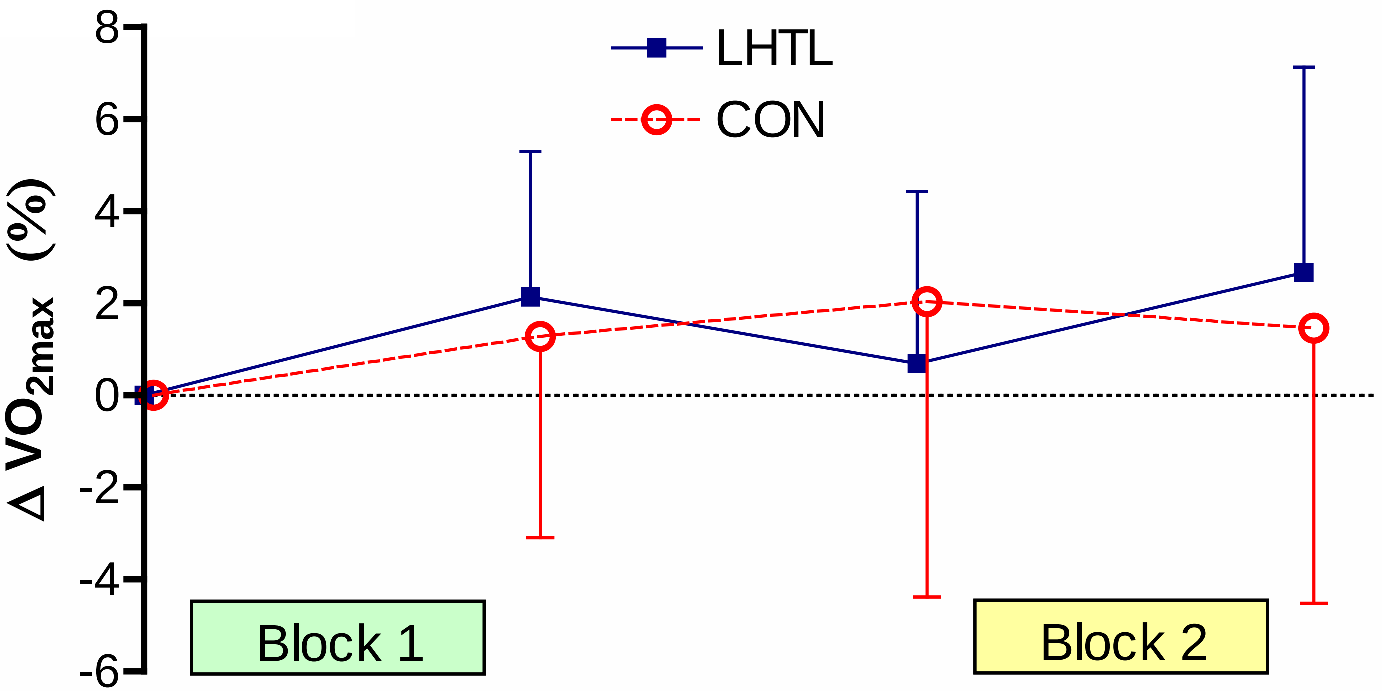
Reproducible LHTL



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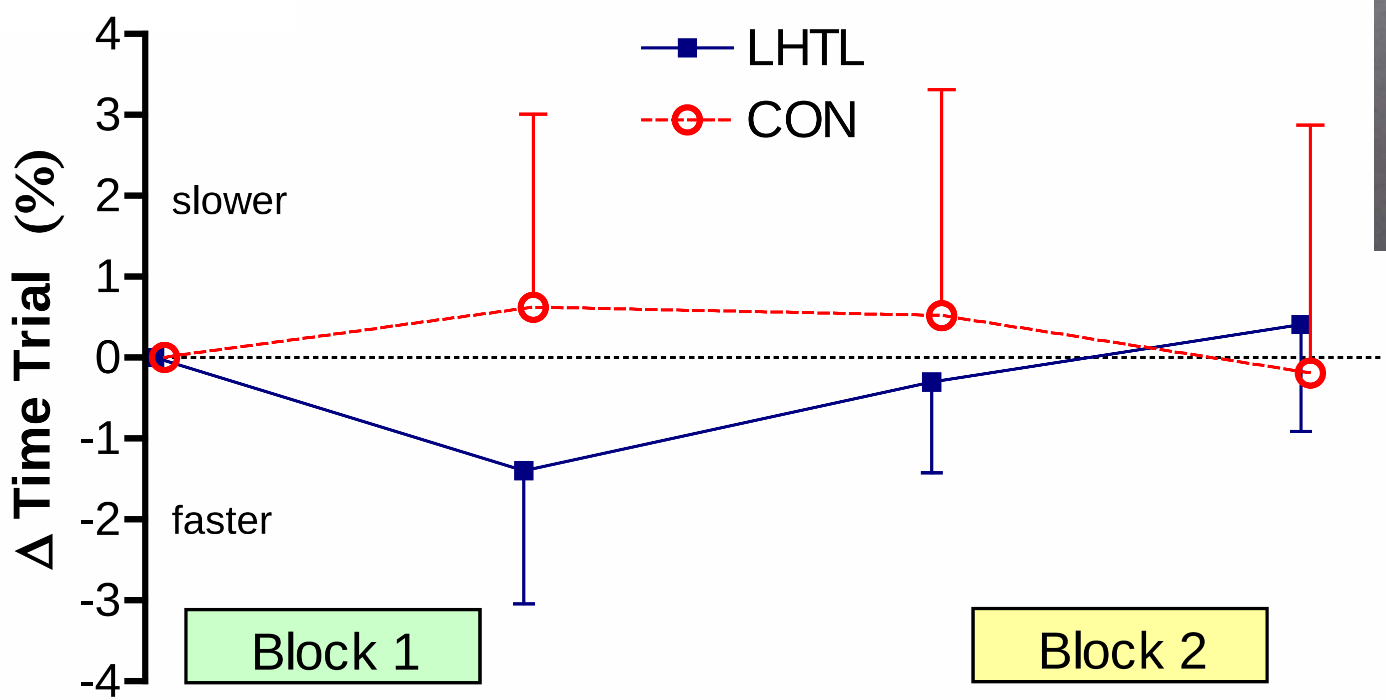
Reproducible LHTL?



-1.4 vs 0.5
= 1.9 ± 1.8 (90%CI)
= Likely faster

0.7 vs -0.7
= 1.4 ± 1.5 (90%CI)
= Likely slower

Robertson et al, *MSSE* In Press. 42(Feb), 2010

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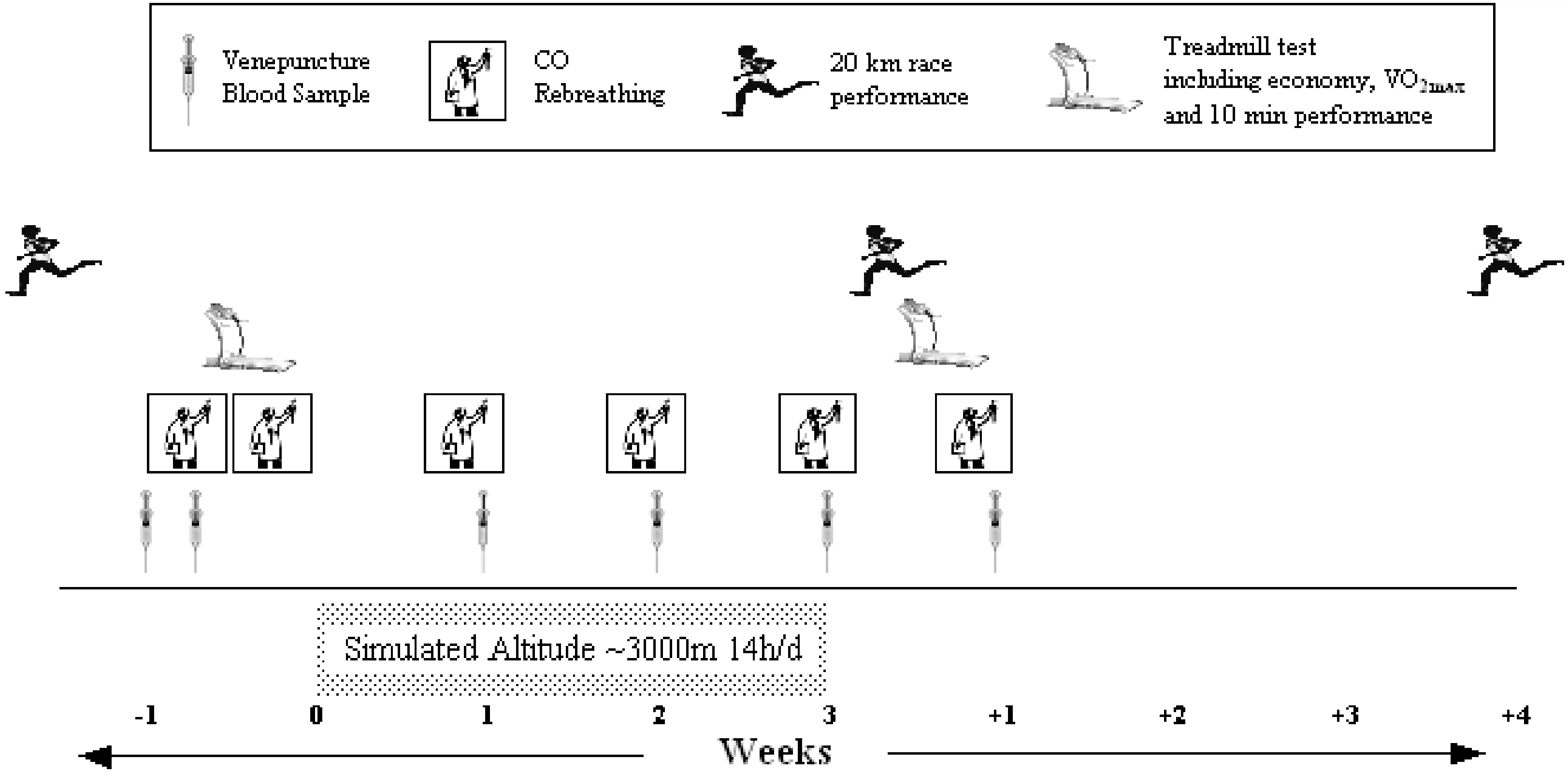
Reproducible LHTL? – Conclusions

- 3-wk simulated LHTL induced reproducible *physiological* adaptations in trained runners, but changes in *performance* were more variable.
- Enhanced physiological capacities did not transfer directly to improvements in time trial performance
  - Competitive *performance* is dependent not only on the physiological adaptations, but on a complex interaction of fitness, fatigue and motivation
  - Time trials do not perfectly re-create competition

Robertson et al, *MSSE* In Press. 42(Feb), 2010

Placebo effects?



Saunders et al, *J Appl Physiol* 2009 In Revision

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Placebo effects?

- Elite Australian and International race walkers (n=17), men &women
- Three groups:
  - *1.* Live High:Train Low (LHTL, n=6)
    14 h.d^{-1} at 3000m simulated altitude
  - *2.* Placebo (n=6)
    14 h.d^{-1} of normoxia (600m) with LHTL group
    (different rooms)
  - *3.* Nocebo control (n=5)
    living in normoxia 24h.d^{-1}

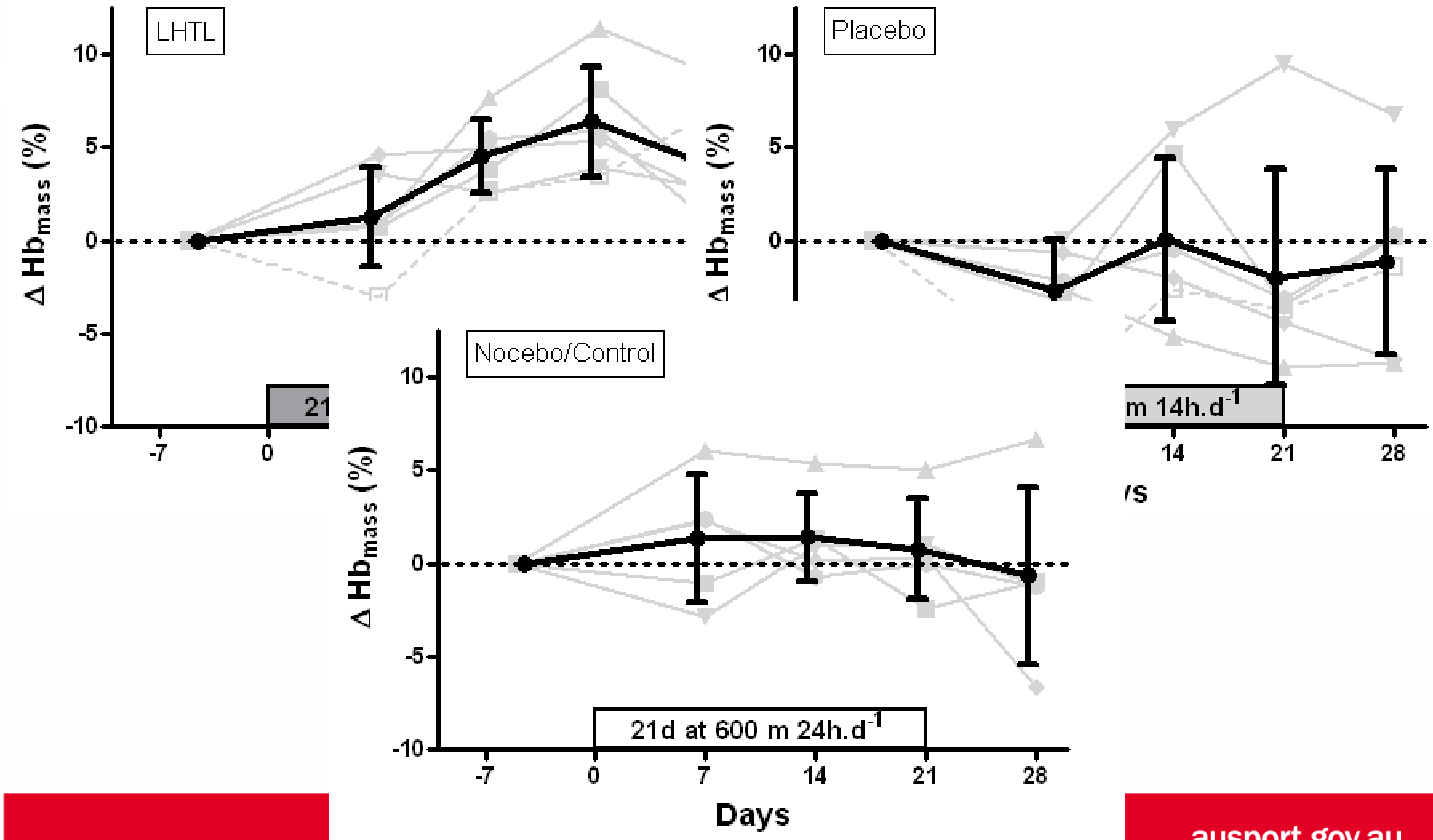
Saunders et al, *J Appl Physiol* 2009 In Revision

Placebo effects?

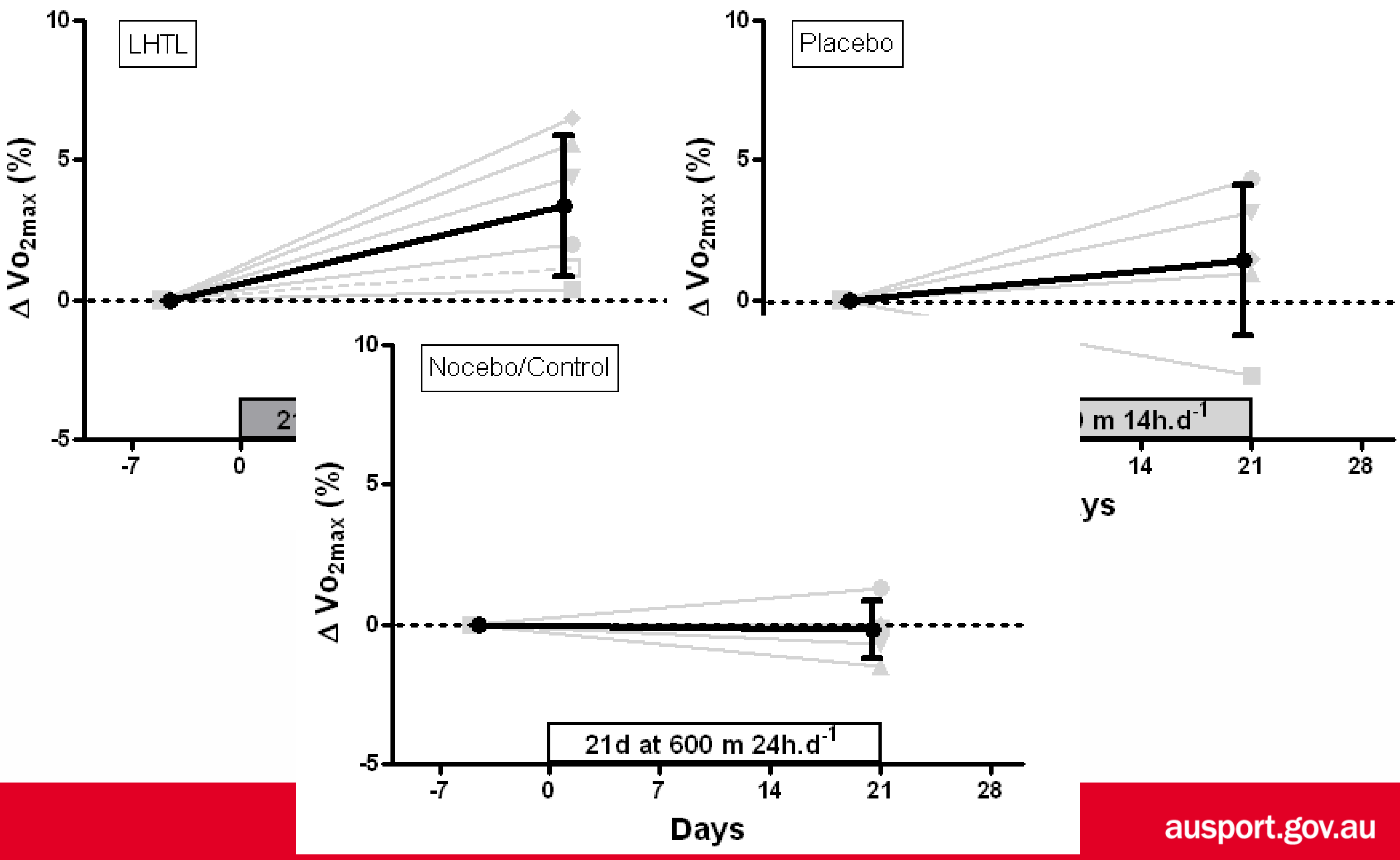
- Group Mean characteristics
  - LHTL (3M, 3F)
  - Placebo (3M, 3F)
  - Control (2M, 3F)
- Age & VO_{2max}
  - 25 y 59 ml/kg/min
  - 23 y 61 ml/kg/min
  - 27 y 60 ml/kg/min

Saunders et al, *J Appl Physiol* 2009 In Revision

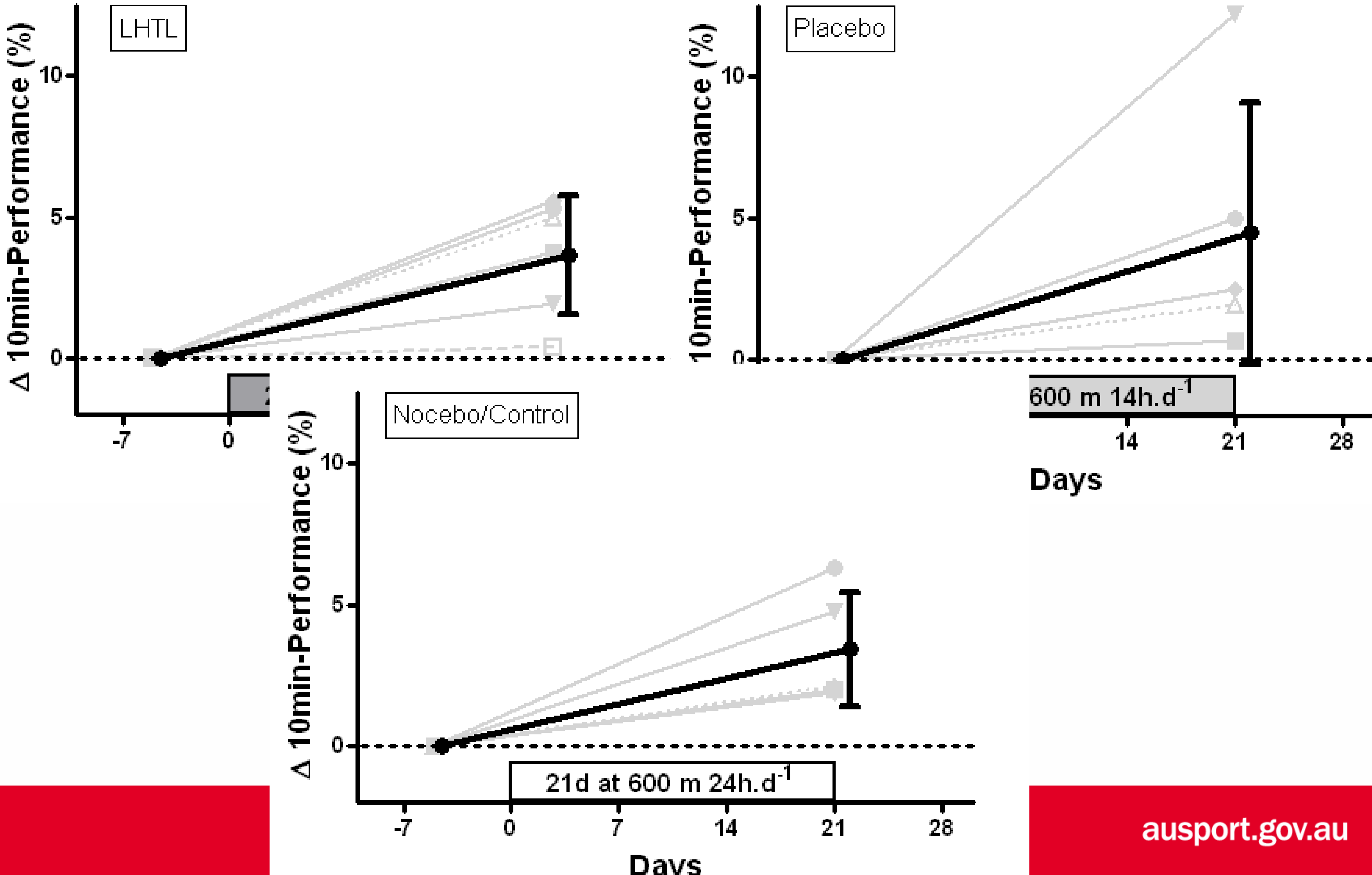
Placebo effects?



Placebo effects?



Placebo effects?



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Effects of hypoxia:
- Erythropoietic changes

- Prevailing paradigm

~4 wk at moderate altitude (~2000-3000 m)

⇨ ↑serum EPO

⇨ ↑red cell volume (RCV)/Hb_{mass}

⇨ ↑VO_{2max}

⇨ ↑performance

(e.g. Levine & Stray-Gundersen *J Appl Physiol* 83:101-12, 1997
Levine, Chapman & Stray-Gundersen *J Appl Physiol* 91:1113-20, 2001
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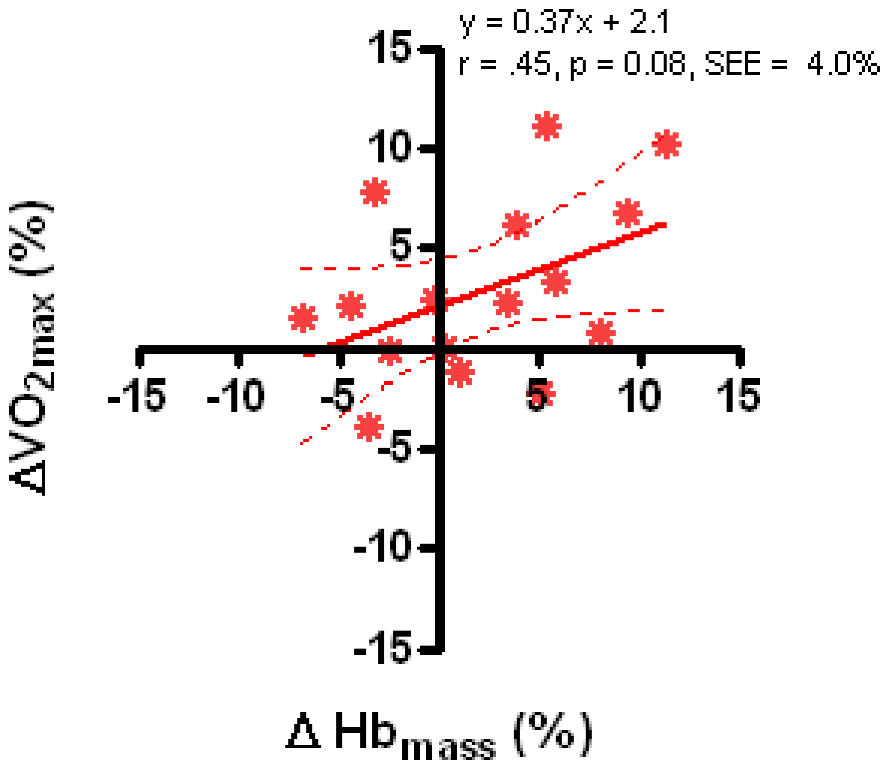
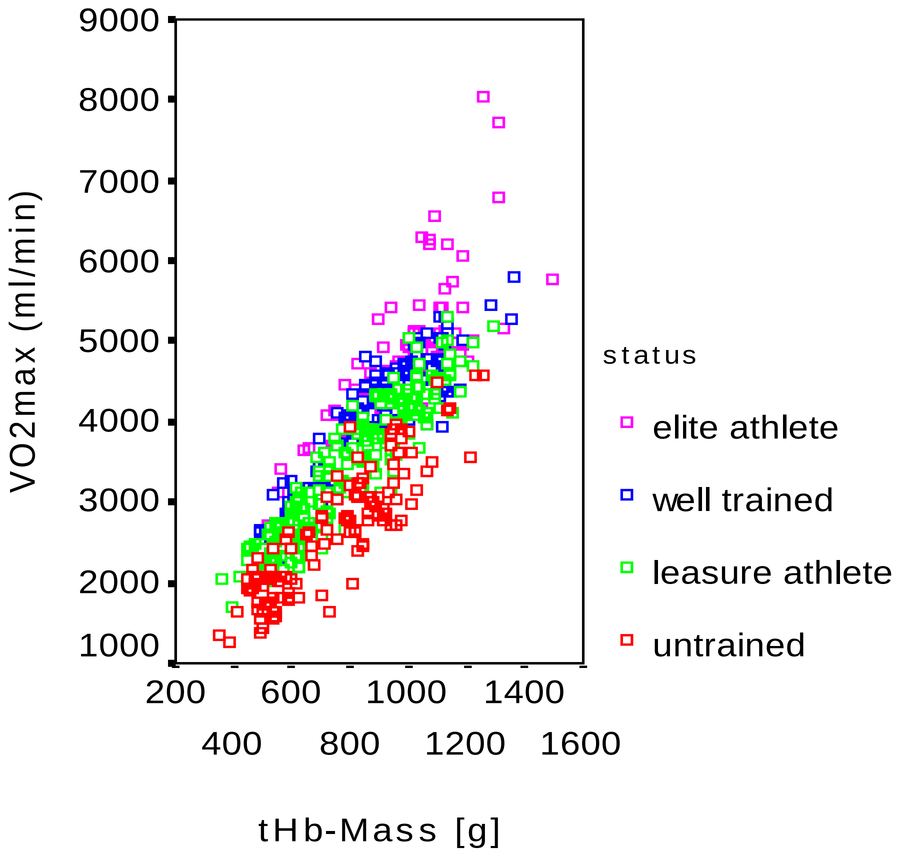
Stray-Gundersen & Levine *Scand J Med Sci Sports* 18 Suppl 1:21-8, 2008)

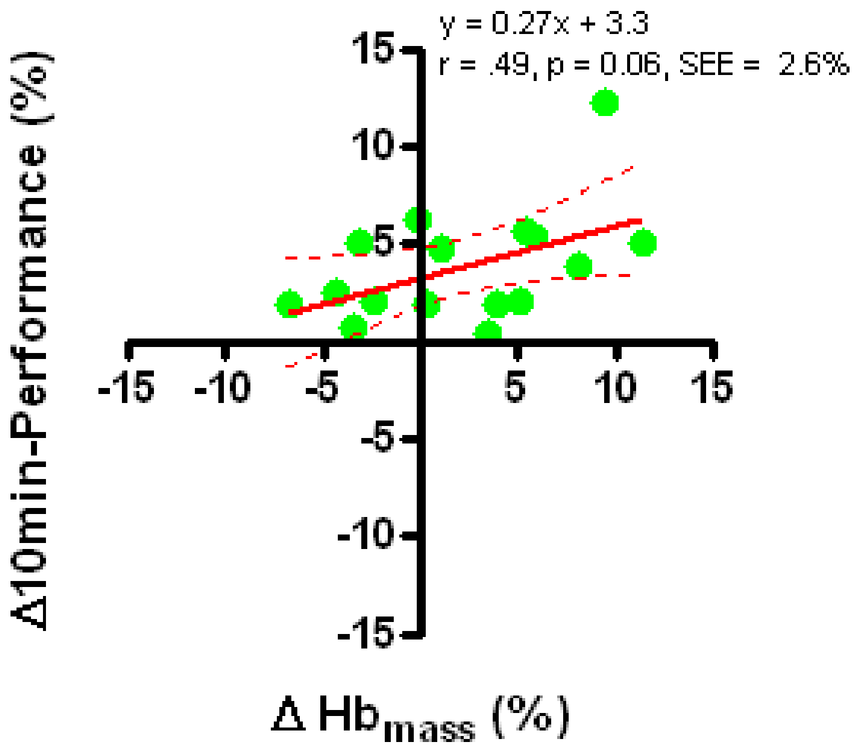
Placebo effects?





Saunders et al, *J Appl Physiol* 2009 In Revision

Placebo effects?



- ~ 1/3 of increase in Hb_{mass} reflected as a change in performance
- If 3% change in Hb_{mass} gives 1% change in performance is difficult to detect as *worthwhile* since signal and noise are similar in magnitude
- But in competition 1% is <u>very</u> worthwhile

Saunders et al, *J Appl Physiol* 2009 In Revision

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Placebo study - Conclusions

- 3-wk LHTL simulated altitude 14 $h.d^{-1}$
  - ↑ Hb_{mass} and VO_{2max} by ~3 & 6%, respectively, more than placebo/nocebo groups
  - But performance improvement (~4%) after altitude was not greater than the training camp effect
- Suggests that the timing of performance *after* LHTL is critical to maximise the increased physiological capacity gained from altitude training

Overall Conclusions & Perspectives

- An adequate dose of hypoxia will transiently increase serum EPO, with downstream increase in Hb_{mass} (and [Hb] & %retics).
- Increase Hb_{mass} (~3-5%) one of likely mechanisms
  - *but not sole mechanism to explain performance*
- Hypoxic performance benefits can be ~1-2% for elite athletes
- Individual response to altitude, can vary from exposure to exposure
  - possibly modulated by training / racing history
- Placebo studies are mostly lacking
- *Race* efforts after hypoxia not well characterised