3rd MS&H - Special event

MANASLU 2008

Oxygen deficit and cardiovascular oxygen transport after chronic exposure to hypobaric hypoxia

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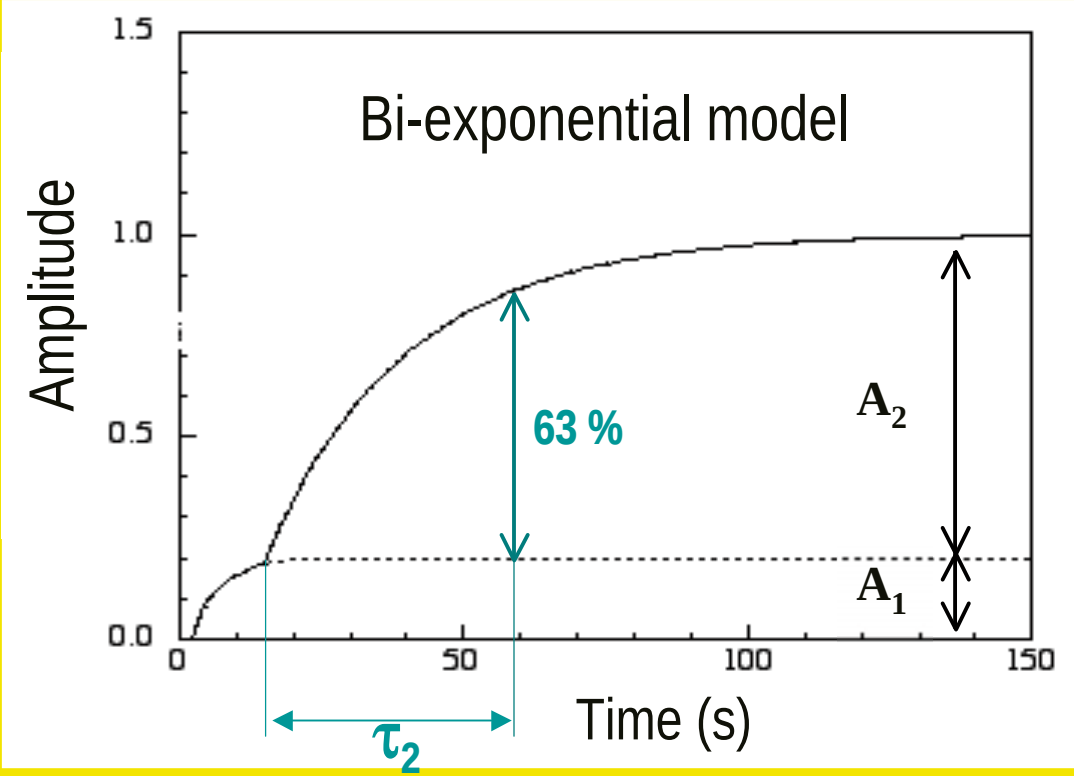
Rovereto 12-14 November 2009

Alveolar V'O_2 kinetics during constant load, moderate intensity exercise

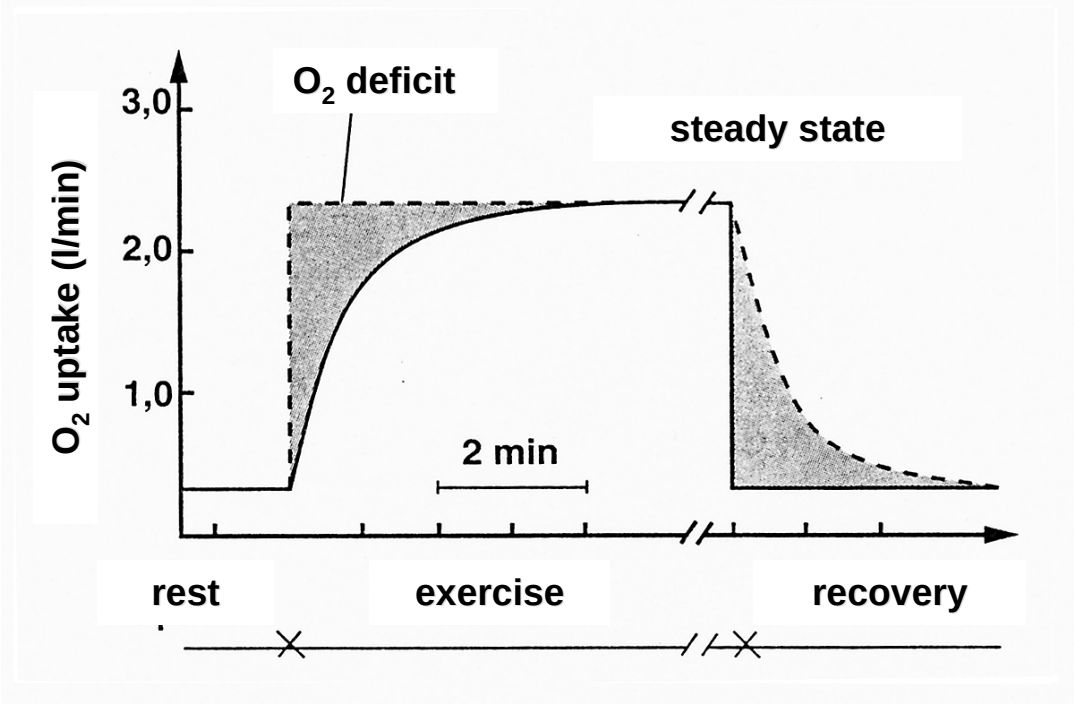
Phase 1 or **cardiodynamic**
- Small Amplitude
- $\tau \approx 5$ s
- $t_d \approx 1$ s

Phase 2 or **metabolic**
- Amplitude $\propto$ work rate
- $\tau \approx$ 25-30 s
- $t_d \approx$ 15-18 s



$$\dot{V}O_2 = H(t - t_{d1})\, A_1 \left(1 - e^{-(t - t_{d1})/\tau_1}\right) + H(t - t_{d2})\, A_2 \left(1 - e^{-(t - t_{d2})/\tau_2}\right)$$

The faster, the better ?



- **Faster** V'O_2 kinetics are associated with **lower** O_2 deficit
- Cellular and horgan homeostasis is **less perturbed**

- *f.i. lower splitting of PCr that remains available for all-out efforts, lower Lactate and H+ accumulation,…..*

$V'O_{2A}$ kinetics: what sets the speed ?

- Several ***C****entral* and/or ***P****eripheral* factors seem to be implied

$V'O_2$ kinetics is

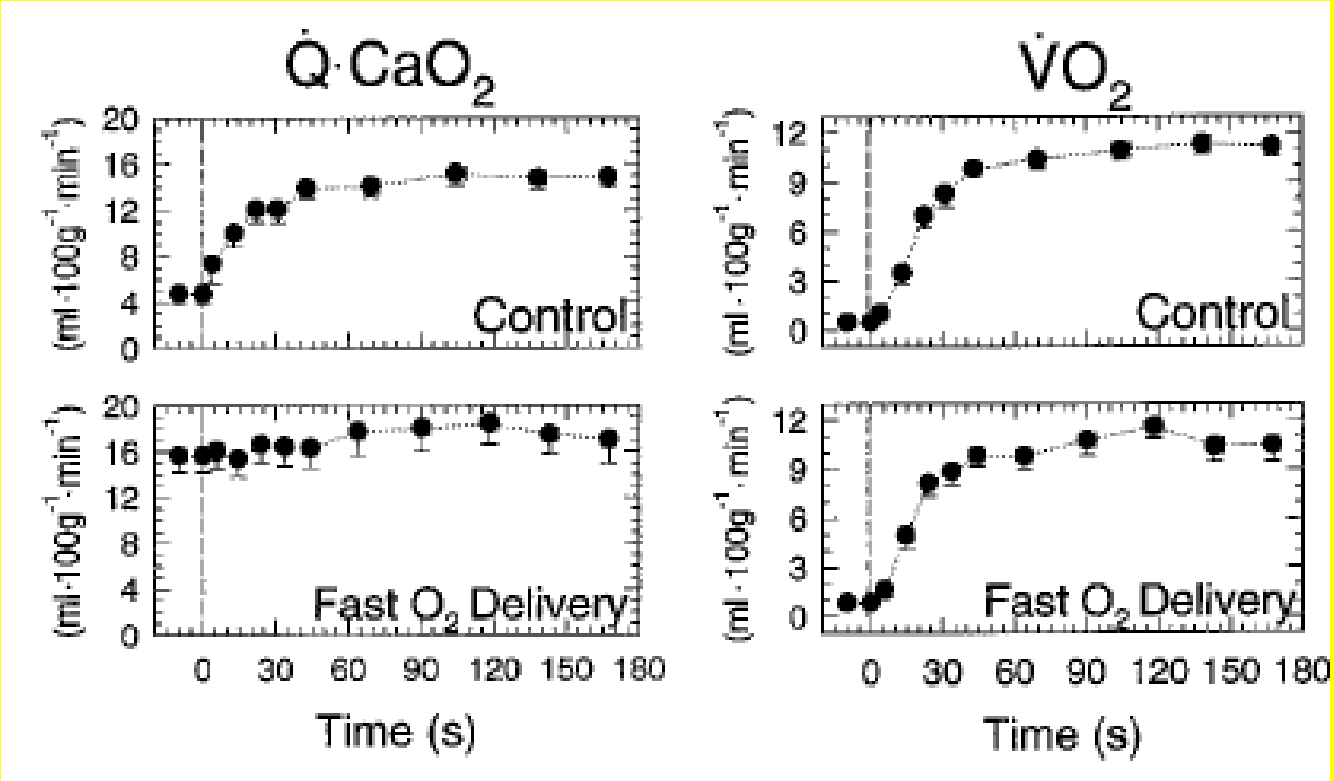
1. Faster

- In trained subjects and in subjects with increased fitness (*C/P*)
- During exercise performed recruiting mainly Type I fibers (*P*)

2. Slower

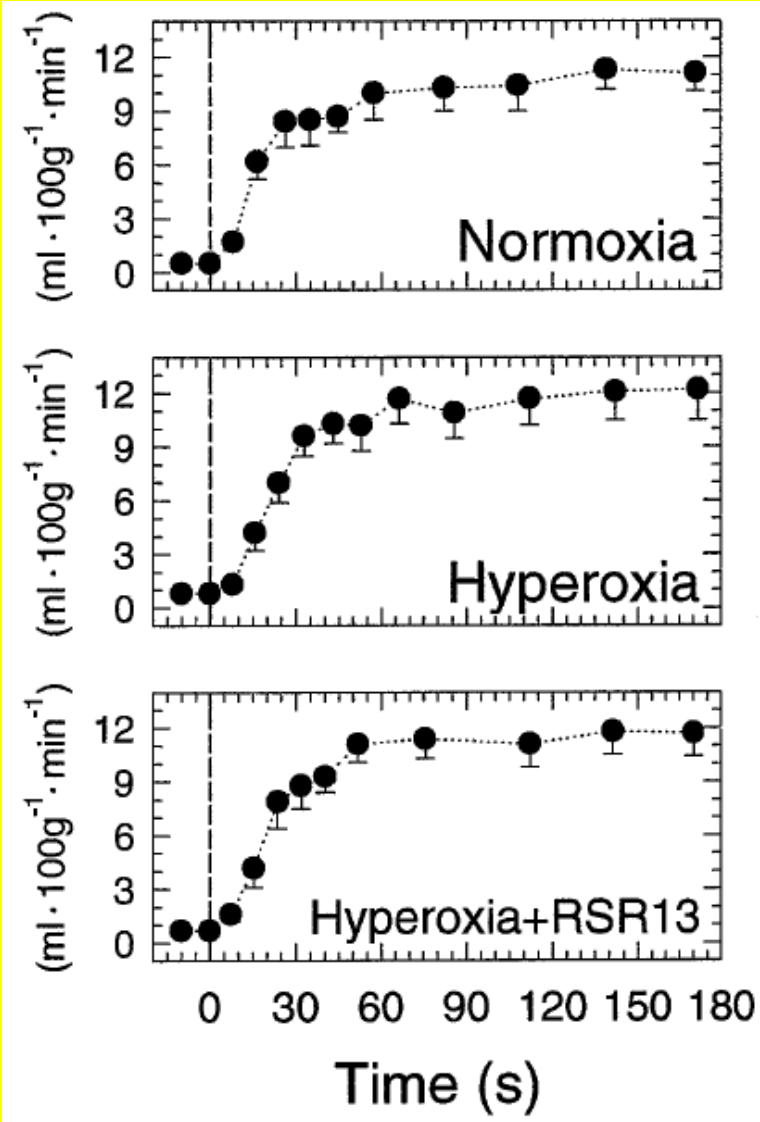
- In the elderly (*C/P*)
- In heart failure (*C/P*)
- In Type II diabtes (*P*)
- In heart transplant recipients (*C/P?*)
- After prolonged HDTBR (*C/P*)

Is bulk O_2 delivery a limiting factor ?



- $V'O_2$ kinetics is not affected by Q'_aO_2 during sub maximal exercise in muscles of the dog in situ *(Grassi, 1996)*

Is O_2 diffusion a limiting factor ?



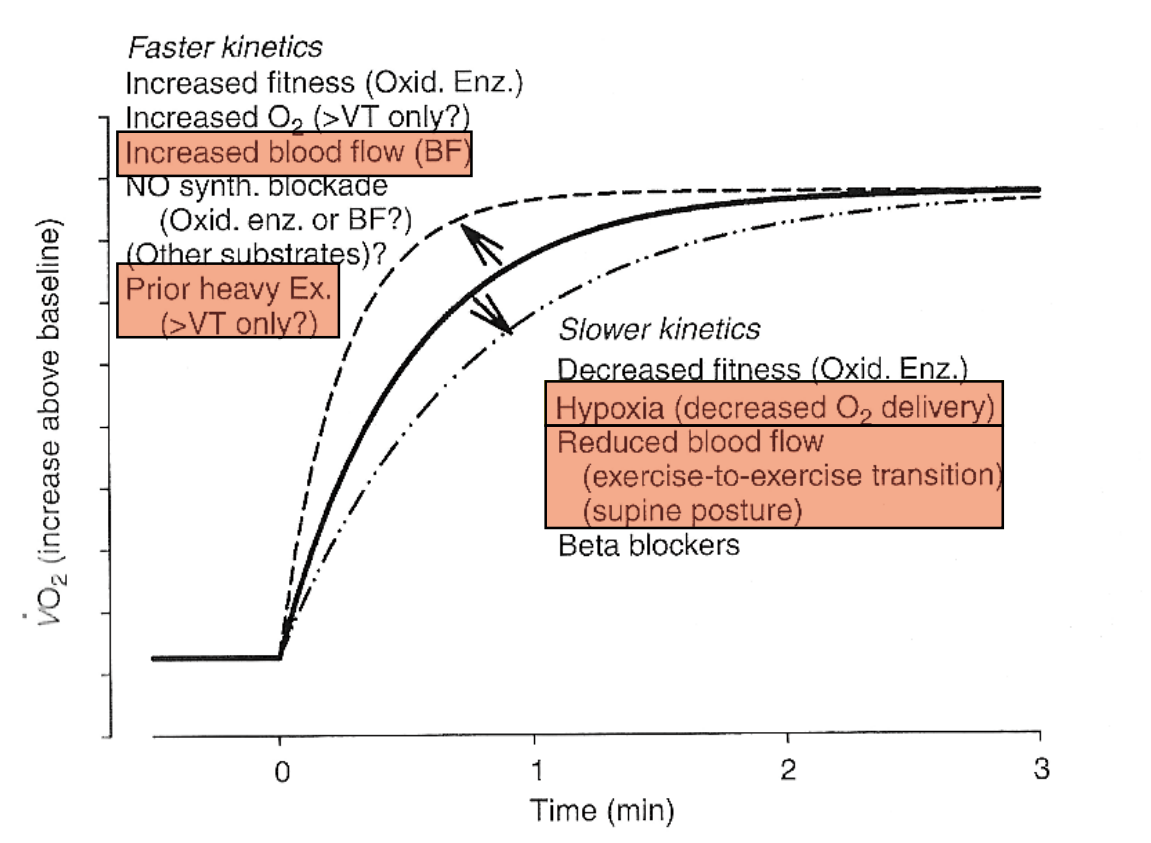
- Normobaric hyperoxia (increased P_aO_2) and rightward shifting of HbO_2 curve do not affect $V'O_2$ kinetics *(Grassi 1996)*

- Other muscular controlling mechanisms, such as the possible limiting role of PDH and the inhibition of mitochondria respiration mediated by NO need to be completely understood or demonstrated yet.

Conclusions

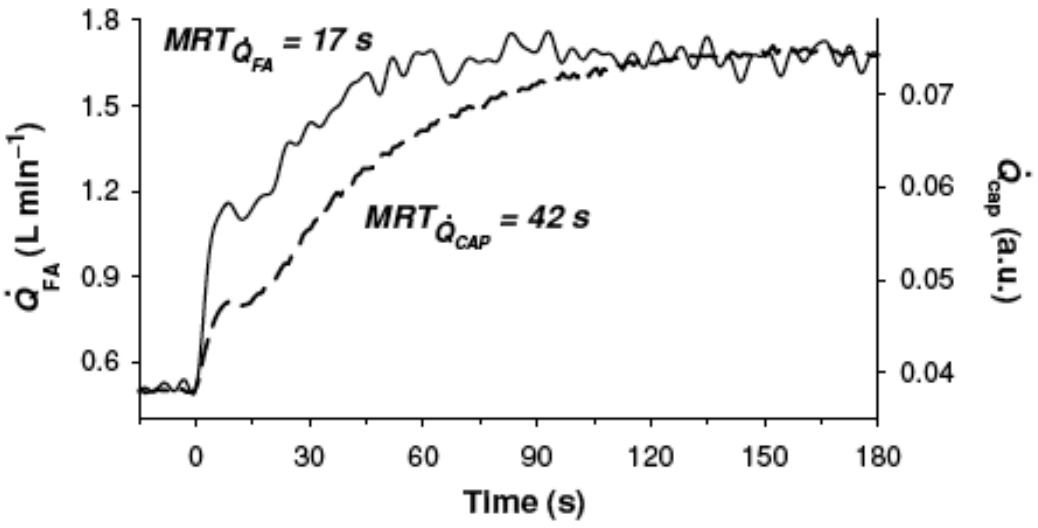
- In normal conditions (moderate intensity exercise, normoxia, absence of pathologies) the limiting factors seem to reside in the muscle.
- $V'O_2$ kinetics seems to depend on the integrated interplay between the several mechanisms providing energy at the onset of the exercise
- F.I., PCr splitting (and glycolisis activation) may act as a high-capacitance buffer and delay the increase of ADP concentration in the cells that follows the increased ATP degradation and may attenuate the rapid acceleration of oxydative phosphorilation

Someone thinks it different



There are situations where $V'O_2$ kinetics are **accelerated** at the onset of **moderate intensity** exercise **by increasing** $\mathbf{Q'_aO_2}$, at least with exercise performed with the forearm muscles.

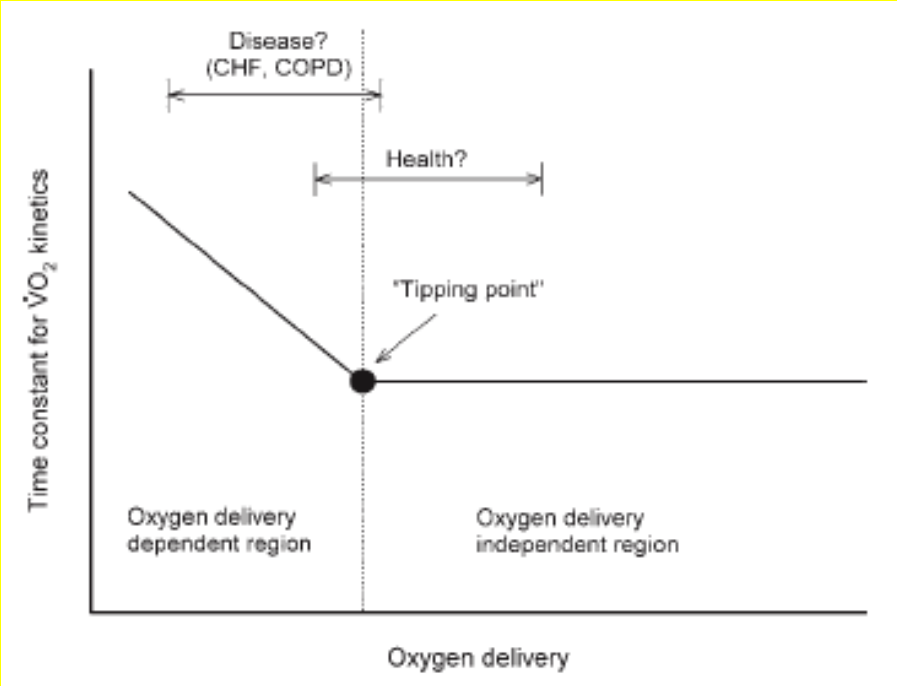
The scenario is even more complicated



- Q'_aO_2 kinetics in conduit arteries is faster than capillary flow response of the active muscles *(Harper et al 2006)*
- The two responses seem to be dissociated Therefore, bulk O_2 delivery may not be considered as a surrogate of local O_2 delivery.

Trying to reconciliate a dicothomy

Maybe the O_2 delivery/utilization debate is based on a false dicothomy

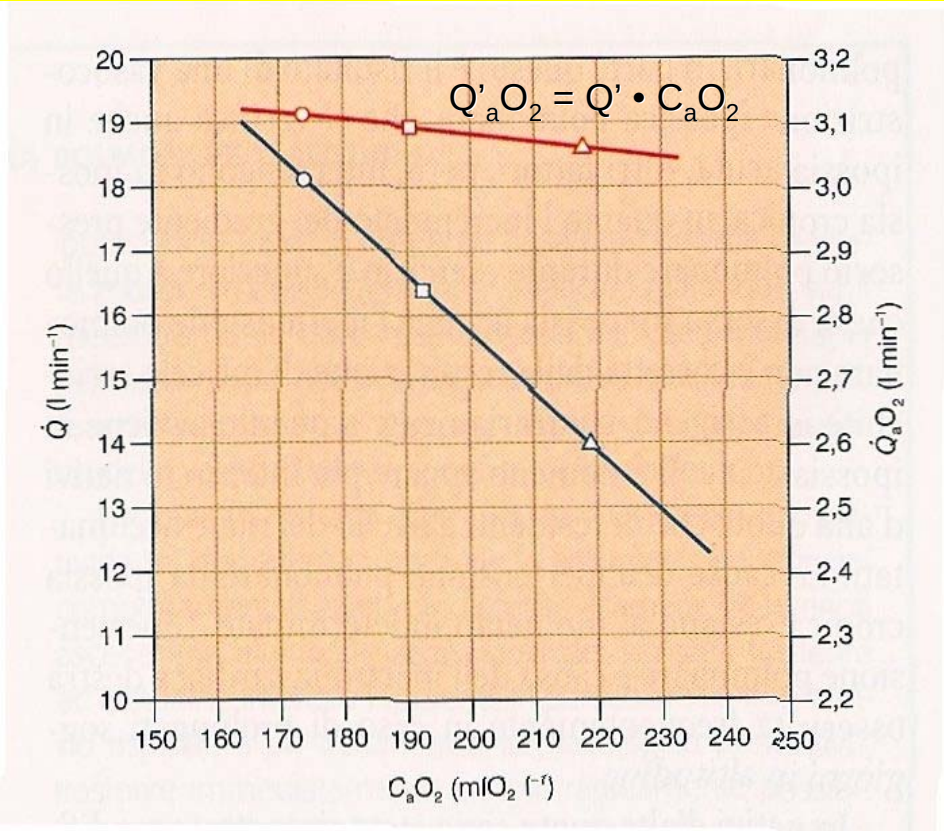


- The relationship between $V'O_2$ kinetics and O_2 delivery is divided **in two regions** by a sort of threshold (here defined "*tipping point*")
- To the right of the point, O_2 kinetics is determined by O_2 utilization rate
- To the left, it is undeniably O_2 delivery dependent *(Poole and Jones, 2005)*
- The condition characterised by O_2 delivery dependance may be typical of pathological conditions or imposed on purpose

Peripheral modifications anc chronic hypoxia

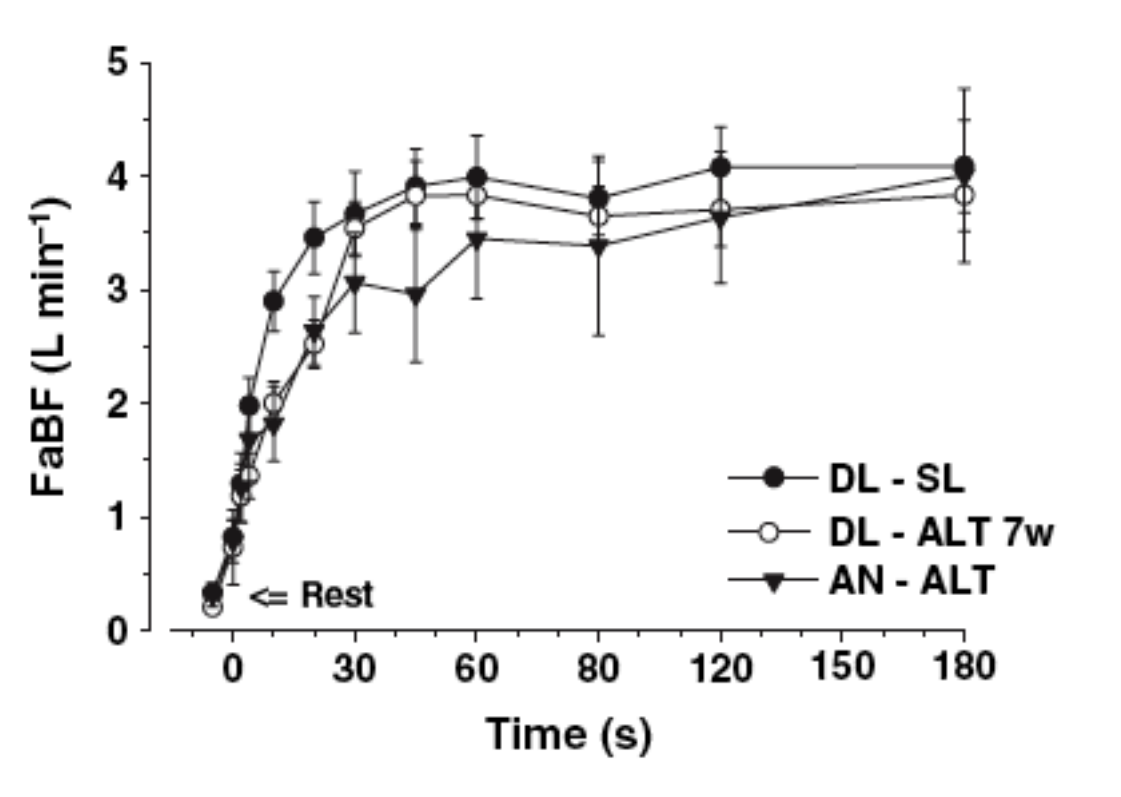
Tissue changes	High altitude
Capillary density in skeletal muscle	Increased due to the reduction of muscle fibers VEGF induction seems to be uneffective for angiogenesis at high altitude
Fiber diameter of skeletal muscle	Decreased, especially Type I
Myoglobin concentration	Increased in skeletal muscle
Muscle enzymes	**4000-5000 m asl** • increased concentration/activities of important enzymes involved in oxidative metabolism **> 6000 m asl** • decreased activities of oxidative enzymes • Increased enzyme activities of glycolisis
Mitochondria	Decresaed relative and absolute volume at very high altitude (> 6000 m) Increased in mitochondrial density at 4500 m asl in animals Specific loss od subsarcolemmal mitochondria

Central modifications and chronic hypoxia



Q' during moderate intensity exercise at steady state is a negative function of C_aO_2.
The drop of Q' compensates for the increase in C_aO_2, so that steady state bulk O_2 delivery remains almost constant
(Ferretti et al, 2005)

Arterial blood flow and chronic hypoxia



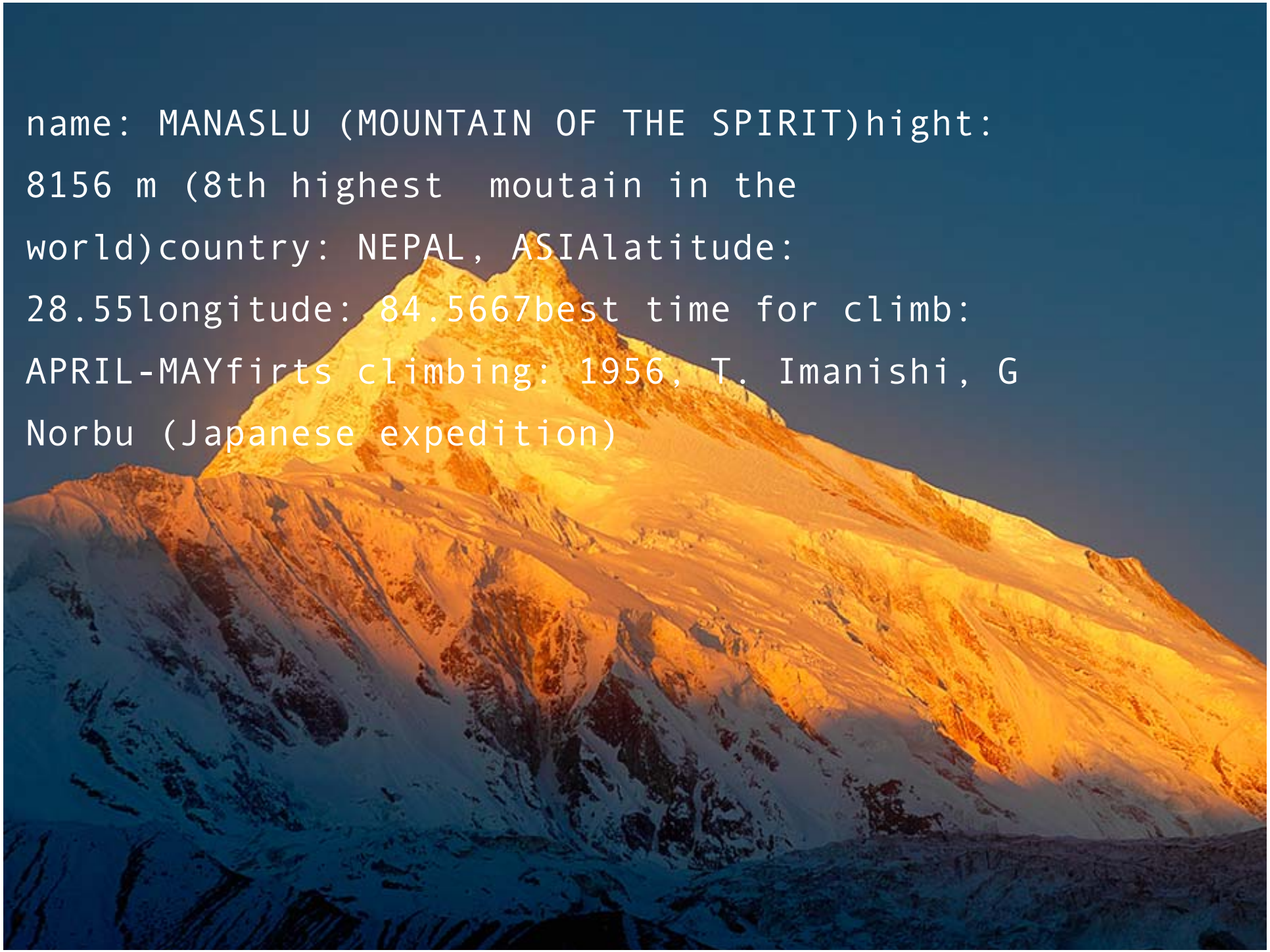
- Femoral arterial blood flow was similar in Danish lowlander at sl (SL) and after 7 weeks at altitude (5300 m asl), as well in natives Aymara
- *(Radegran et al. 2008)*
- Therefore, bulk O_2 delivery response at the onset of exercise is not affected by high altitude exposure

Hypothesis

- The augmented muscular oxidative capacity occurring after high altitude adaptation would enable to sustain a given O_2 uptake at lower ADP and P_i and PCr concentrations.
- $V'O_2$ kinetics would be likely accelerated after chronic hipoxia and cell homeostasis less perturbed
- Sytemic O_2 delivery would not be affected
- These results would strenght the hypothesis that the adapatation of O_2 muscular uptake are mainly regulated by mechanisms intrinsic to the muscles, at leat during moderate intensity exercise.

Material and methods

- Subjects: six male subjects (40 yy ± 14; 79.3 kg ± 14.7; 171.7 ± 10.0)
- Experimental design: Subjects were studied before and upon the return (15 dd) from chronic exposure to hypoxia (about 21 days at 5000 m asl)
- Protocol: Constant-load cycling exercise at 100 W, two repetitions, $V'O_2$ BbB and Q' BbB, blood lactate concentration [La]b at the end of the exercise and during recovery
- Incremental ramp test until exhaustion ($V'O_{2max}$, $V'O_{2AT}$)



name: MANASLU (MOUNTAIN OF THE SPIRIT)hight: 8156 m (8th highest moutain in the world)country: NEPAL, ASIAlatitude: 28.55longitude: 84.5667best time for climb: APRIL-MAYfirts climbing: 1956, T. Imanishi, G Norbu (Japanese expedition)


C.B. Manaslu 2008
© 2008 Europa Technologies
Image © 2008 TerraMetrics
Image © 2008 DigitalGlobe
© 2008 Google
Google
28°34'17.80" N 84°36'38.76" E
4954 m elev
8 Nov 2003
5.85 km Alt

Material and methods

- ***Methods***
  - BbB V'O_2 at the mouth (Quark b^2, Cosmed, I)
  - BbB Q' from the analysis (Modelflow) of non-invasive recordings of arterial pressure (Portaprs, TNO, The Netherlands)
  - Q' at steady state by means of a inert gases, closed circuit rebreathing method (Innocor, Innovision, DK)
  - Cycle ergometer (Lode Excalibur, Lode, The Netherlands)
  - $[La]_b$: Biosen C Line, EKF Diagnostic, D
  - [Hb]: Emocue, Sweden

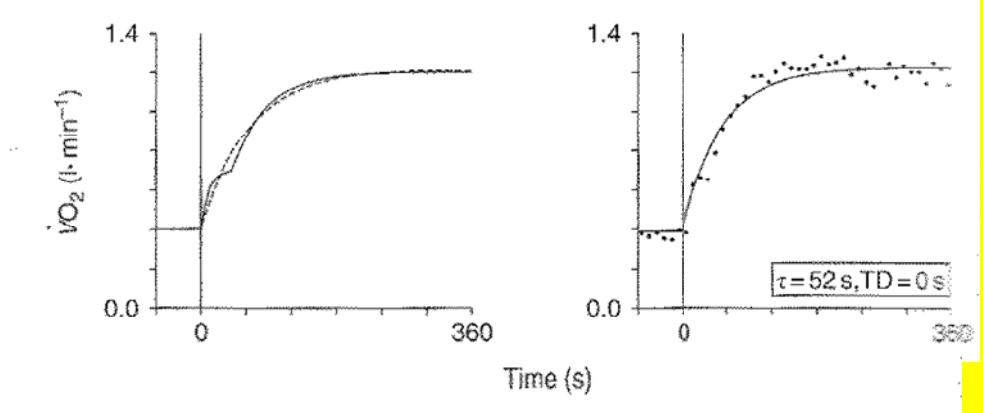
Material and methods

- ***Data analysis***
  - Q'_aO_2 obatained as Q' times C_aO_2
  - Q' corrected with the corresponding ss values measured with inert gas rebreathing
  - Q'_aO_2 kinetics: interpolated by using a biexponential model

$$Y = A_1 * (1 - \exp^{(-(t-td1)/\tau 1)}) + A_2 * (1 - \exp^{(-(t-td2)/\tau 2)})$$

  - $DefO_2$: calculated as the difference between the volume of O_2 that would have been consumed if a steady state had been immediately attained minus that actually taken up during exercise

MRT of V'O_2 kinetics

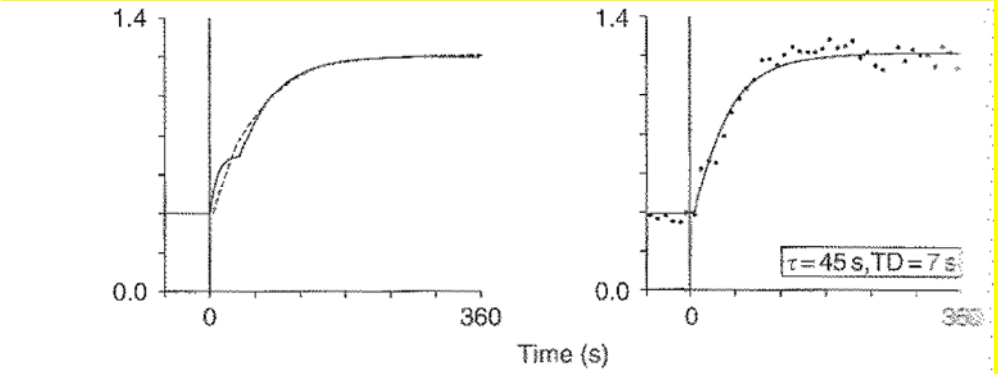


Monoexponential, TD = 0

$V'O_2\ (t) = A\ (1-e^{-(t/\tau)})$

Monoexponential

$\tau = DefO_2 / A$



Monoexponential, TD=C

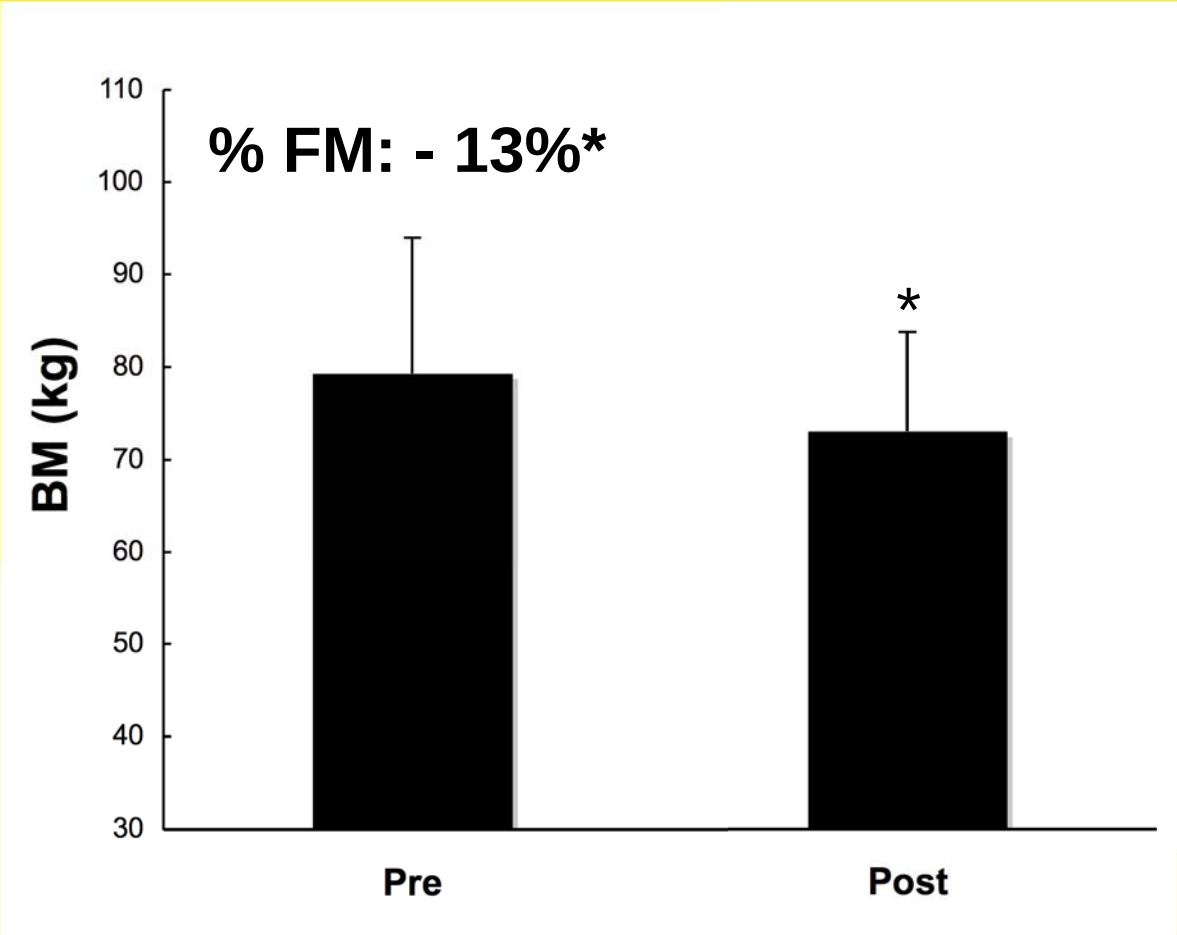
$V'O_2\ (t) = A\ (1-e^{-((t-TD)/\tau')})$

MRT = Def O_2 / A

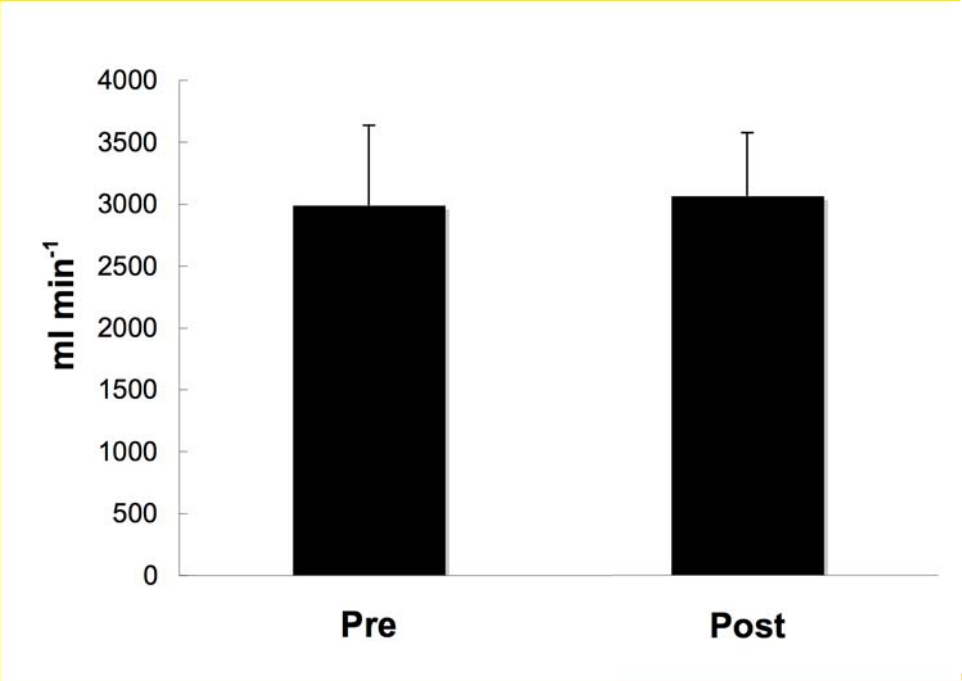
MRT = τ'+TD = τ

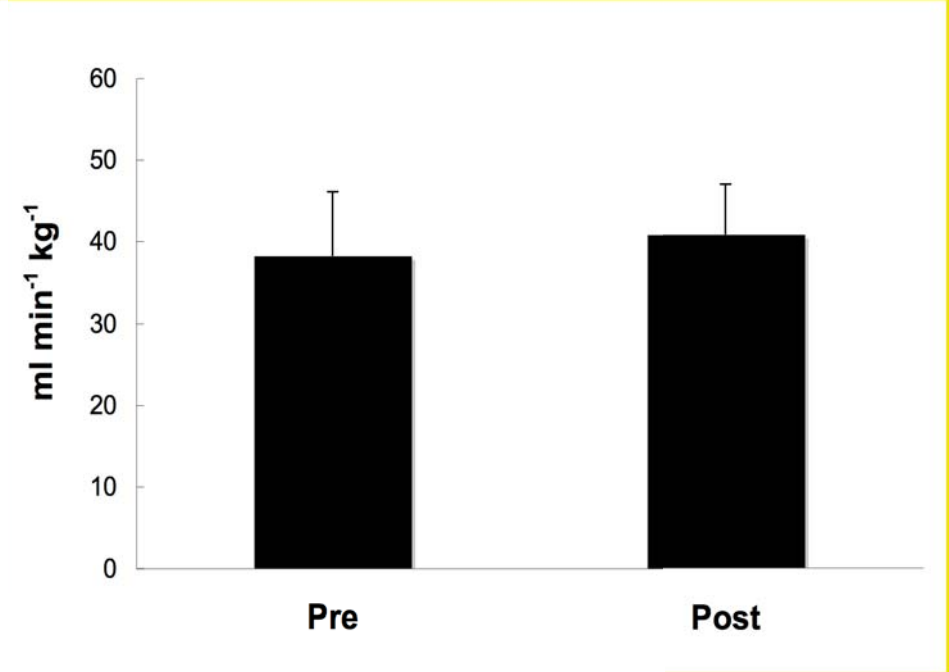
The value of the MRT is identical to the time constant obtained by fitting the same O_2 response to square-wave exercise with a simple exponential function without a time delay

Results - Body mass

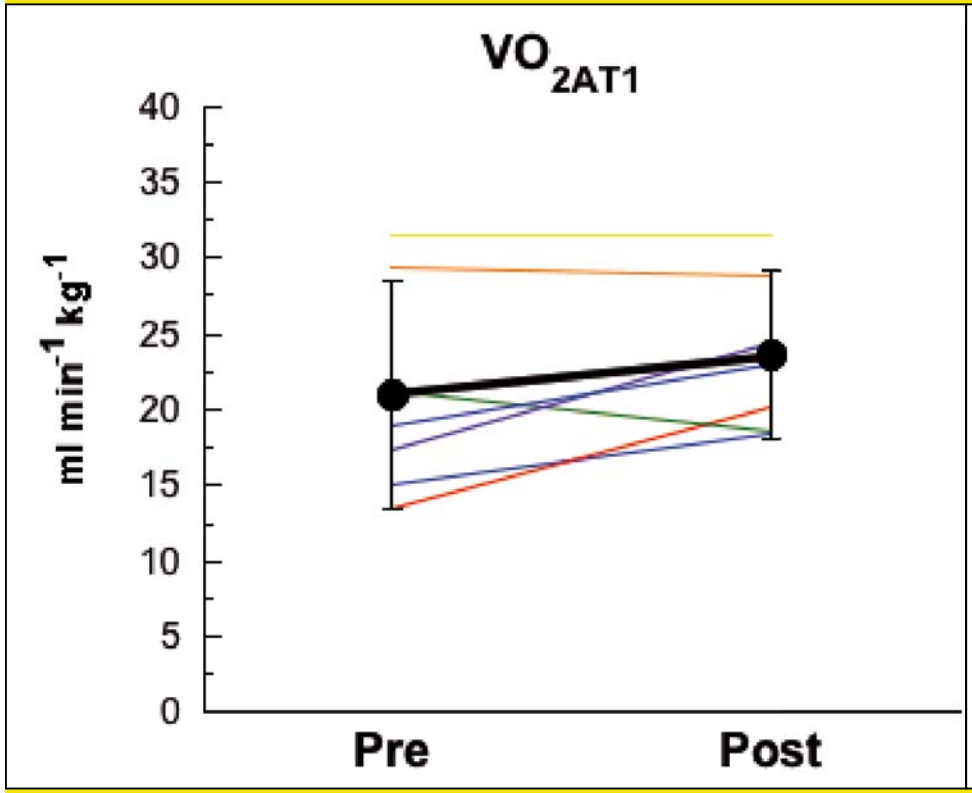


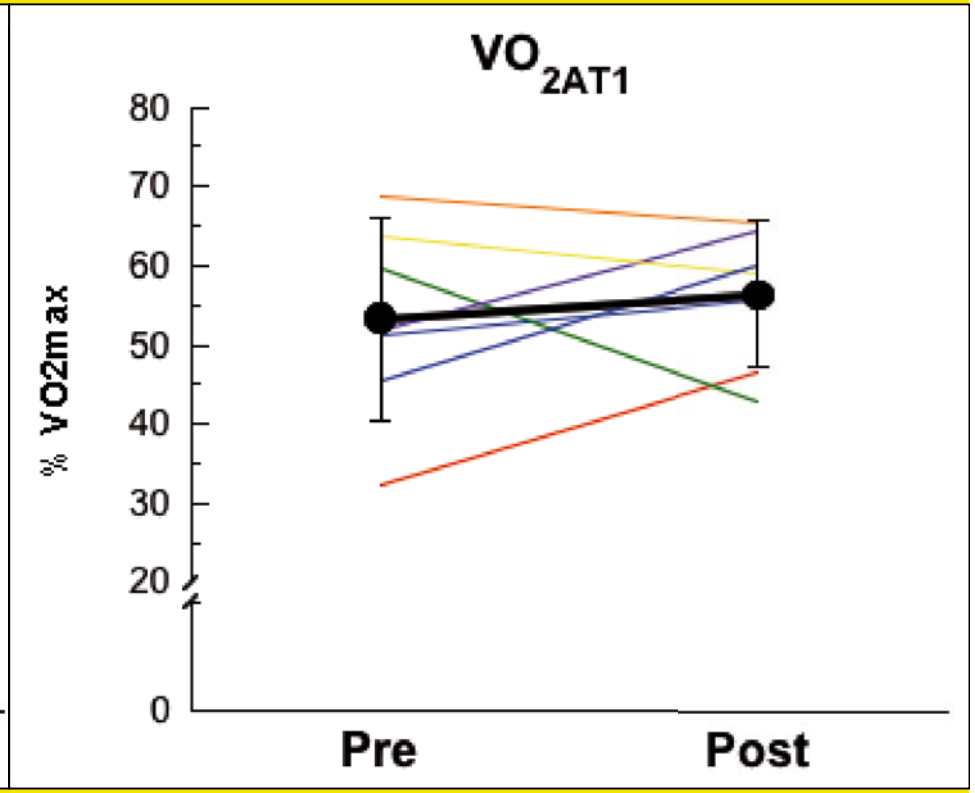
Results - V'O_{2max}



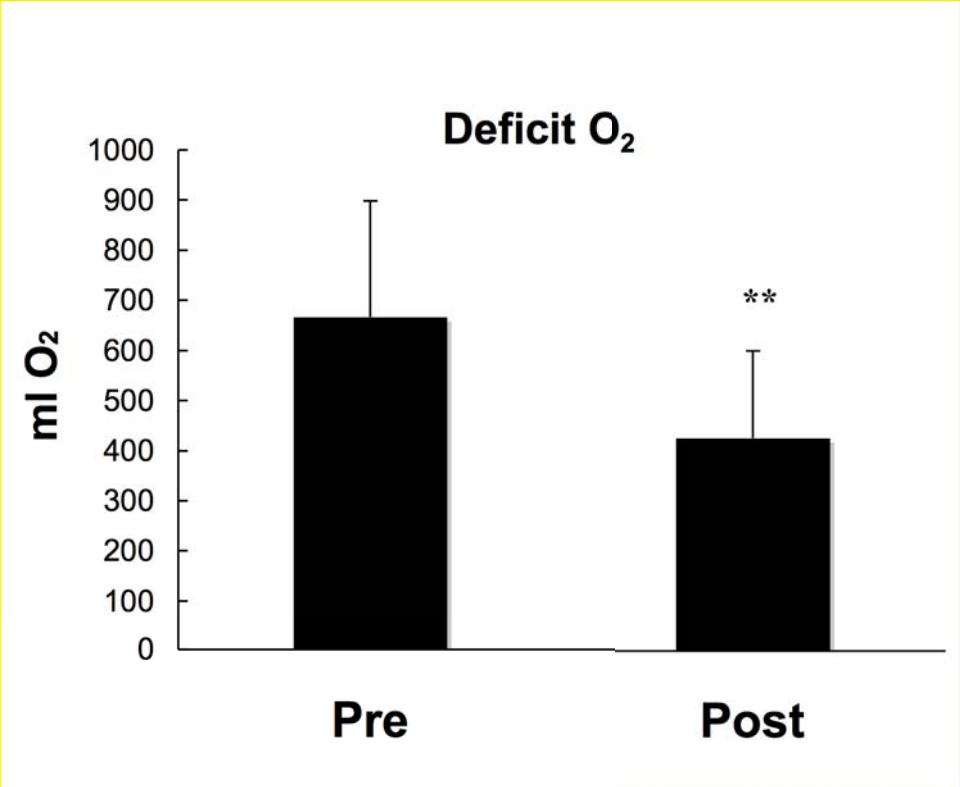


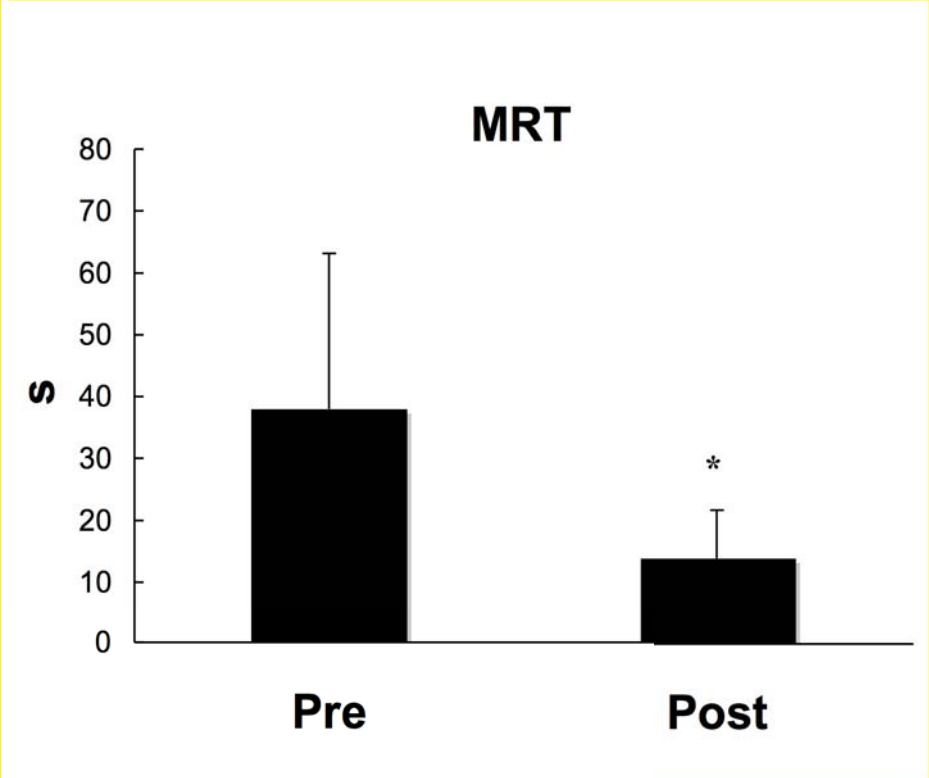
Results - V'O_{2AT}



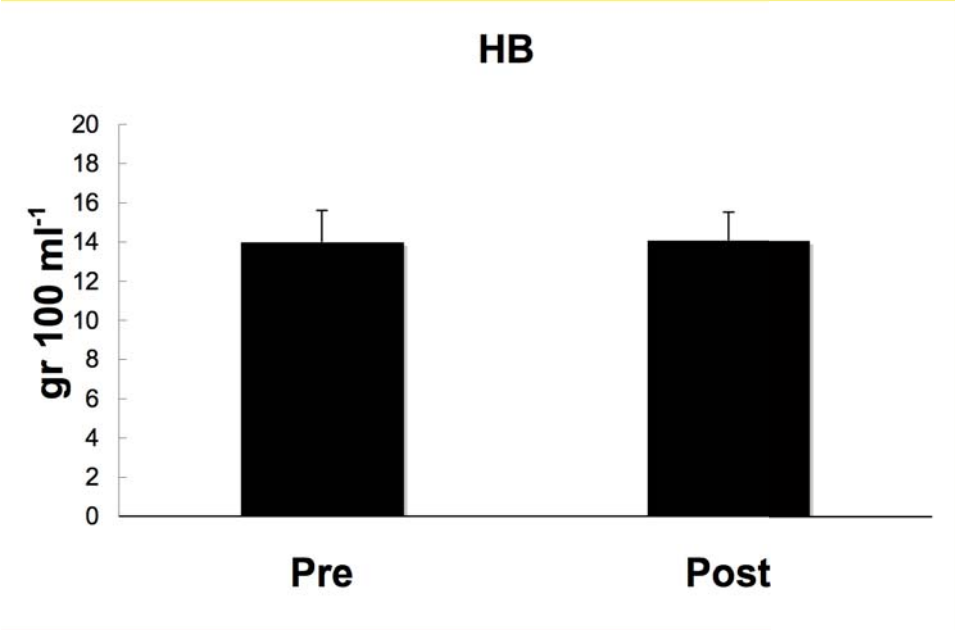


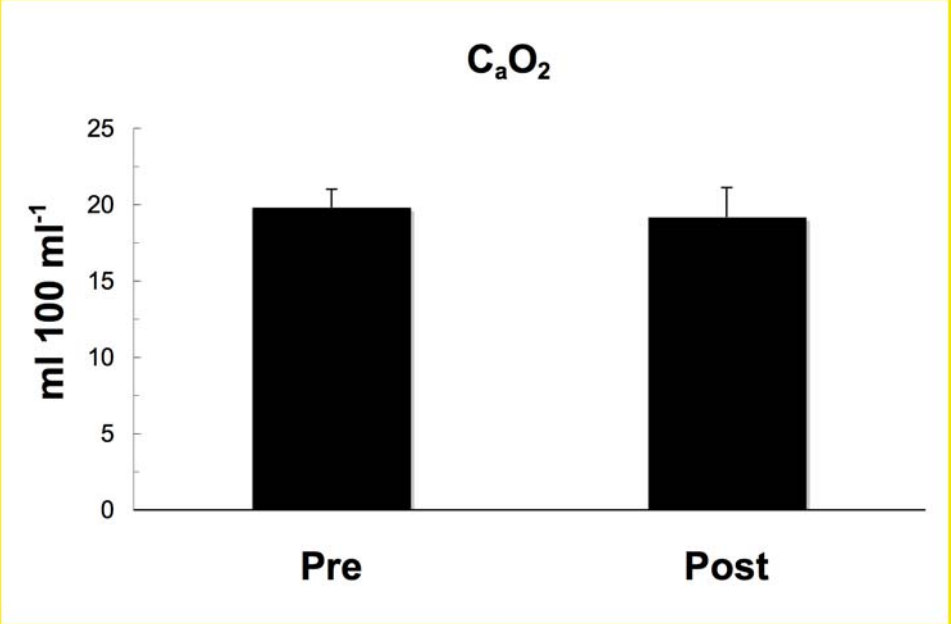
Results - DefO_2 and MRTV'O_2



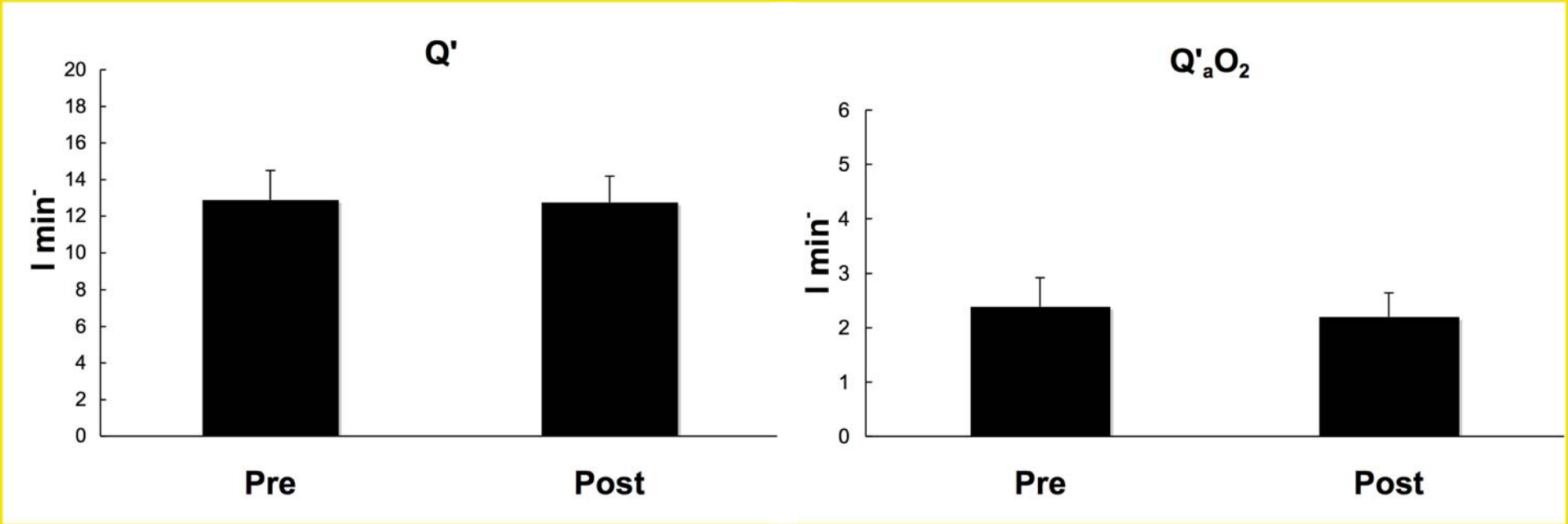


Results - Hb and C_aO_2

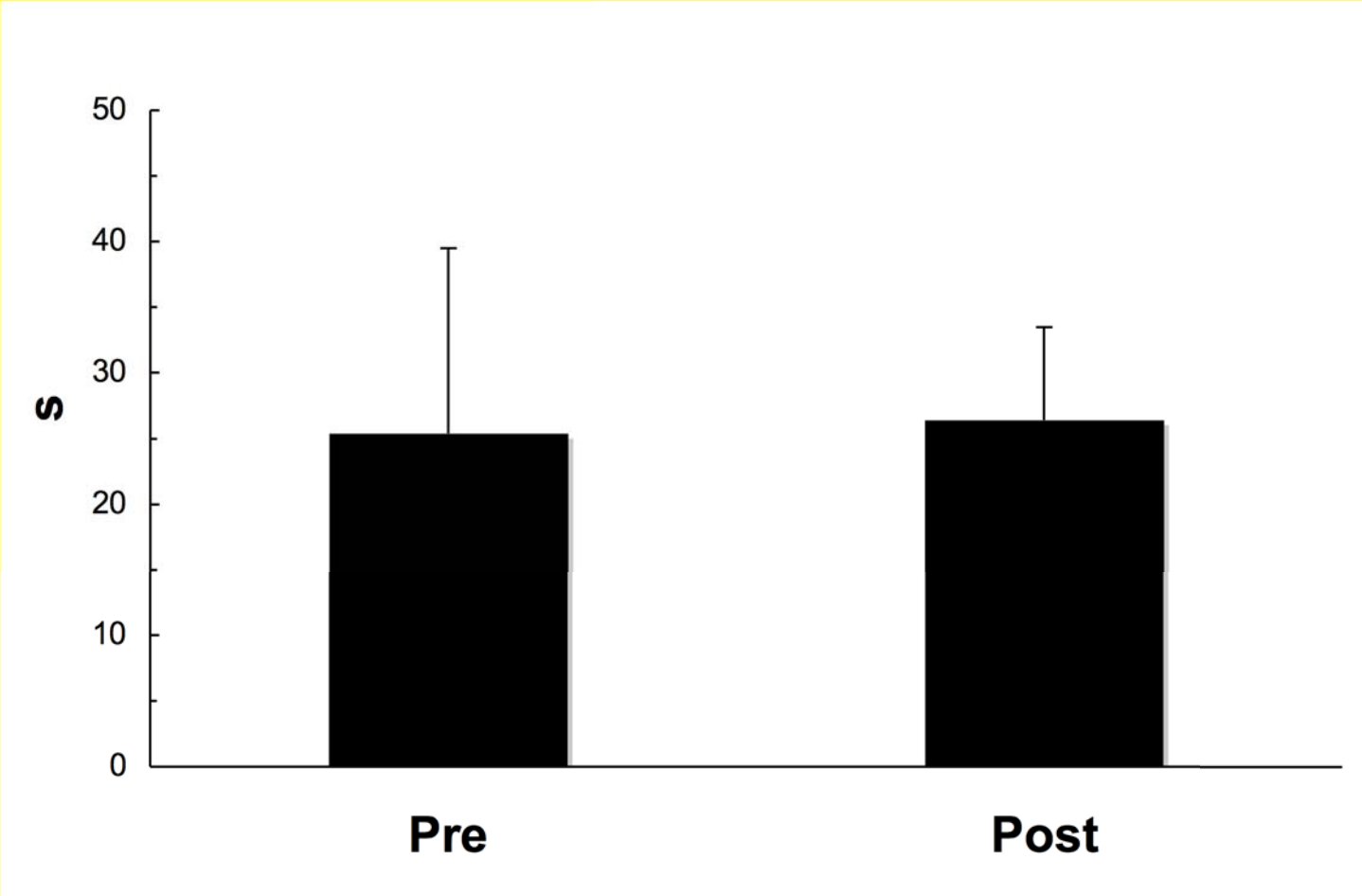




Results - Q’ and Q’$_a$O$_2$



Results - MRT Q'_aO_2



Conclusions

- O_2 kinetics and and DefO_2 turned out to be faster and smaller, respectively, upon the return to sea level
- AT_V increase, although not significantly so
- This findings disagree with those of Boutellier et al (1984) who found slower V'O_2 kinetics after 6 weeks at 5.200 m asl.
- That was attributed to a greater utilization of the O_2 stores due to increased [Hb]
- In our case, however, [Hb] was the same before and after acclimatization
- Our findings are in partial agreement with those of Fokuoka and Grassi (2002) who showed that in adults V'O_2 kinetics is more sensitive to training than V'O_{2max} (Changes in the muscles?)

Acknowledgements

- Members and staff of expedition Shisha Pangma 2008
- Giorgio Fanò and his gulls and gills
- CEBISM
- ….and in particular to….:
  - Alessandra Adami
  - Gabriela De Roia
  - Valeria Marconi
  - Silvia Pogliaghi

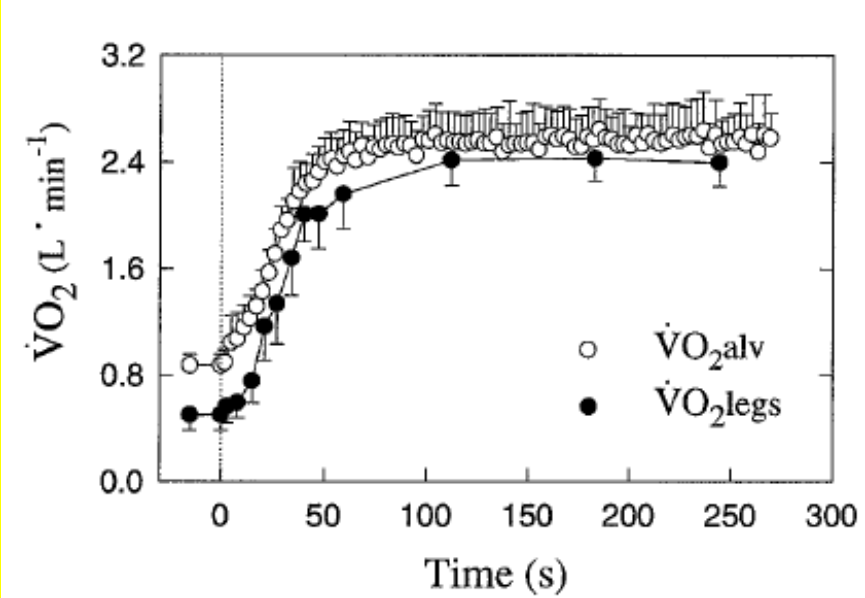
$V'O_{2A}$ kinetics and Phase 1 and 2

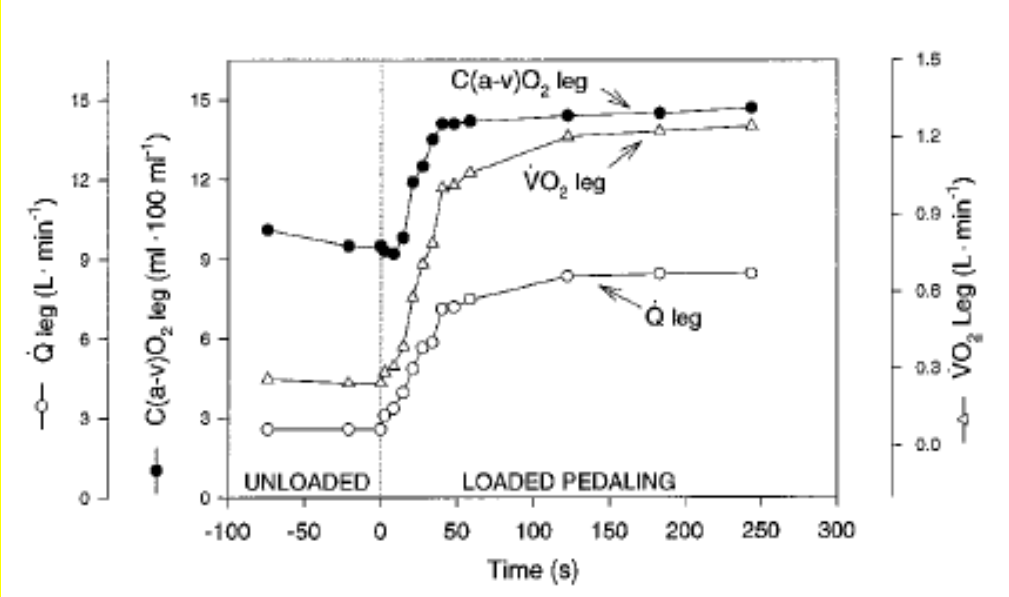
Fick's Principle

$$V'O_{2A} = Q' (C_a - C_v)_{O_2}$$

- Phase 1 is mainly related with the increase of Q' at the onset of the exercise ($(C_a - C_v)_{O_2}$ almost unchanged)
- Phase 2 is mainly related with the progressive decrease of C_{vO_2} due to the peripheral utilization of O_2. It is assumed to describe the response of muscular O_2 uptake.
- $V'O_2$ kinetcs provides an integrated view of the systems dictating O_2 transport and utilization

Alveolar and muscular V'O_2





1. VO_{2A} e $V'O_{2m}$ kinetics are similar
2. Bulk O_2 delivery to the muscles (Q'_aO_2) does not seem to limit $V'O_{2m}$ kinetics in this condition