November 12 – 13, 2015 – Rovereto (TN), Italy

6th International Congress Mountain, Sport & Health

Friday, November 13, 2015, 10:45 – 12:30

Thematic session 3 – Adaptations to Hypoxia

EFFECTS OF PHYSICAL TRAINING AND HIGH ALTITUDE EXPOSURE ON OXIDATIVE METABOLISM AND MUSCLE COMPOSITION IN HUMANS

- Capelli C

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Altitude training: *The Dawn*

- Anecdotal reports on world level athletes who started to incorporate altitude training after the 1968 Olympic Games of Mexico City following the dominance of East Africa Runners who were living and training at moderate-high altitudes

- Well planned, but almost ignored study of **Mellerowicz in 1970!**

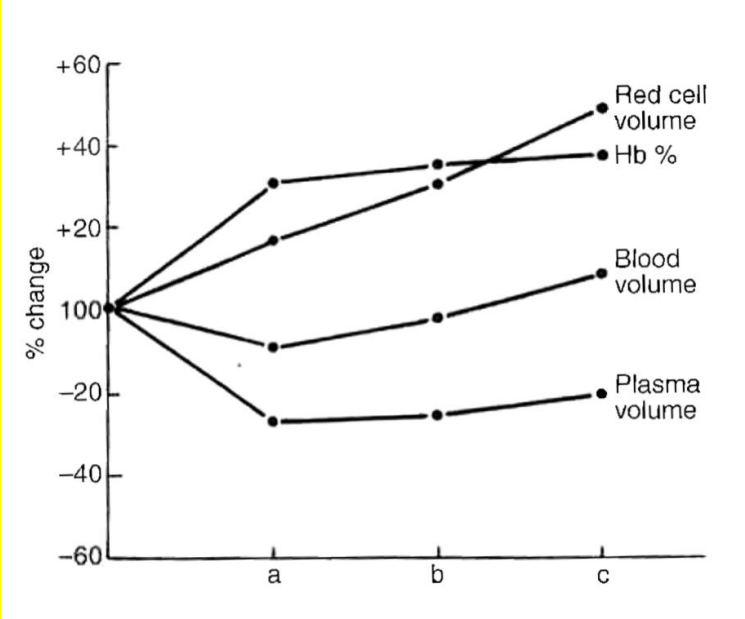
- 22 East German, moderately active police officers exposed to 4 weeks of rigorously planned training at:
  1. 2020 m asl;
  2. Sea level

- **Main outcomes**
  - **$V'O_{2max}$**
  - **3000 m performance time**

- **Improved in the hypoxic group** and **remained higher for two weeks after the end of training in hypoxia** in comparison with the ones observed in the normoxic, control group

Altitude training: *The Rationale*

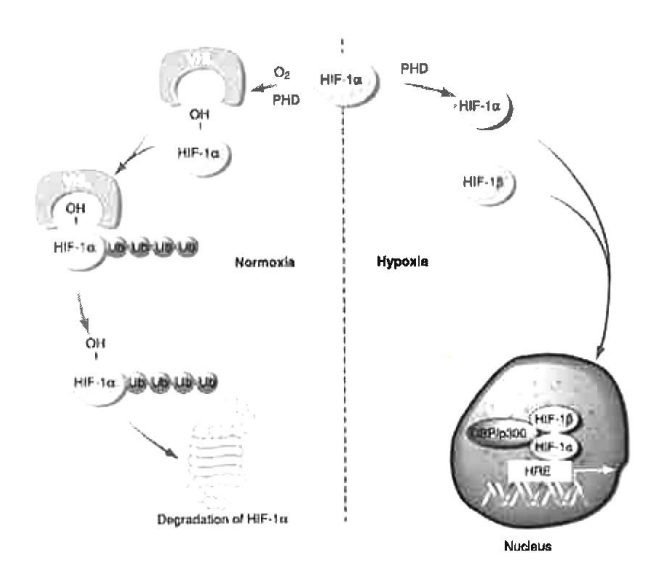
- **Aims of Training and Living at altitude**
  1. Increase in RBCV and in Hb mass
  2. Increase of Q'_aO_2 upon the return to sea level competition



Pugh et al 1964

Altitude training: *The Rationale*

- **Aims of Training and Living at altitude**
  3. Superimpose to the stimulus induced by **training** on peripheral tissues an additional one due to **hypoxia**

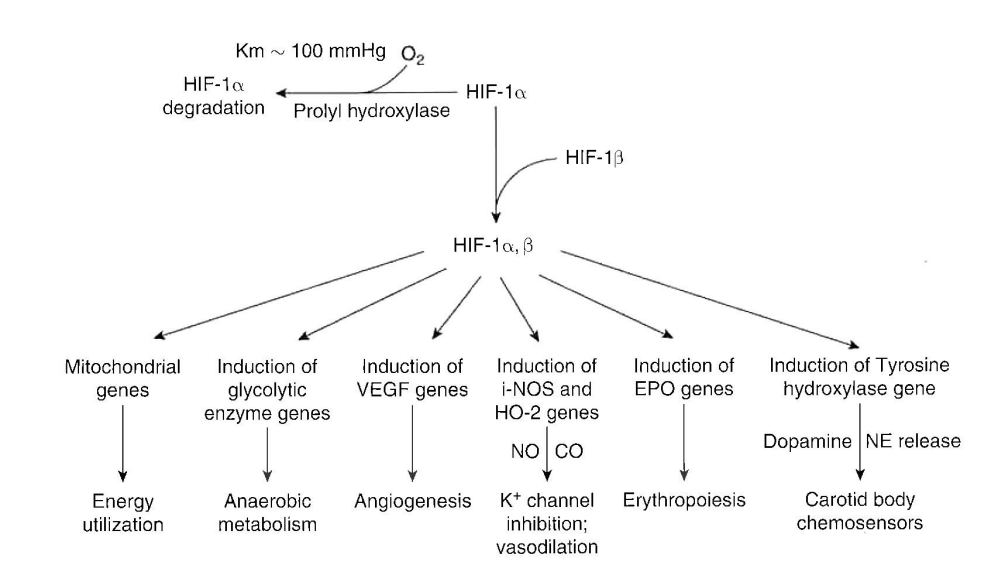


Shimoda and Semenza, 2011

- The transcription factor HIF-1α is stabilised in hypoxic conditions as PHD proteins activity is decreased
- Then, it translocates to the nucleus where it binds to HIF-1β and combines with co-activators at the hypoxia response element (HRE)
- This results in activation of several target genes

HIF-1α and gene expression

- A large numbers of target genes are up-regulated by HIF

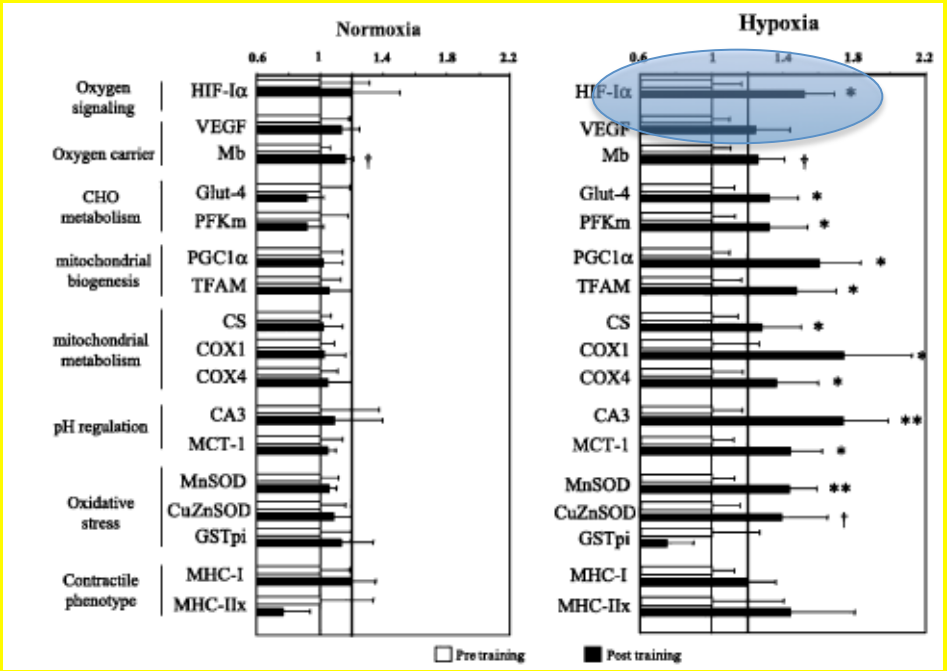


- *Erythopoiesis*
- *Angionesis*
- *Glycolisis*
- *pH regulation and lactate transport*
- …

Wilson et al, 2005

- Moreover, it has been shown that HIF-1α and HIF-2α are transiently increased after single bouts of endurance exercise (one leg exercise) (*Lundby et al, 2006*)

HIF-1α and gene expression



(Hoppeler, 2008)

- Steady-state mRNA concentrations of HIF-1α are increased after hypoxic training according to the LLTH paradigm
- It is suggested that "*the more pronounced transcriptional response of genes to hypoxic training is importantly – but not exclusively – related to increased level of HIF-1α under hypoxic conditions*"

Living High-Training High- LHTH

"Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance

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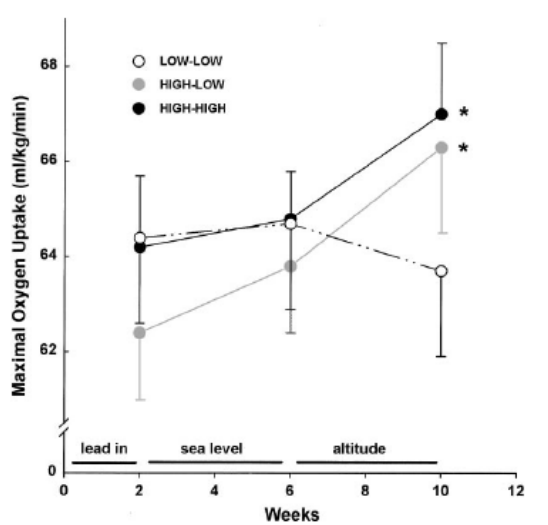
[2]*Baylor/The University of Texas Southwestern Sports Science Research Center, The University of Texas Southwestern Medical Center, Dallas, Texas 75235*

- After 4 ww of SL training, 39 distance runners were randomly assigned to
  - Control group (SL)
  - **Training High – Living High (2500-2700 m asl) – 4 ww**
  - *Training Low (1400 m asl) – Living High – 4 ww*



Levine, Stray-Gundersen, 1997

- **Main Outcomes**
  - **$V'O_{2max}$ increased in LHTH and LHTL**
  - **5000 m running performance time improved only after LHTL**

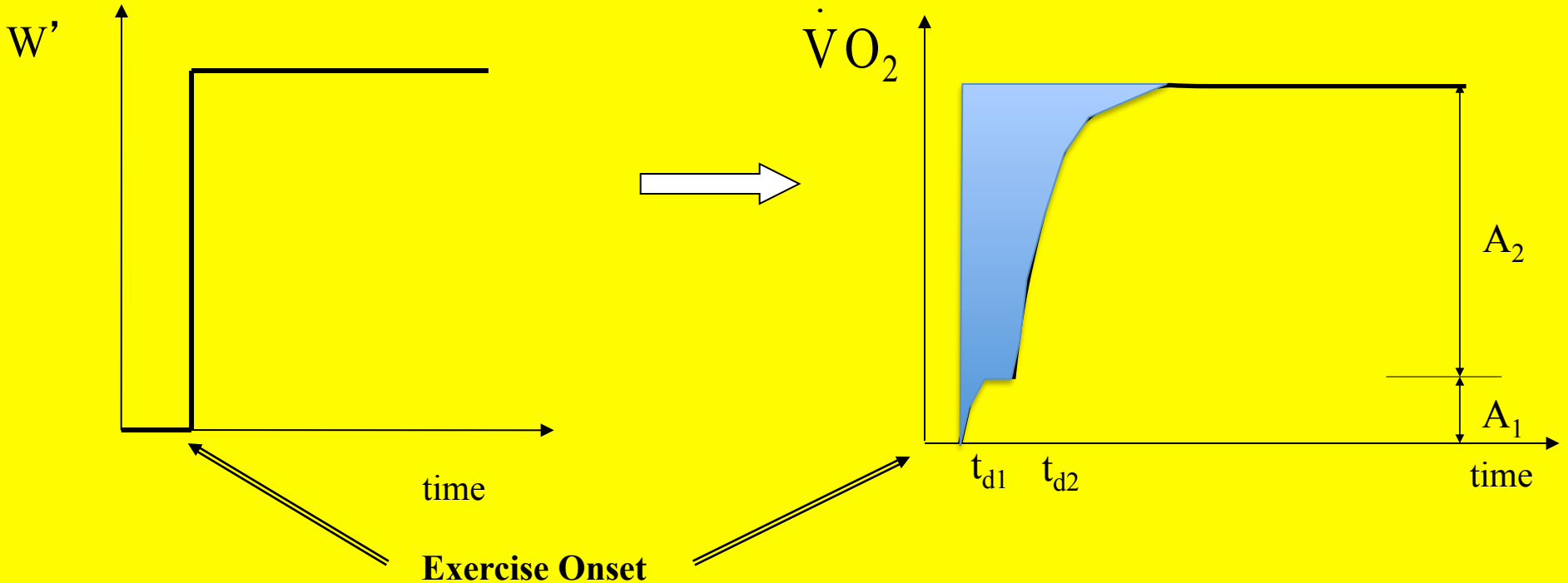
Living High-Training High- LHTH

- **Wrap up**
  - LHTH may increase SL performance in some, but not in all athletes
  - It is recommended to live at an altitude starting from 2000 m asl
  - The duration of the exposure should not be less than 3 – 4 weeks

Living High-Training High- LHTH

- **Muscle adaptation to prolonged exposure to severe hypobaric hypoxia**
  - Acute exposure of lowlanders to high altitude for up to 2 months did not cause the 'favourable' expected adaptations of skeletal muscle tissue - *larger capacity for oxygen use and delivery*
    - Loss of body volume
    - Decreases of muscle fiber CSA (Type I and II) with increased capillary density
    - Moderate reduction of muscular oxidative capacity (SDH, HEXO)
    - Reduction of subsarcolammal population of mitochondria
    - Increases of the intramuscular lipofuscin levels

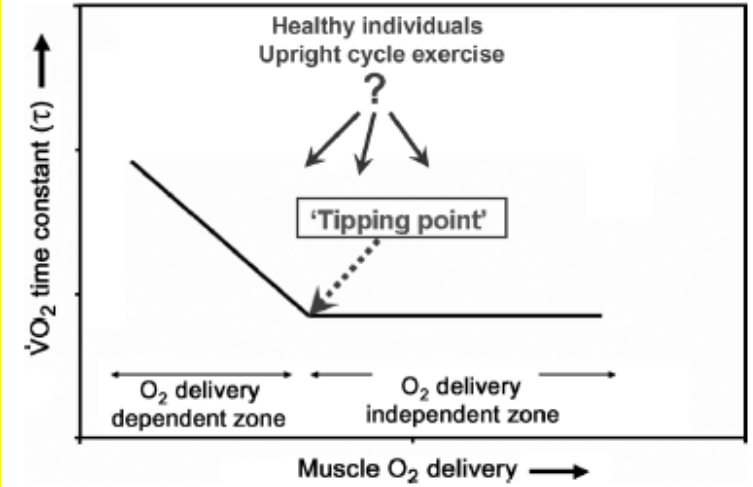
A different approach…*submaximal exercise*



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

Factors affecting gas exchange kinetics ?

- $V'O_2$ kinetics is dictated by the intrinsic slowness of oxidative metabolism to adapt to changes in energy demand (Grassi 2000, 2006).
- It may be also controlled by the speed of bulk/peripheral convective O_2 delivery or by peripheral O_2 diffusion to muscles (*Grassi 2006; Hughson et al. 1996*).



- *…as O_2 delivery is reduced moving from right to left, at some "tipping point" an O_2 limitation occurs, and $V'O_2$ kinetics become progressively slowed (Poole DC et al., MSSE 40: 462- 2008)*

Gas exchange kinetics and endurance training

- $V'O_2$ kinetics responds quickly to endurance training in young and adult subjects
- Type I fibers are characterised by **larger metabolic stability**: lower modifications of [ADP], [PCr], [ATP], [P_i]
- Endurance training induces an **increase in mitochondrial enzymes** involved in the **oxidation** of carbohydrates and fatty acids and an **increase mitochondrial volume density**
- Therefore, **after training**, the muscle may show a **higher metabolic stability** allowing a given respiratory rate to be achieved with **smaller disturbances** in the intermediate metabolite concentrations
- This however **results in a lower $DefO_2$ with a faster $V'O_2$ kinetics**
- Faster $V'O_2$ kinetics is correlated wit the amelioration of running performance

Aim of Study #1

Improved VO_2 uptake kinetics and shift in muscle fiber type in high-altitude trekkers

C. Doria,[3] L. Toniolo,[1] V. Verratti,[3] P. Cancellara,[1] T. Pietrangelo,[3] V. Marconi,[2] A. Paoli,[1] S. Pogliaghi,[2] G. Fanò,[3] C. Reggiani,[1,4] and C. Capelli[2,5]

[1]*Department of Anatomy and Physiology, University of Padova;* [2]*School of Exercise and Sport Sciences, University of Verona;* [3]*Department of Neurosciences and Imaging, University of Chieti-Pescara, Chieti;* [4]*CNR, Institute of Neuroscience, Padova; and* [5]*CeRiSM, Rovereto, Trento, Italy*

J Appl Physiol 111: 1597-1605, *2011*

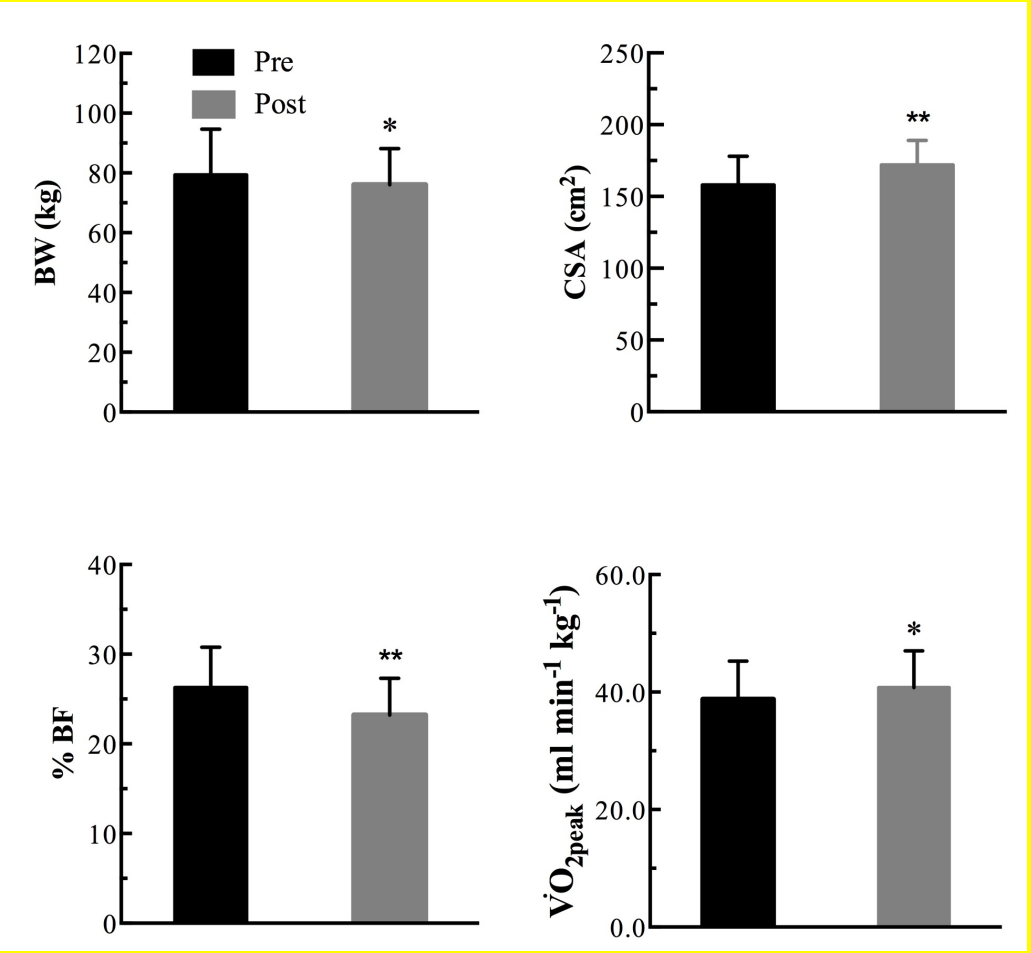
- The effect of a prolonged stay at HA associated with the increase of physical activity:
  - On the dynamic response of the oxidative metabolism to the sudden imposition of exercise
  - The parallel muscular structural changes

- Possible interference of prolonged hypobaric hypoxia on the effects induced by training

Subjects and experimental design

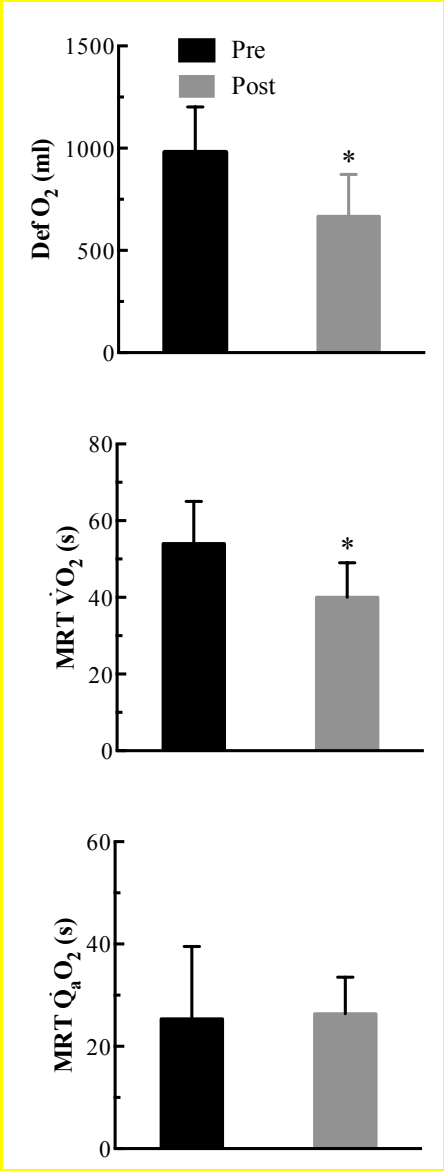
- Seven **men, healthy, moderately active mountaineers** (39.4 yy ± 14.9)
- 23 days at 5000 m asl, with short periods at 5900 and 6400 m asl
- 13 days of trekking before and after the stay at HA
- Before and after the expedition:
  - Anthropometrics, CSA of quadriceps
  - Isometric strength of quadriceps, peak and average power of lower limbs muscles
  - $\dot{V}O_{2peak}$ (ramp test to exhaustion)
  - $\dot{V}O_2$ and $\dot{Q}_aO_2$ kinetics during square wave transition @ 100 W (#2)
  - Muscle biopsies of *vastus lateralis*
    - Myosin isoforms, single muscle mechanics, TOM20

#1- Results – Functional parameters

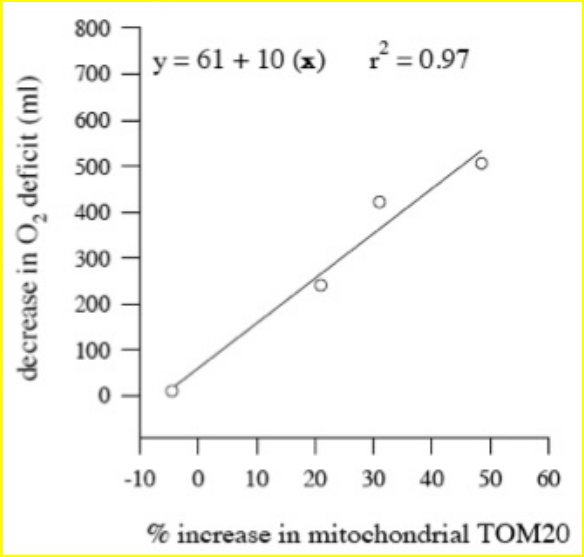


- Absolute $V'O_{2peak}$ and MVC did not change
- $V'O_2$ at VT did not change
- Peak and average muscle power decreased (- 9%, on the average)

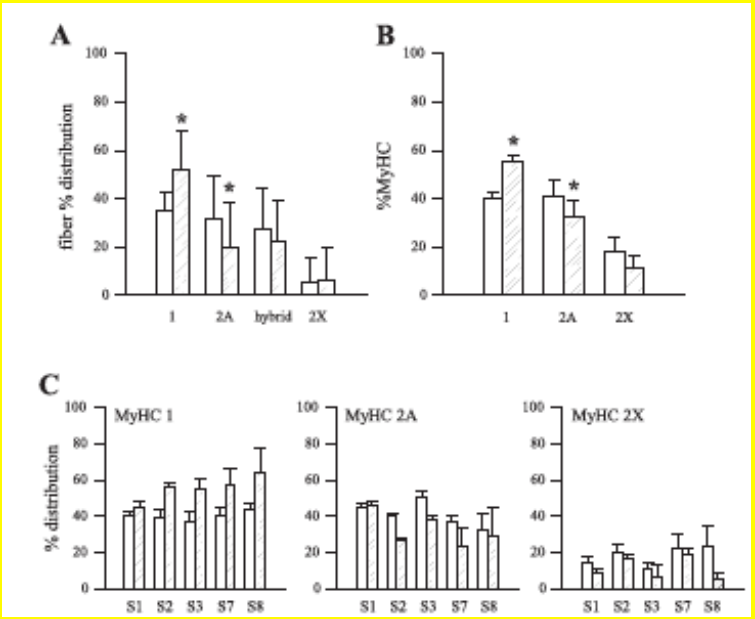
#1 Results – $V'O_2$ and Q'_aO_2 kinetics



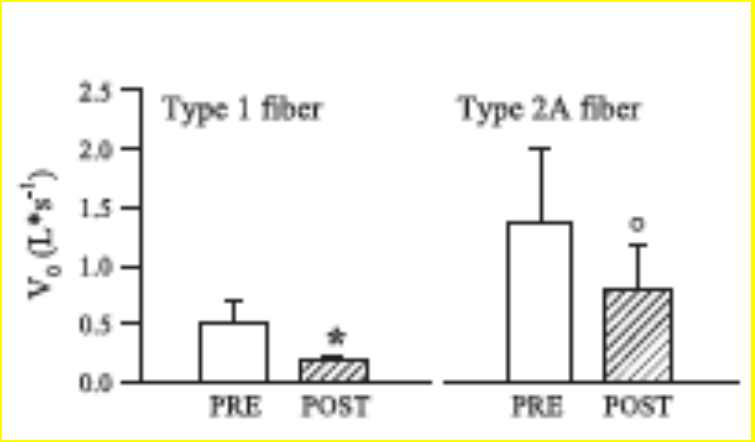
- The kinetics of O_2 bulk cardiovascular delivery was not affected
- $V'O_2$ kinetics was faster and $DefO_2$ was lower after expedition and its % decrease was correlated with % increase in TOM20



#1 - Results – MyHC distribution



- Significant and homogenous transition in isoform distribution from 2A to 1



- Maximal shortening velocity decreased
- This may explain the observed decrease in AP and MP of the lower limb muscles in spite of the increase of CSA

Conclusions – Study #1

- The observed isoform transition were rather unexpected findings
- They may be likely the effect of the endurance training
- Relatively untrained subjects increased their physical activity at AH
- We can however suggest that a prolonged stay in a hypoxic condition above 5,000 m does not necessarily imply deterioration, but can even **induce an improvement of the muscle oxidative metabolism.**

Study #2

Gokyo Khumbu/Ama Dablam Trek 2012: effects of physical training and high-altitude exposure on oxidative metabolism, muscle composition, and metabolic cost of walking in women

E. Tam[1] · P. Bruseghini[1] · E. Calabria[1] · L. Dal Sacco[1] · C. Doria[2] · B. Grassi[3] · T. Pietrangelo[2] · S. Pogliaghi[1] · C. Reggiani[4] · D. Salvadego[3] · F. Schena[1,5] · L. Toniolo[4] · V. Verratti[2] · G. Vernillo[5,6] · Carlo Capelli[1,5,7]

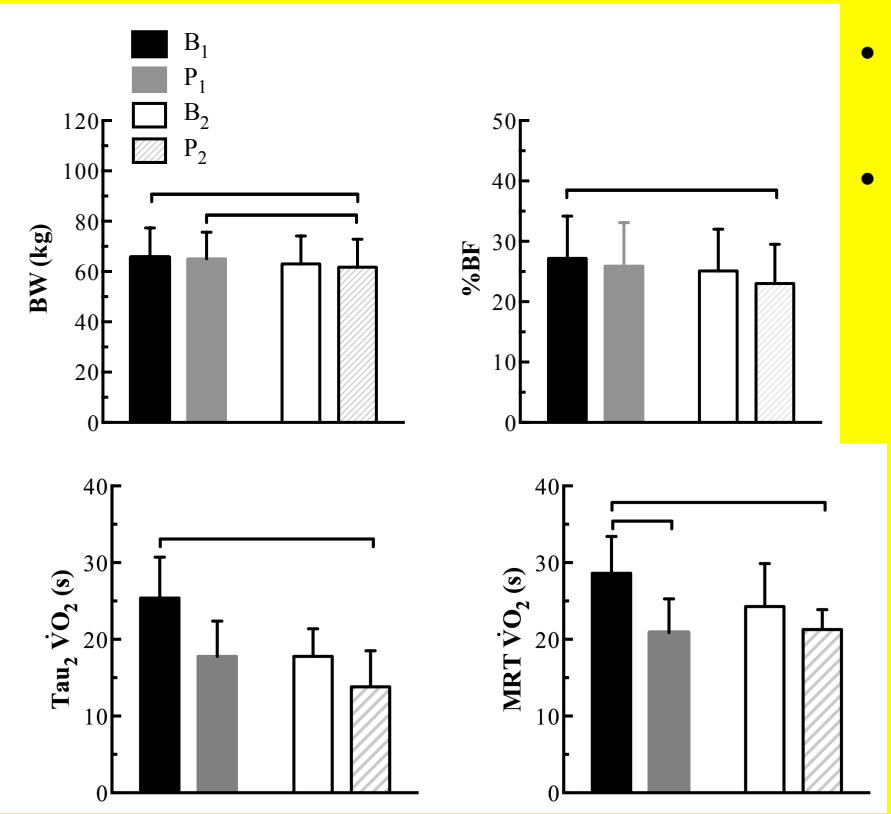
- **General Aim**
  - To understand whether the modification induced by adaptation to training may may modulated / potentiated by hypoxia

- **Subject and experimental design**
  - Seven **adult, moderately active women** (36.3 yy ± 7.1)
  - Two expeditions:
    - At sea level, 12-14 days, 600 m asl
    - After four months of wash out, at HA (4100 m asl), 14 days

Study #2

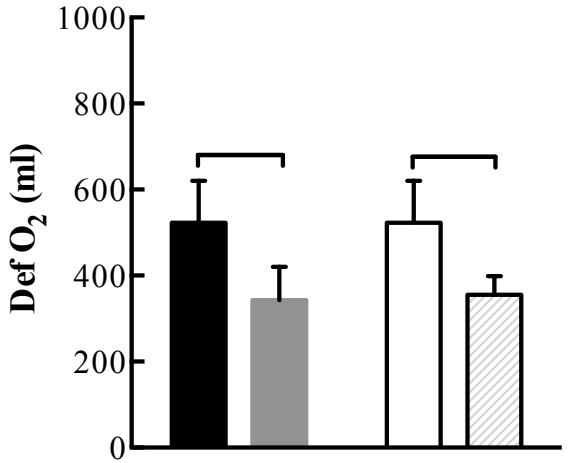
- **Before and after the two expeditions**
  - Anthropometrics, CSA of quadriceps, isometric strength of quadriceps, peak and average power of lower limbs muscles, $V'O_{2peak}$ (ramp test to exhaustion), $V'O_2$ and Q'_aO_2 kinetics during square wave transition @ 100 W (#2), energy cost of walking
- **Before the study and after the exercise interventions (trekkings)**
  - Muscle biopsies of *vastus lateralis*
    - Myosin isoforms, TOM20
    - Mitochondrial oxidative capacity and efficiency with high-resolution respirography

#2 - Results – Functional parameters

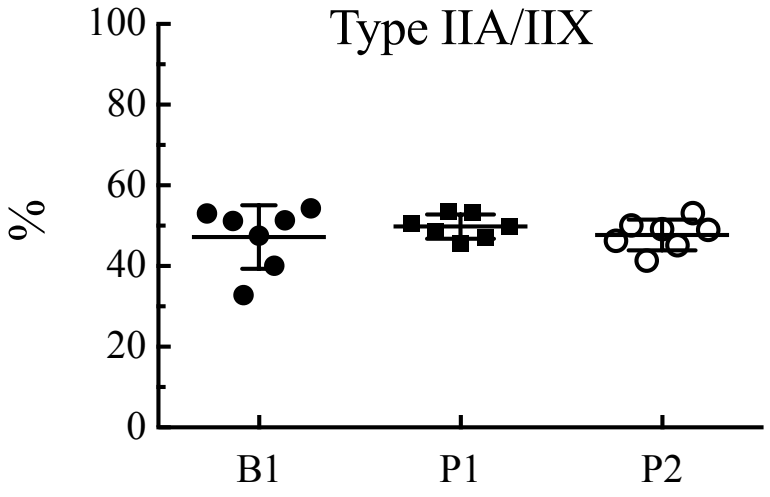


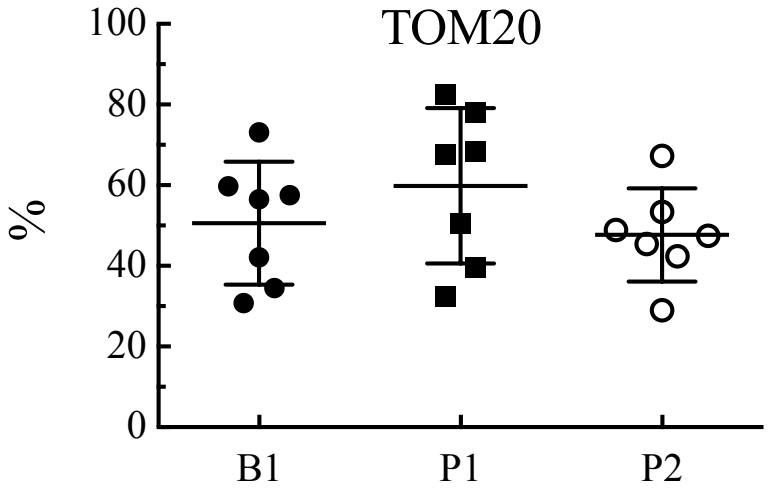
- Absolute and relative $V'O_{2peak}$, Q'_aO_{2peak}, MVC and muscular power did not change
- $V'O_2$ at VT was not affected

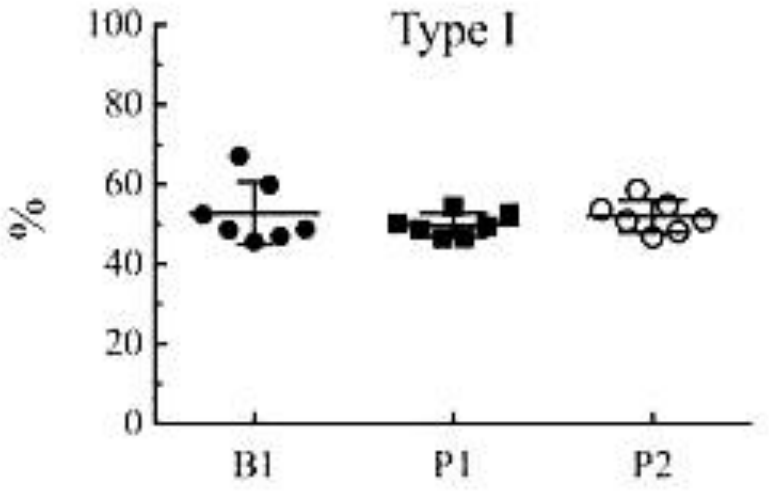
- $DefO_2$ decreased after trekking at sea level and at altitude



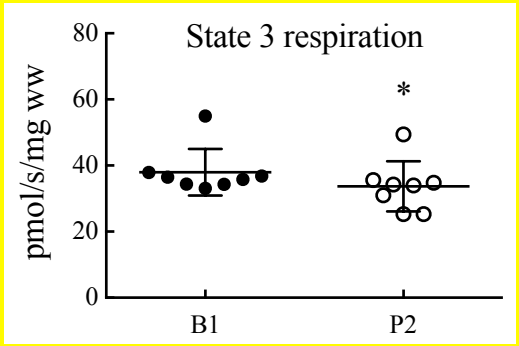
#2 - Results – MyHC distribution - TOM20



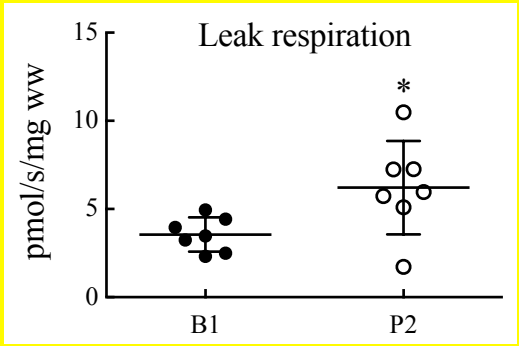




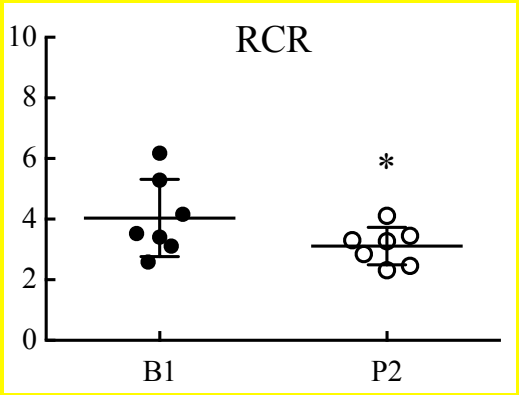
#2 - Results – Mitochondrial respirometry



- ADP-stimulated mitochondrial respiration (**State 3**) was significantly **lower** (-10%) in P_2 vs. B_1



- **Leak respiration**, reflecting the basal O_2 consumption not coupled to ATP synthesis, was significantly **greater** (+ 73%) at P_2 than at B_1



- The respiratory acceptor control ratio (RCR), i.e., the **ratio** between **State 3 and leak respiration** in the presence of malate and glutamate as substrates, decreased from B_1 to P_2 indicating a **less strict coupling between oxidation and phosphorylation**

Conclusions – Study #2

1. **Why a faster V'O_2 kinetics without mitochondrial neogenesis?**
   - Recent data suggest that V'O_{2A} kinetics **accelerates after endurance training** mainly **because of the increase of the so-called each-step activations of OXPHOS** *(Zoladz et al, 2014)*
   - This may **preceed mitochondrial neogenesis** (*Zoladz et al, 2014)*
2. **No functional modifications** and **unaltered muscular characteristics** after HA, including mitochondrial mass/density
3. **Maximal mitochondrial respiration** (State 3) and **Mitochondrial coupling efficiency** were **negatively** affected after HA
4. The current findings, together with the past ones, suggest there is **a progressive loss of <u>intrinsic</u> skeletal muscle respiratory capacity with HA exposure**, and this attenuation may be **dependent on the length of exposure**

General conclusions-Take home message

- Although HA exposure might induce muscular modifications that **potentially impair the aerobic muscle metabolism**, it seems that **exercising at HA** is still able to **elicit beneficial functional adaptations** of the oxygen transport-utilization systems.
- **Moderate-intensity exercise** performed at HA can induce beneficial effects on physical performance in spite of the occurrence of muscular changes that may potentially impair the aerobic metabolic energy-yielding pathway

Thank you for your kind attention

Rovereto (TN), November 13th 2015

Acknowledgements

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- University G. D'Annunzio of Chieti-Pescara, I
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- University of Padova, I
  - P. Cancellara, A. Paoli, C. Reggiani, L. Toniolo
- University of Udine, I
  - B. Grassi, D. Salvadego
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  - F. Schena, G. Vernillo