Mitochondrial bioenergetics and response to high altitude

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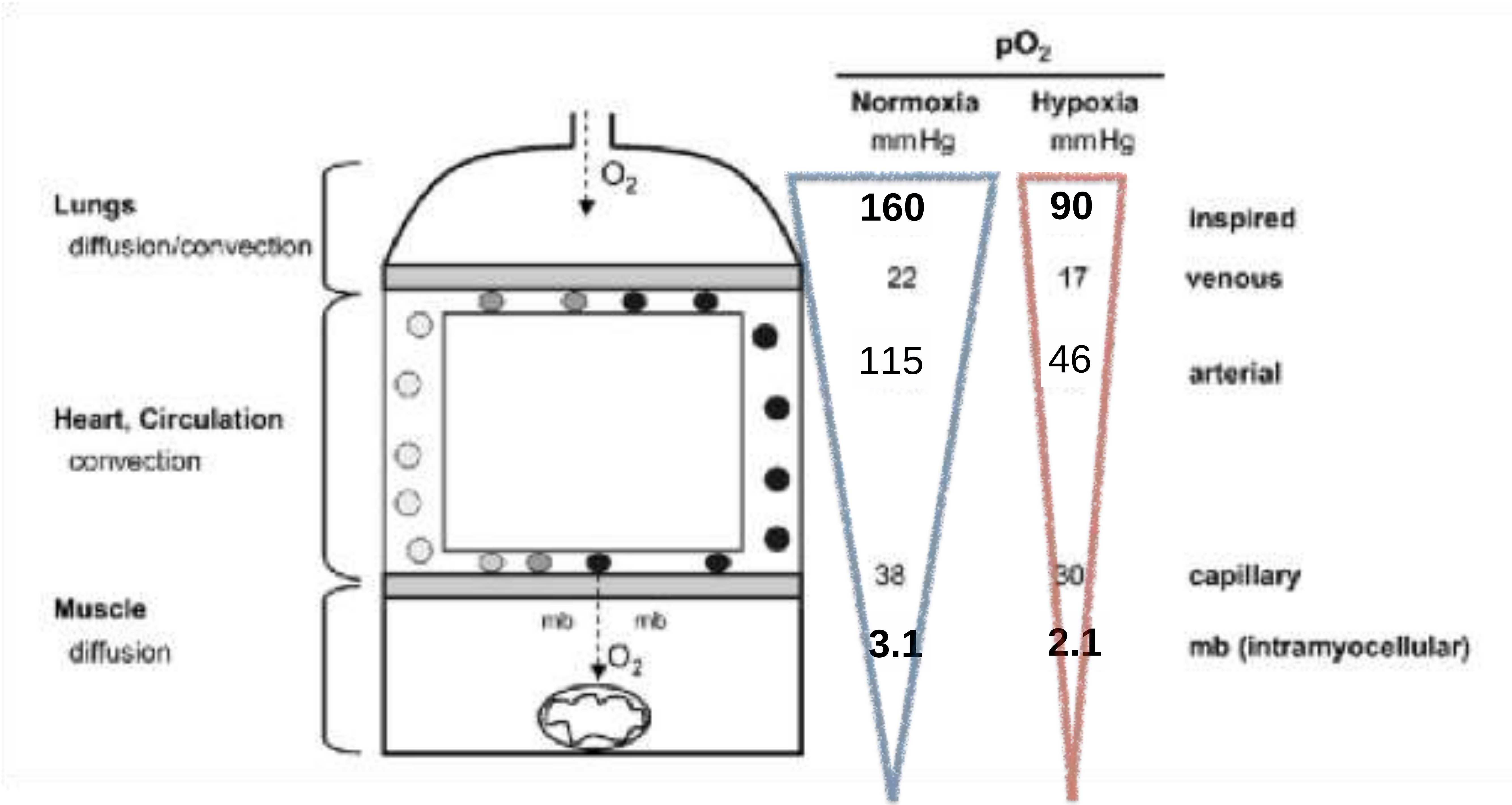
6th International Congress
Mountain, Sport & Health
Updating study and research from laboratory to field

UNIVERSITÀ DEGLI STUDI DI
VERONA

DNM

OROBOROS INSTRUMENTS

The path of oxygen



In mitochondria O2 is rapidly consumed and its partial pressure tends to zero.

Environmental hypoxia

Normobaric

↓

hypoxia chamber

Hypobaric

↓

high altitude

Hypoxia adaptations can be conditioned by:

Temperature

and

Activity

In most tissues of the body ATP production occurs mainly via mitochondrial oxidative phosphorylation

ATP homeostasis → cellular function

Mammalian cells utilize multiple homeostatic mechanisms to modulate O2 consumption, glucose metabolism and mitochondrial respiration in response to changes in cellular O_2 availability

Tissue or cellular hypoxia results when supply of oxygen from the blood-stream does not meet demand from the cells in the tissue.

Cellular hypoxia

In most tissues of the body the primary source of energy is ATP, deriving mainly from oxidative phosphorylation at the inner mitochondria membrane.

=> HYPOXIA poses a challenge to cellular metabolism, and **to maintain cellular energy homeostasis several adaptations must occur**.

High altitude as a model

Hypoxia is a feature of many human diseases (COPD, anemia, heart failure…).

==> studying the adaptations occurring in healthy humans acclimatizing at high altitude can be considered a useful model to investigate the responses of the body to hypoxia in absence of confounding factors associated with pathologies.

Environmental hypoxia induced adaptations

improved oxygen delivery:

- changes in resting ventilation rate
- concentration of circulating hemoglobin
- capillary density

peripheral oxygen utilisation:

metabolic remodeling of the tissue that alters oxygen utilization and ATP synthesis.

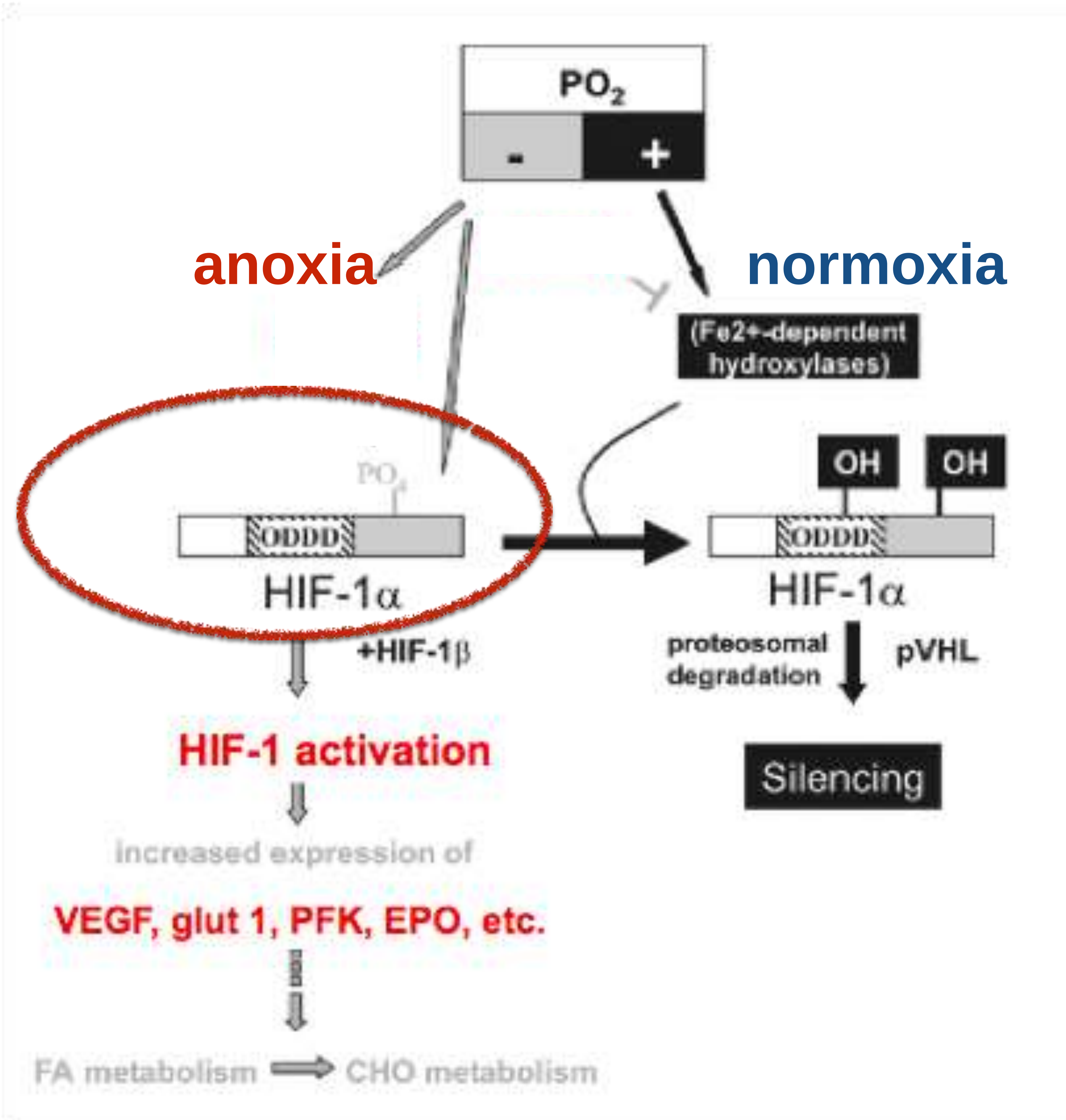
Adaptations to altitude are set on to optimize oxygen supply to tissues and the efficiency of oxygen utilization.

Environmental stressor	Alteration
Altitude >2300 m	
Immediate	Hyperventilation; body fluid alkalosis; Increased submaximal HR and Q; SV and maximal Q same or slight reduction
Longer term	Hyperventilation; right-to-left shift in oxyhaemoglobin dissociation curve; excretion of base (HCO_3^-) by kidneys; decreased alkaline reserve; increased sympathetic neurohumoral activity; submaximal HR remains increased; submaximal and maximal Q decrease; SV and PV decrease; mass and lean body mass decrease. Increased: haematocrit, haemoglobin concentration, red blood cell count and 2,3-diphosphoglycerate concentration, skeletal muscle capillarization, mitochondrial density and aerobic enzyme concentrations

from MJ Tipton 2015 Exp Phys

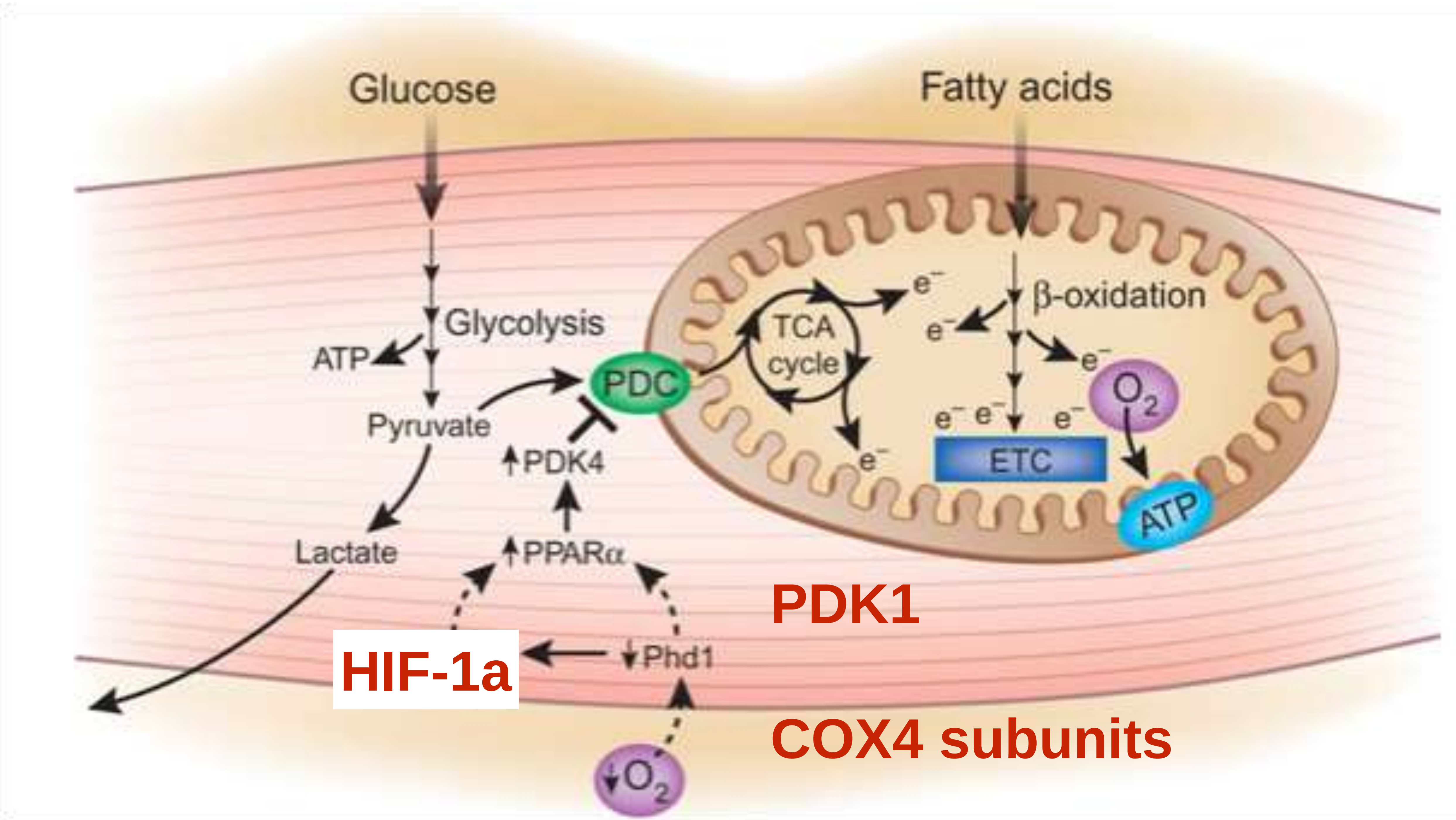
We will try to collate evidences describing the rebalancing of mitochondrial function in skeletal muscle in vivo in response to environmental hypoxia

The influence of hypoxia on mitochondria has become a topic of interest since **several mitochondrial proteins have been identified as being regulated by hypoxia**. (Semenza 2007)



PO2
-
+
anoxia
normoxia
(Fe2+-dependent hydroxylases)
PO2
ODDD
HIF-1α
OH
OH
ODDD
HIF-1α
+HIF-1β
proteosomal degradation
pVHL
HIF-1 activation
Silencing
increased expression of
VEGF, glut 1, PFK, EPO, etc.
FA metabolism
CHO metabolism

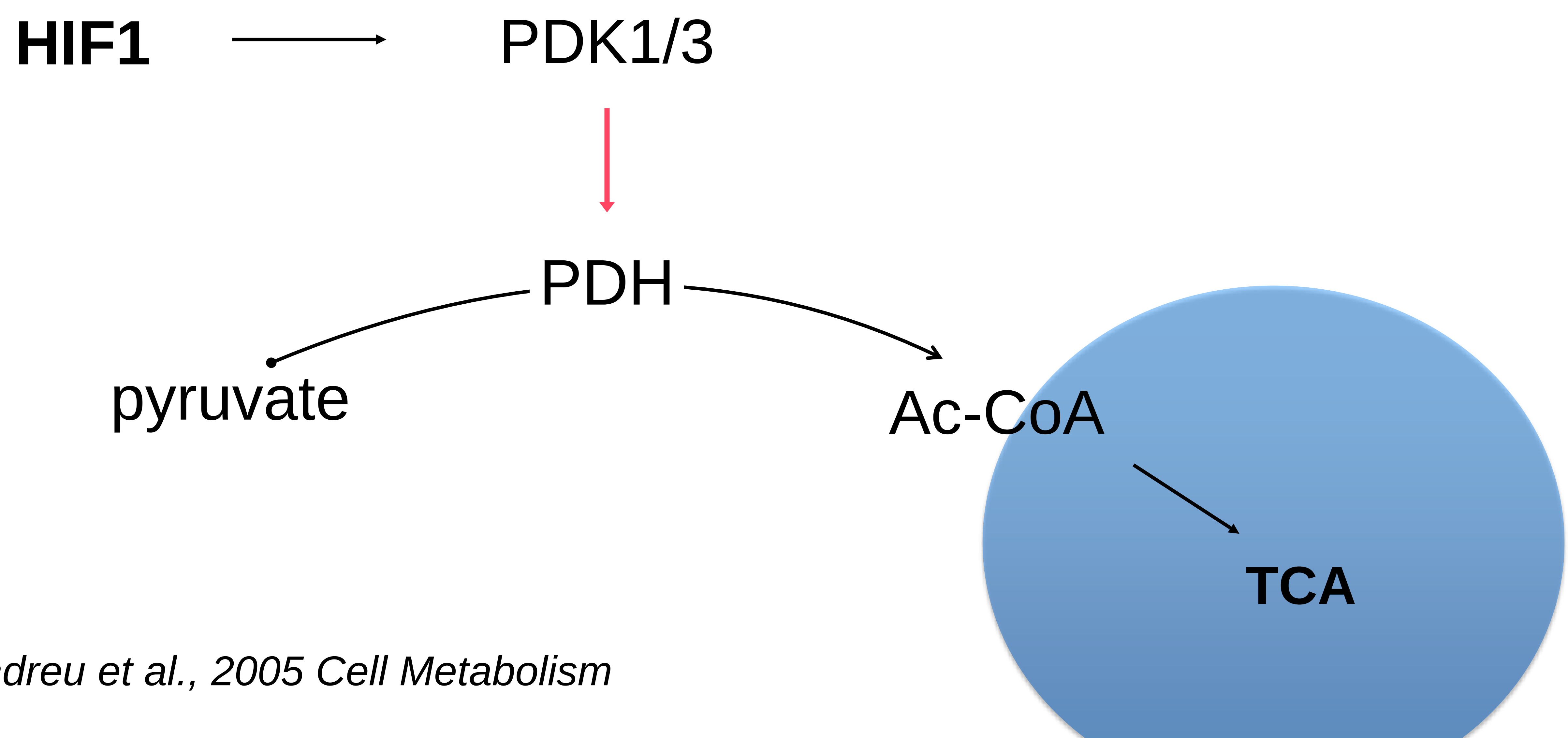
Mitochondria work in response to several physiological stimuli



Aragones et al., 2008 Nature Genetics

HIF-1 is both necessary and sufficient for reducing mitochondrial oxygen consumption in hypoxia

6 hours of hypoxia —> reduction of oxygen consumption in vitro.
Reverted by 6 hr re.oxygenation



Papandreu et al., 2005 Cell Metabolism

It is generally assumed that hypoxic exposure has diminishing effects on mitochondria.

hypoxia
9 to 75 days

→

Skeletal muscle

biochemical function

mitochondrial morphology

Physiological function ??

Limitations given by analysis on isolate enzymes…

One of the effects of acclimatization to altitude in skeletal muscles of lowlanders is a decreased mitochondrial density.

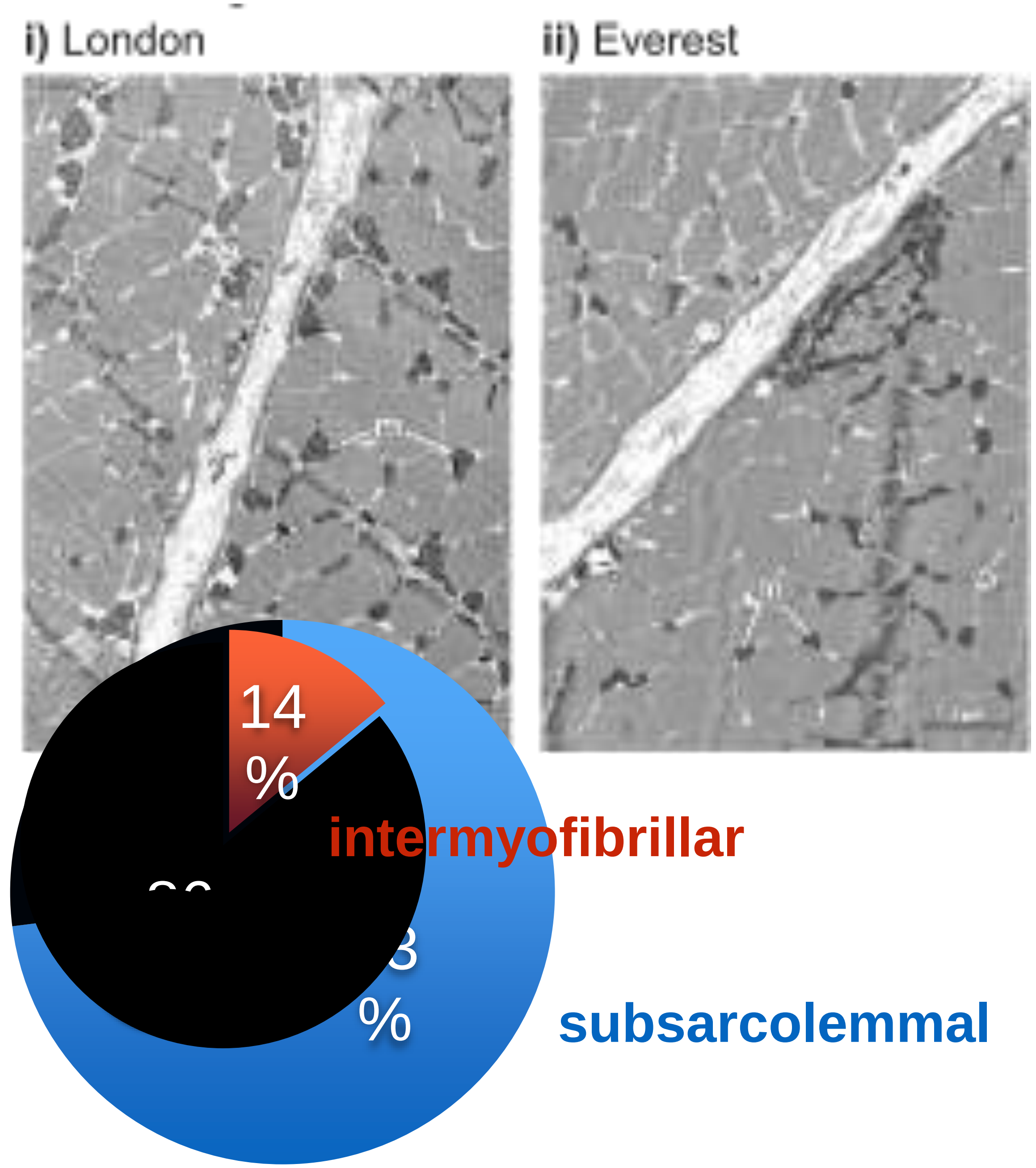
(Levett et al., 2012)

Metabolic efficiency

$$\frac{\text{ATP produced}}{O_2 \text{ consumed}}$$

Loss of mitochondrial density

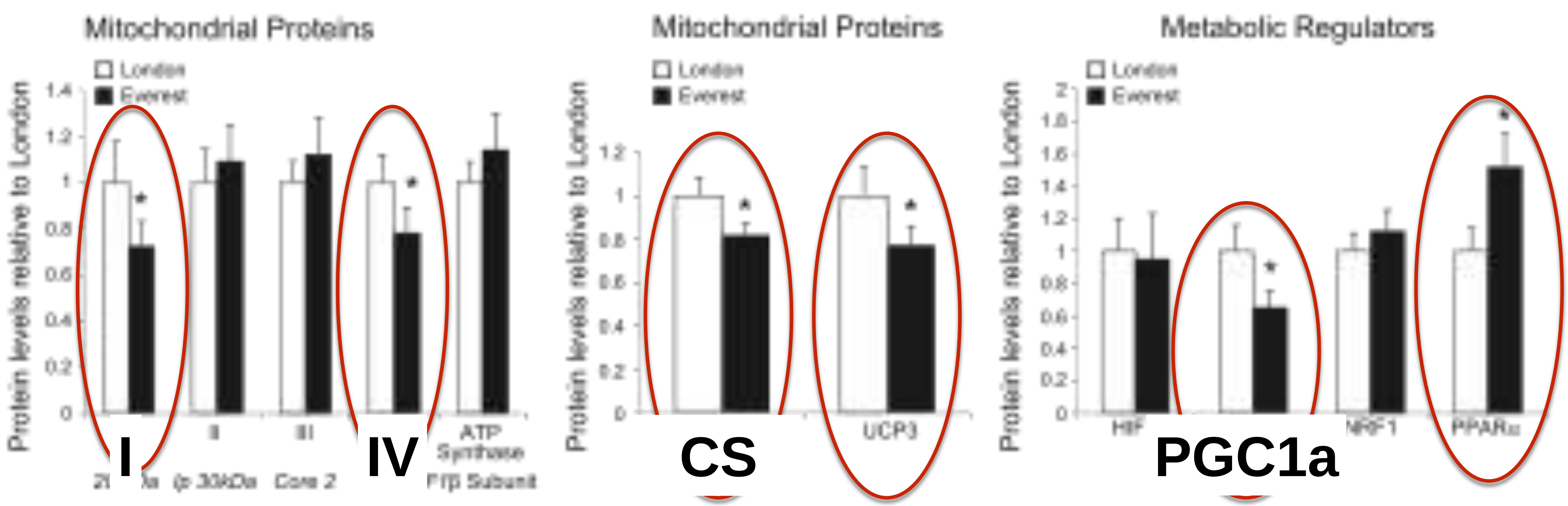
A team of climbers (n=12) showed a loss of 21% of total mitochondrial density ofter <u>66d</u> of hyopbaric hypoxia (Everest ascent).



Adapted from Levett et al., 2012)

Prolonged exposure to hypoxia leads to a better match the decreased O_2 supply and muscle O_2 demand.

In a prolonged exposure to hypoxia (66d) the reduction of mitochondrial density is accompanied by a reduction of citrate synthase and PGC1a.



Adapted from Levett et al., 2012)

However the physiological significance of these alterations is far from being understood.

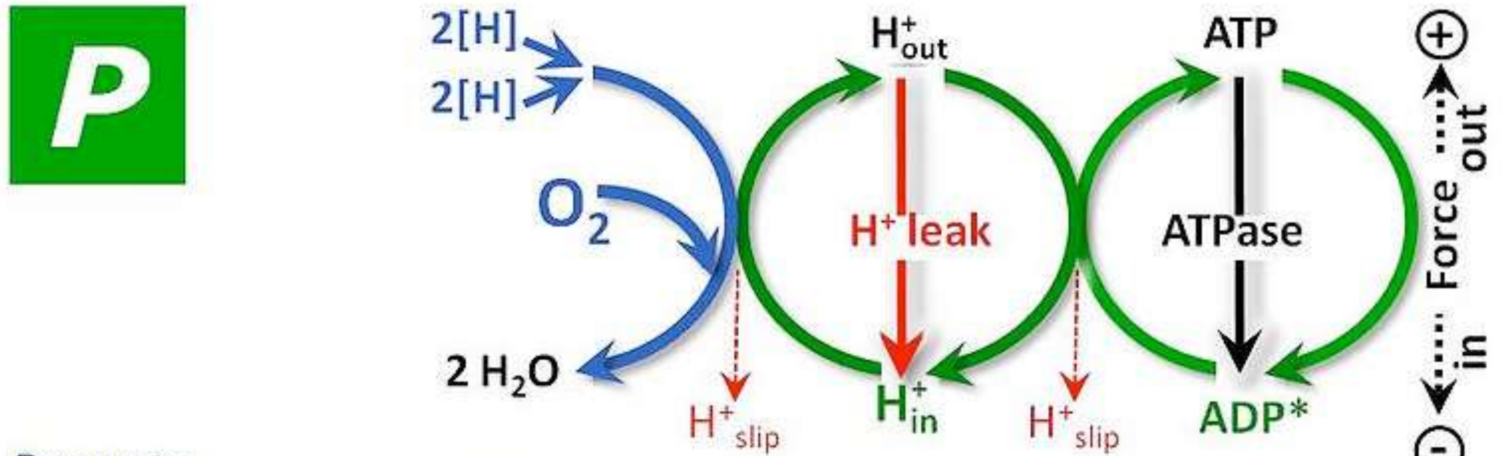
↓

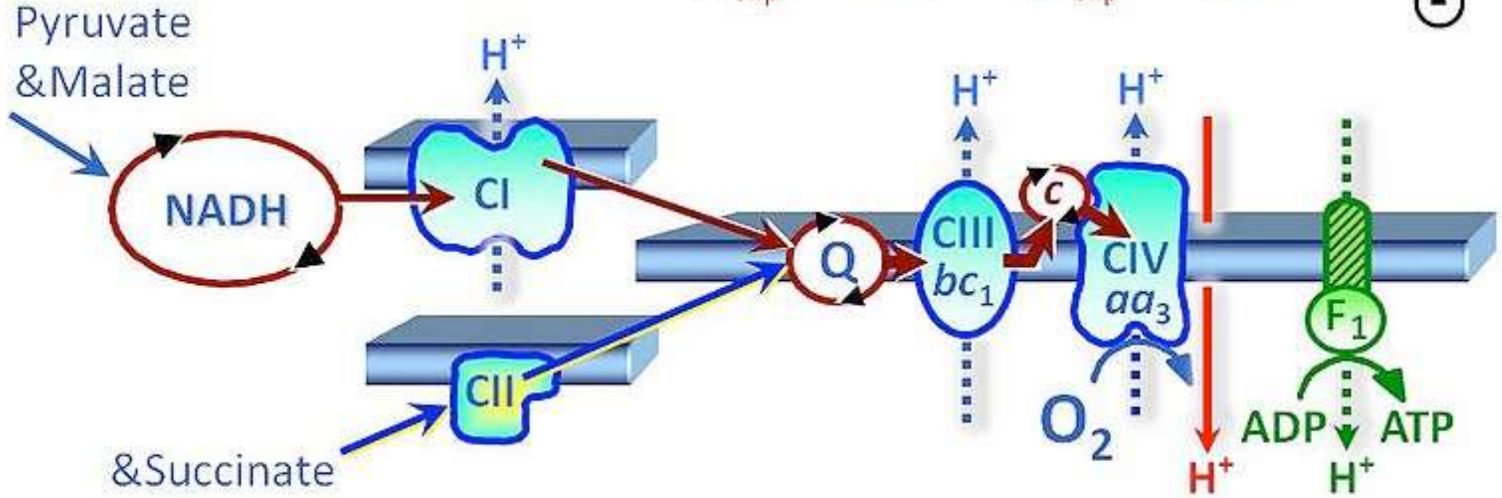
Respirometric measures allow for more complete analysis of integrated cellular function.

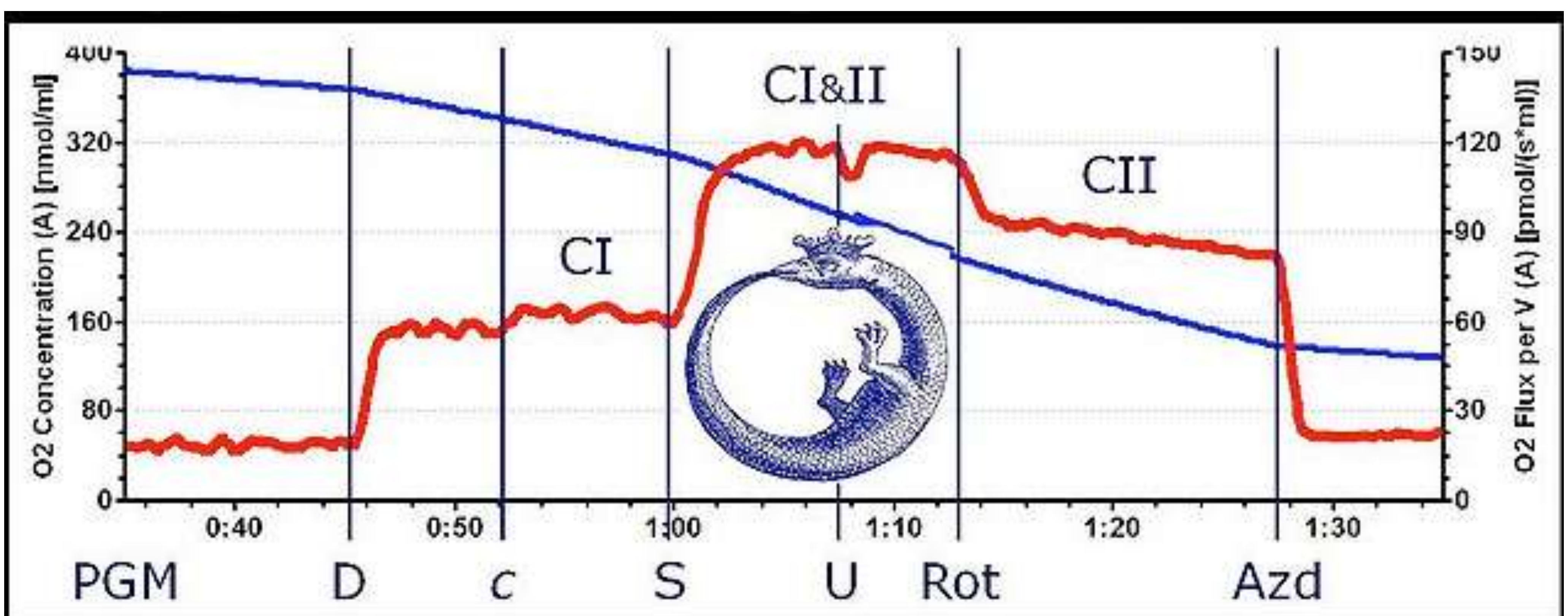
HRR - High Resolution Respirometry

..to investigate hypoxia-dependent control of mitochondrial function

OXPHOS capacity: saturating [ADP]

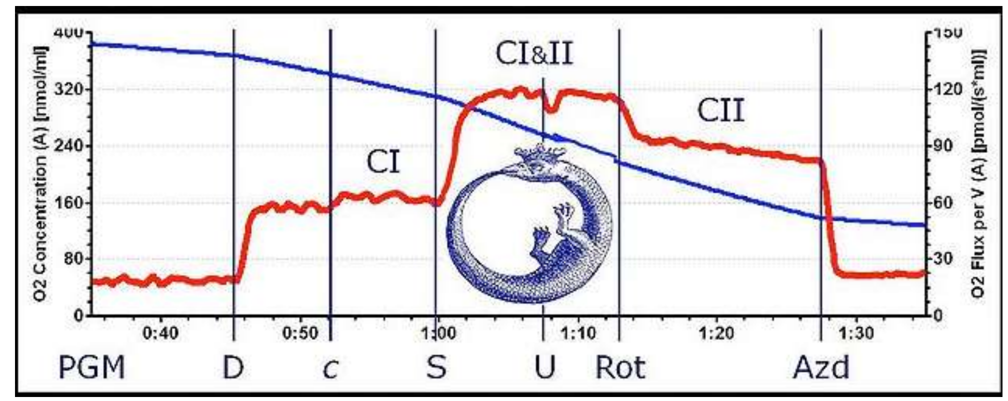






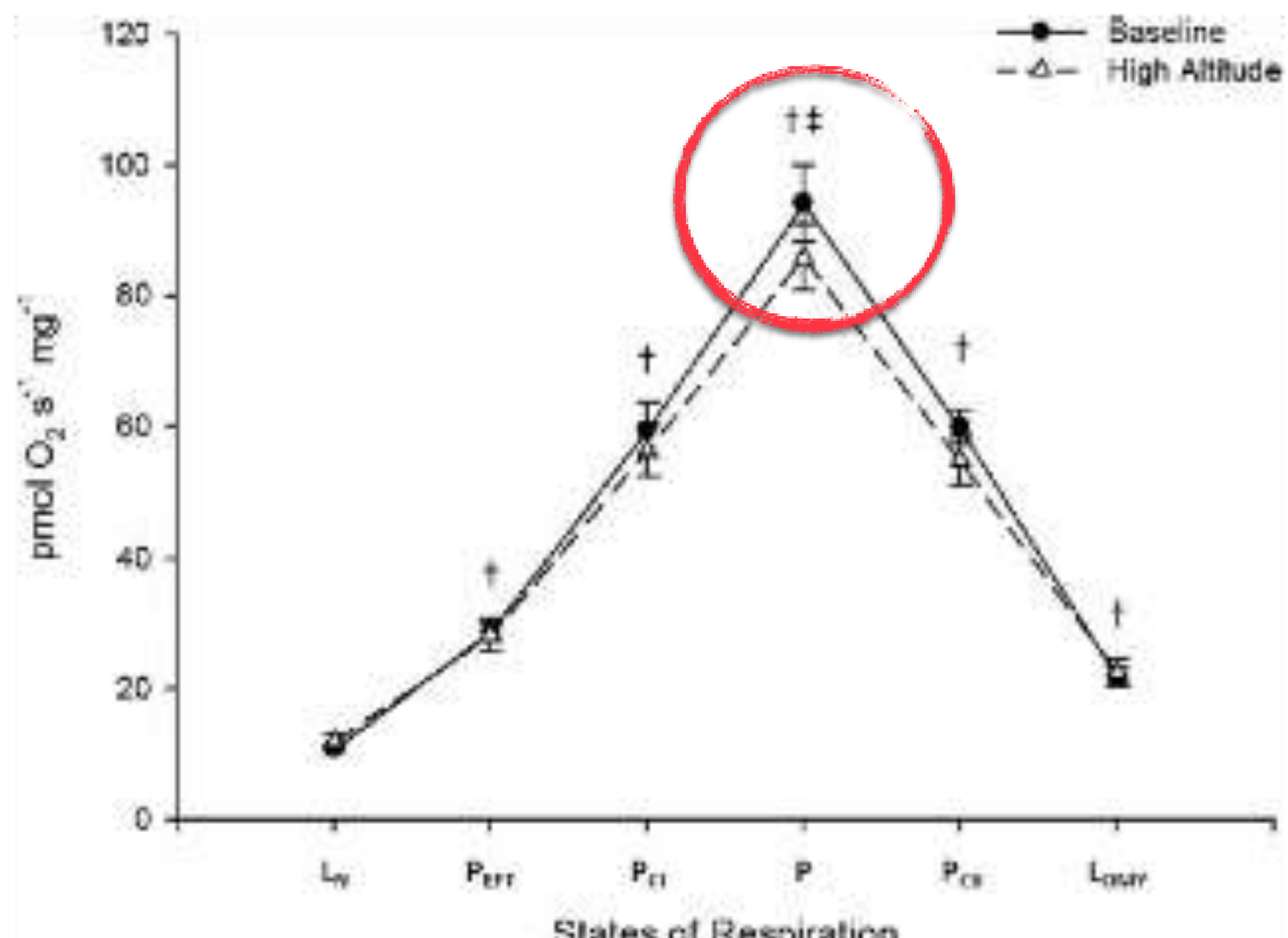
Changes in mitochondrial function following altitude exposure

How is mitochondrial function affected by **10 days** to high altitude (4559 mt)?



- no differences for any respiratory state

- **a trend for reduced maximal oxidative phosphorylation**.



Jacobs et al., 2013

Changes in mitochondrial function following altitude exposure

10 days of exposure at high altitude had no effect on metabolic efficiency

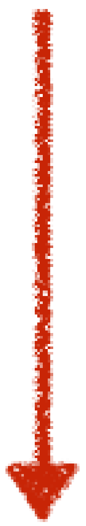
Table 2. Mitochondrial efficiency

Conditions	ETF coupling control	Respiratory control ratio	Leak (L_{Omy}) coupling control
BL	0.39 ± 0.02	4.44 ± 0.42	0.24 ± 0.02
HA	0.42 ± 0.02	4.02 ± 0.30	0.26 ± 0.02

Proteomic analysis shown that proteins involved in :

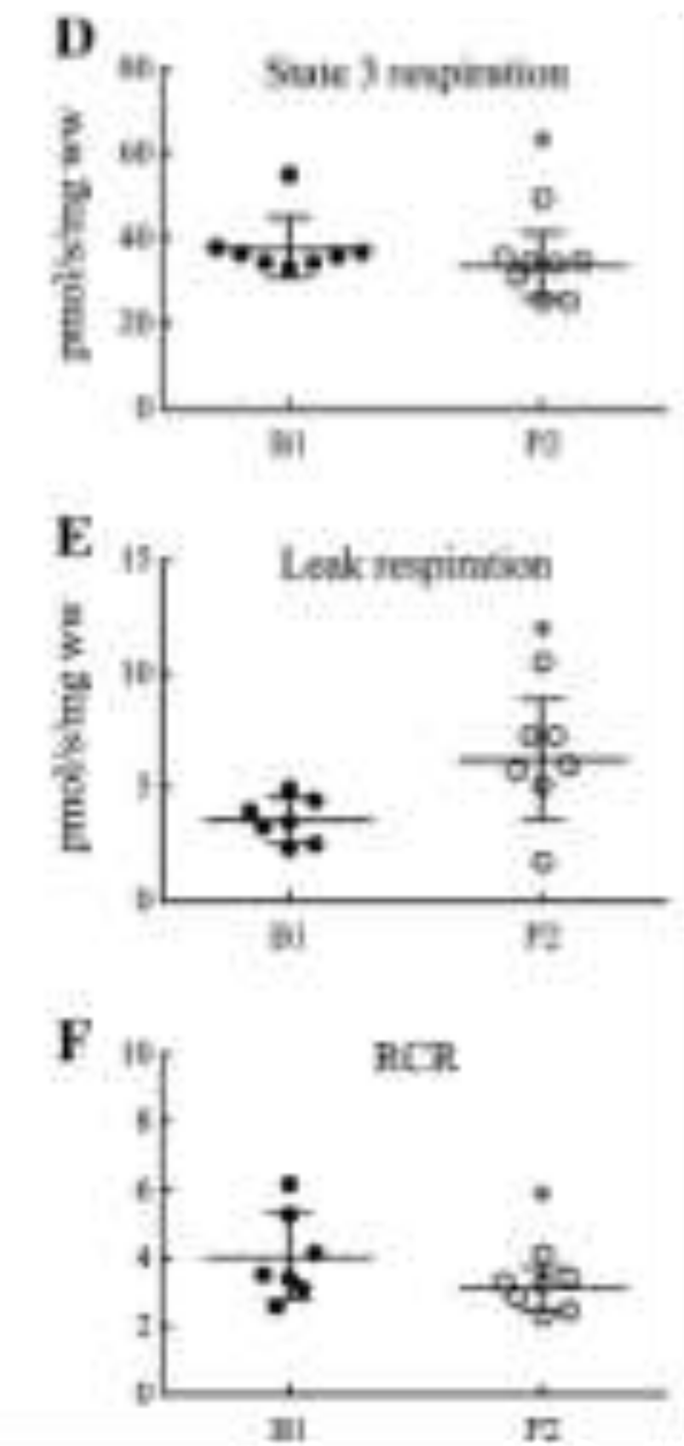
- iron transport,
- TCA cycle,
- oxidative phosphorylation,
- oxidative stress responses

- protein synthesis



(Vigano' et al., 2008)'

Changes in mitochondrial function following altitude exposure (Gokyo Khumbu/Ama Dablam Trek)



7 <u>women</u>
14d at 3400-5000 mt

mitochondrial mass preserved (TOM20)

maximal respiratory capacity in mitochondria was reduced

Tam et al., 2015

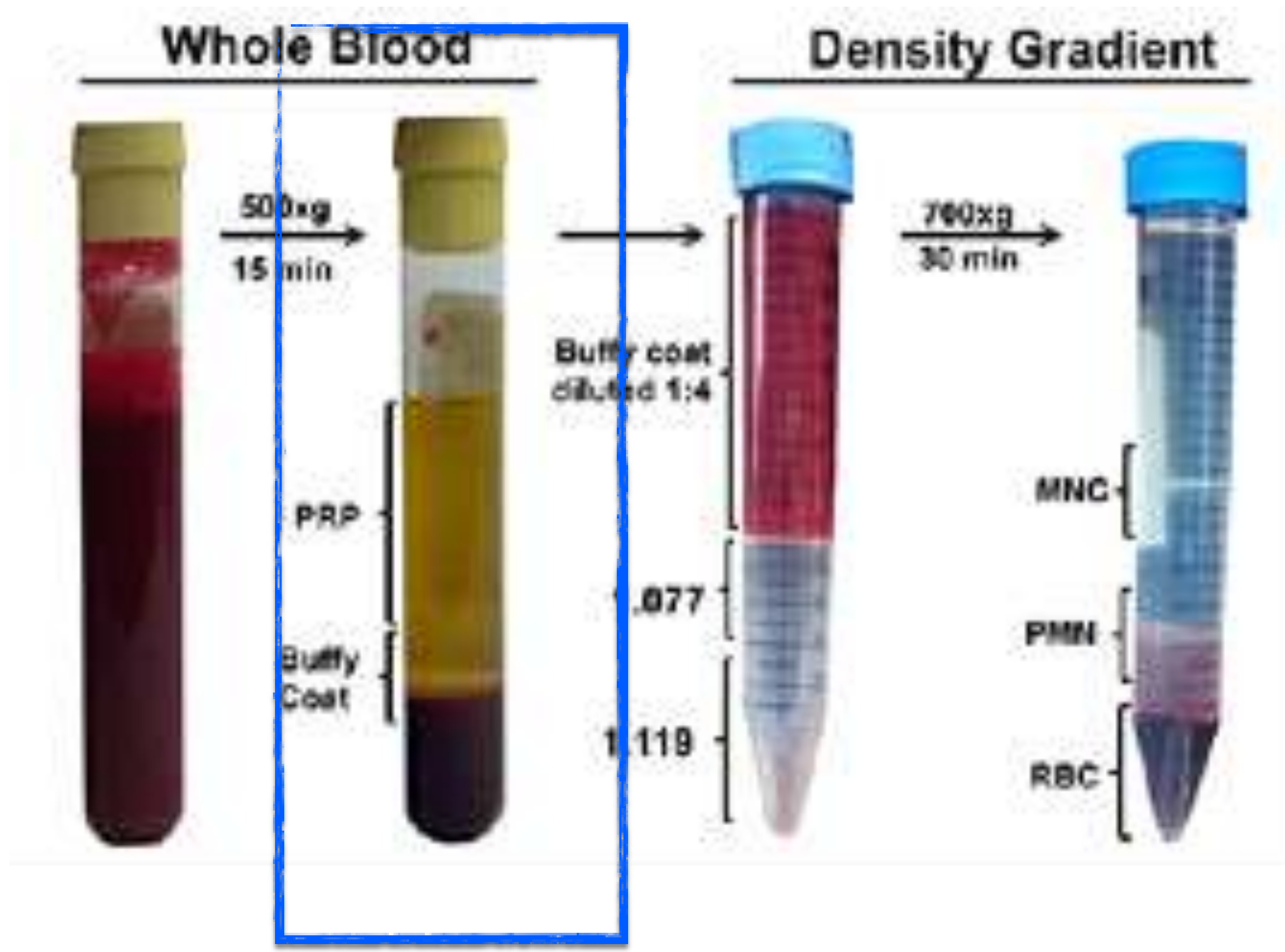
These studies are difficult to realize and the use of muscle biopsie is a limiting factor, because there invasive.

=> There’s the need of less invasive strategies allowing to monitor altitude adaptations.

Blood cells as a surrogate to study mitochondrial function

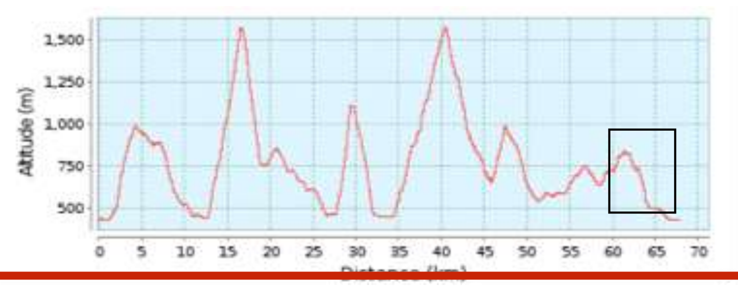
Respiratory capacity of human PBMCs is linked to physical fitness

==> mitochondrial function in human blood cells can be used as a systemic mitochondrial marker.



Blood cells as a surrogate to study mitochondrial function response to exercise - Bergmarathon Ultratrail

The influence of an ultramarathon on mitochondrial respiration in human platelets

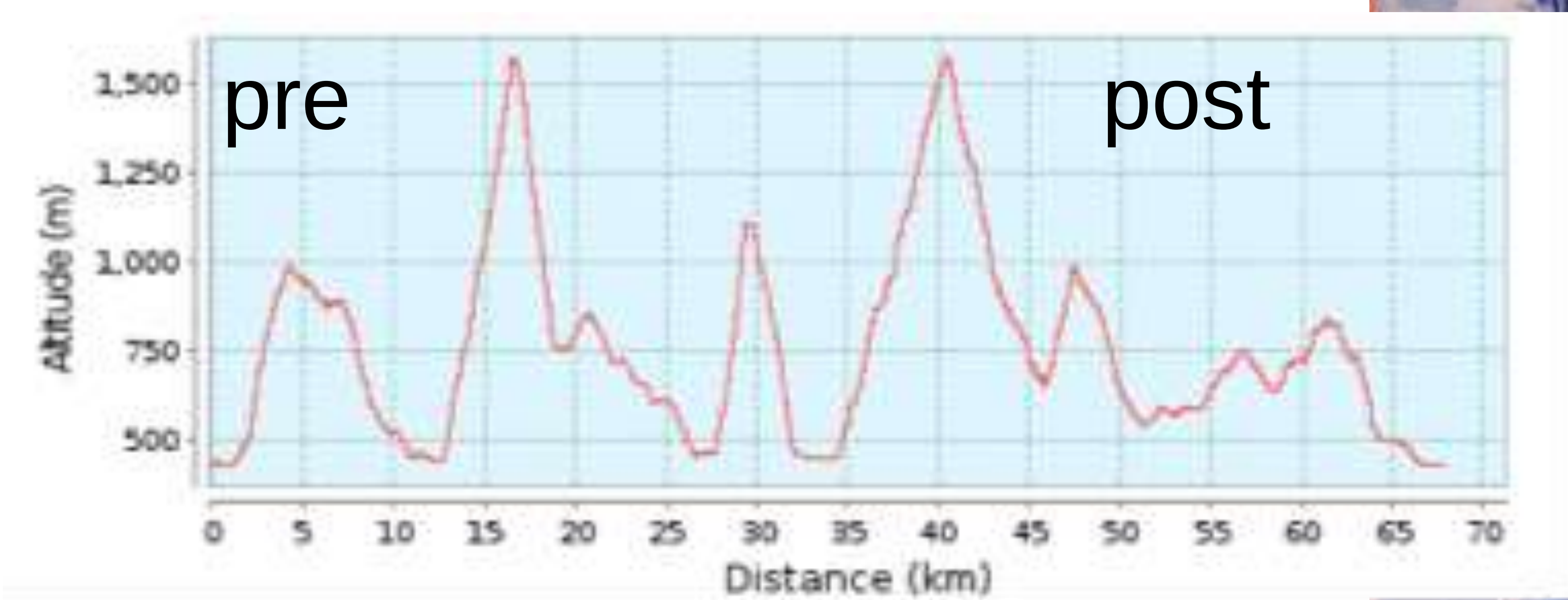


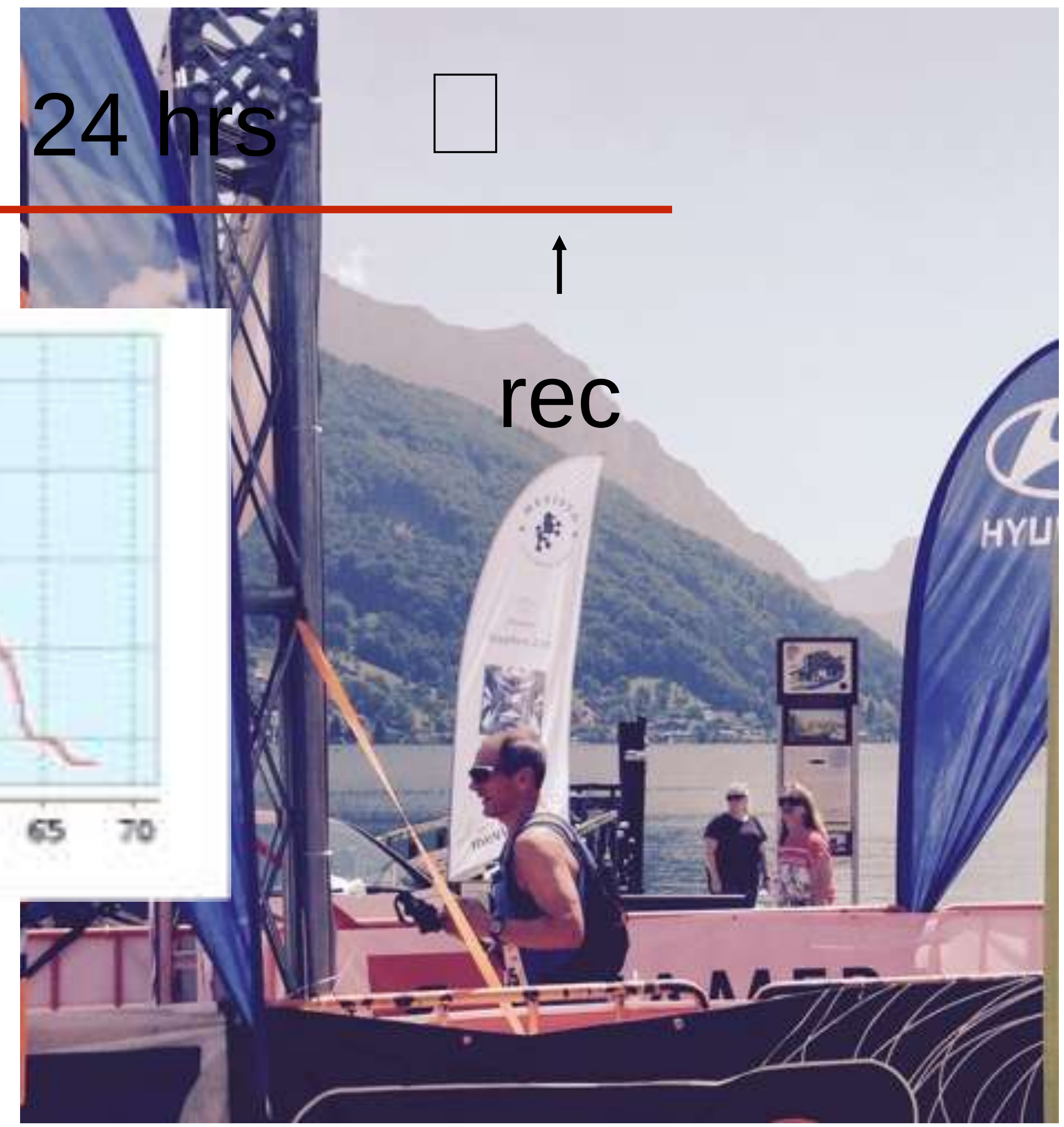
24 hrs

pre

post

rec



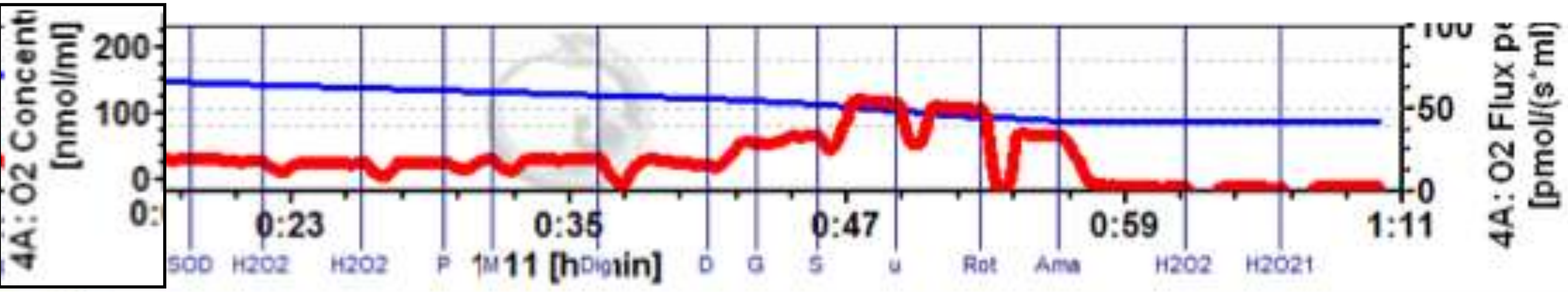


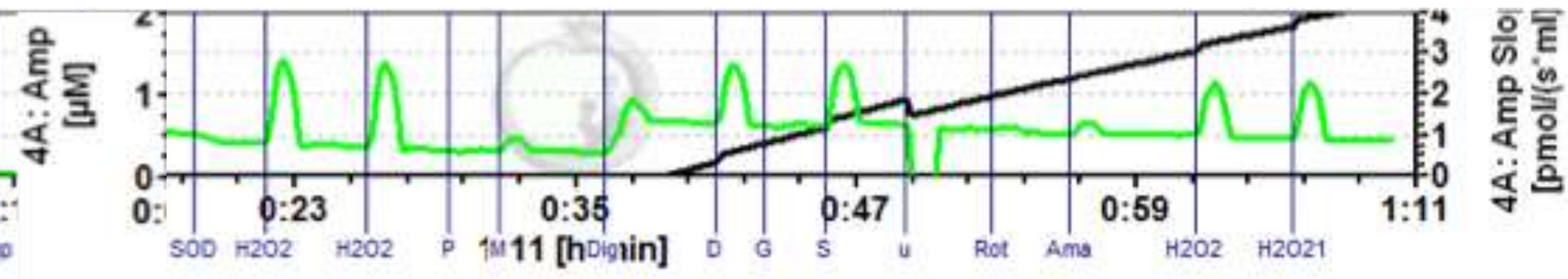
10 males recreational athletes

competition: 67 Km, 4500mt ascent

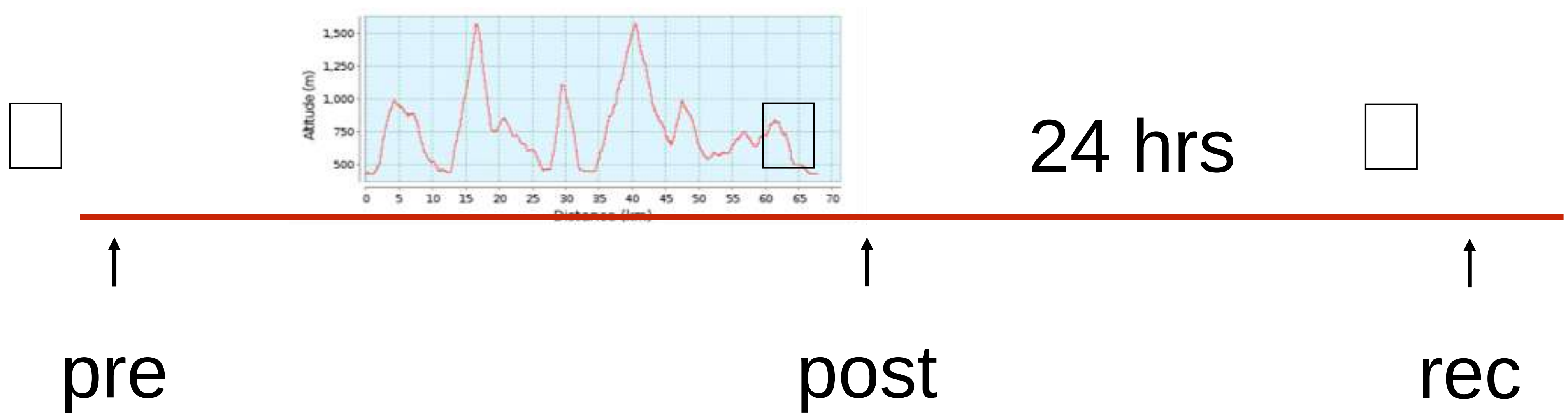
Oxygen flux

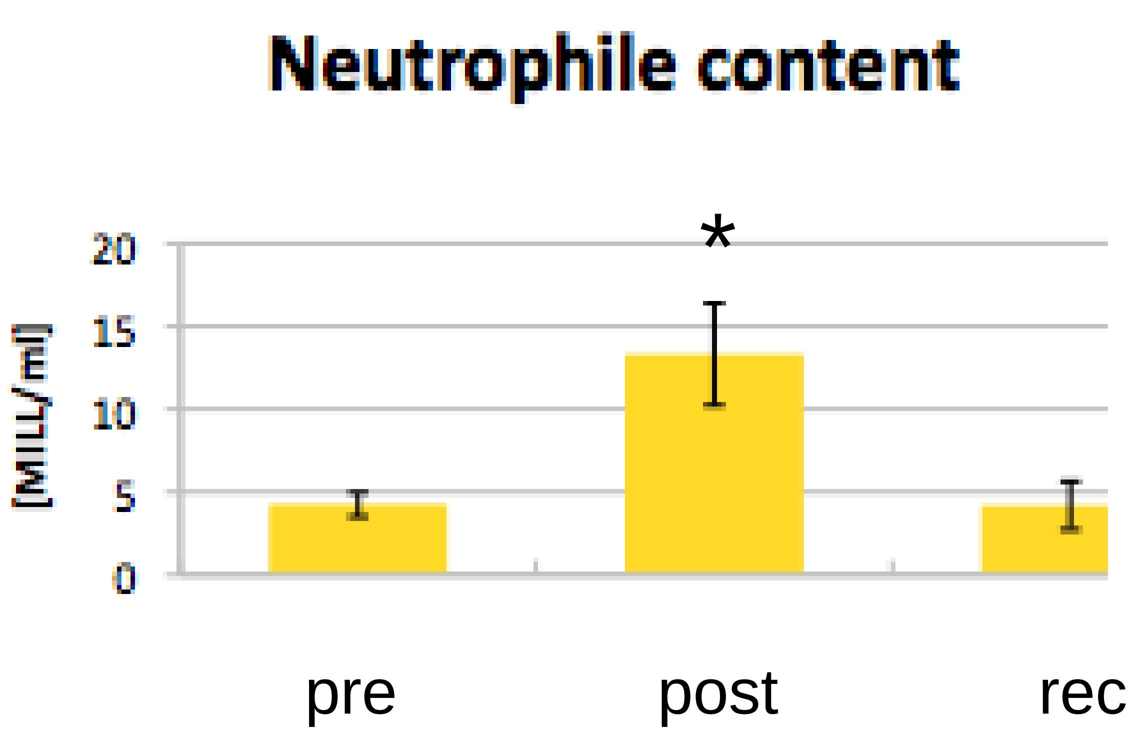
H2O2 production -ROS

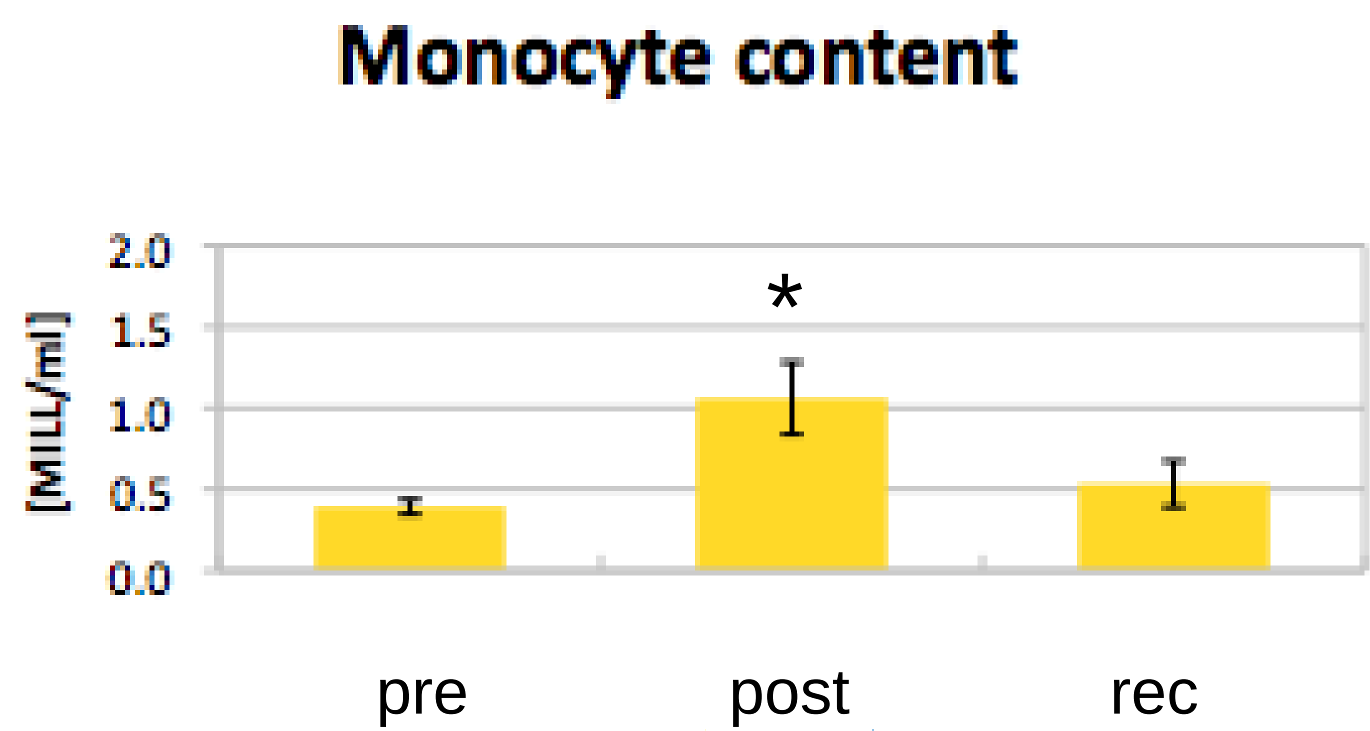




Blood cells as a surrogate to study mitochondrial function







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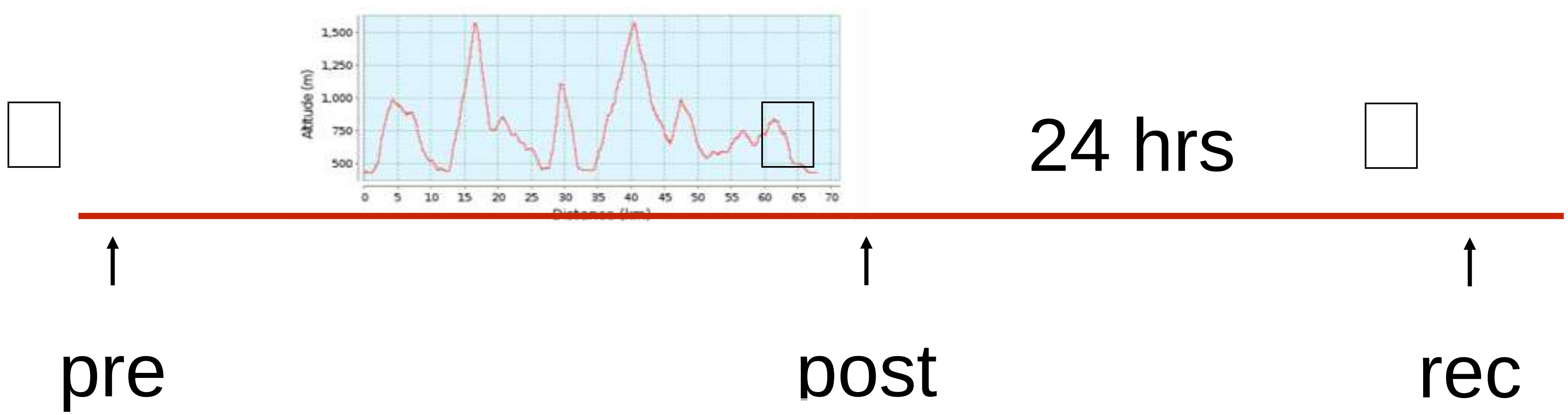
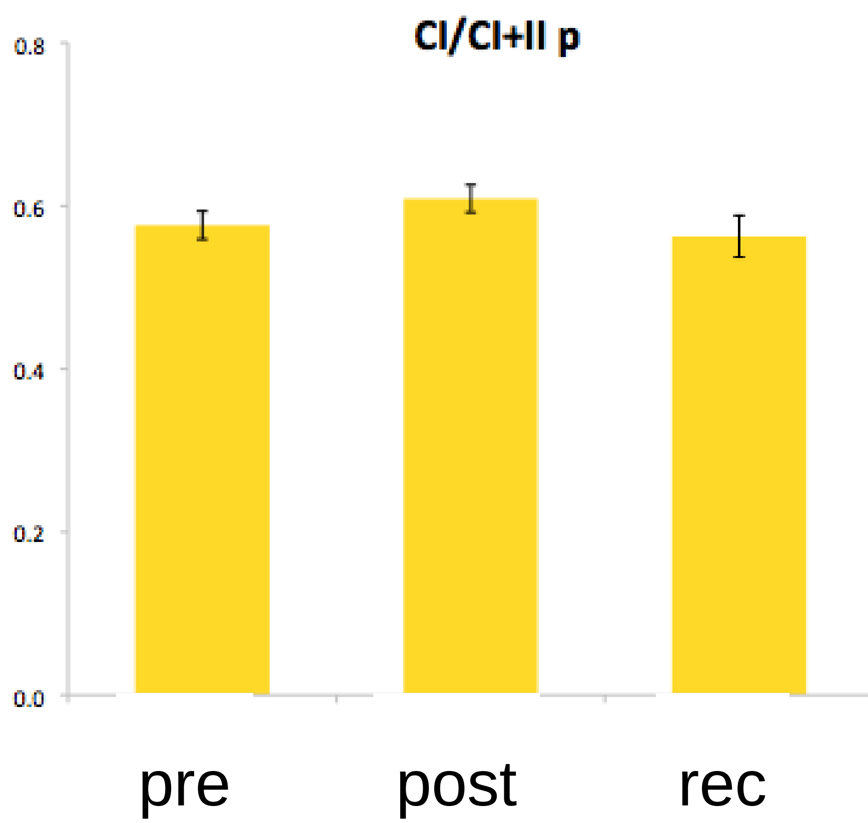
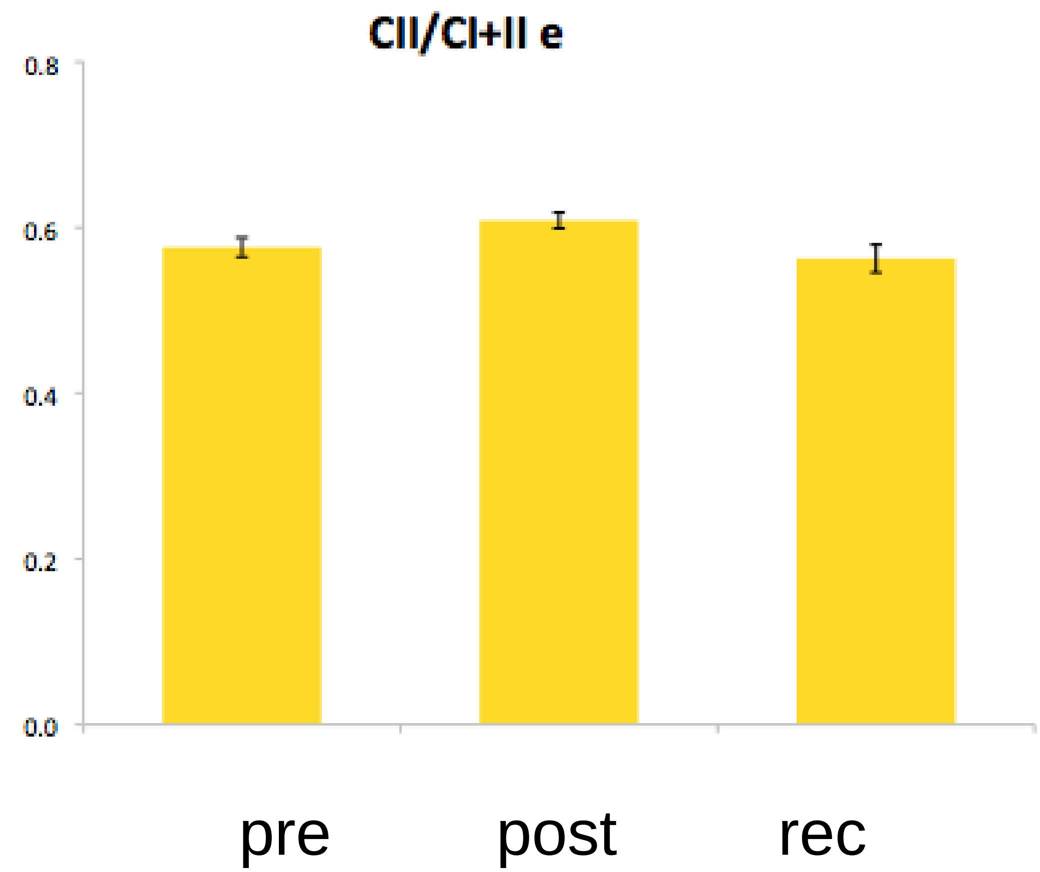
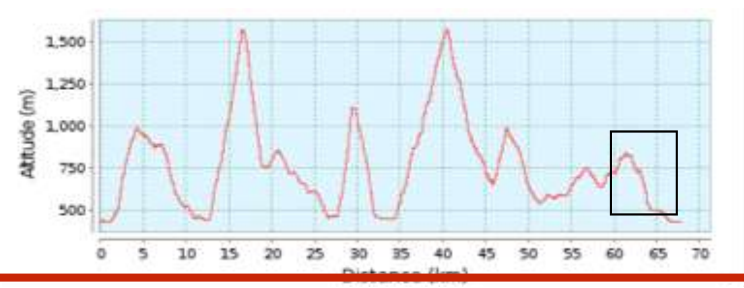






No significant changes were found in respiratory substrate control ratios CI/CI&II and CII/CI&II

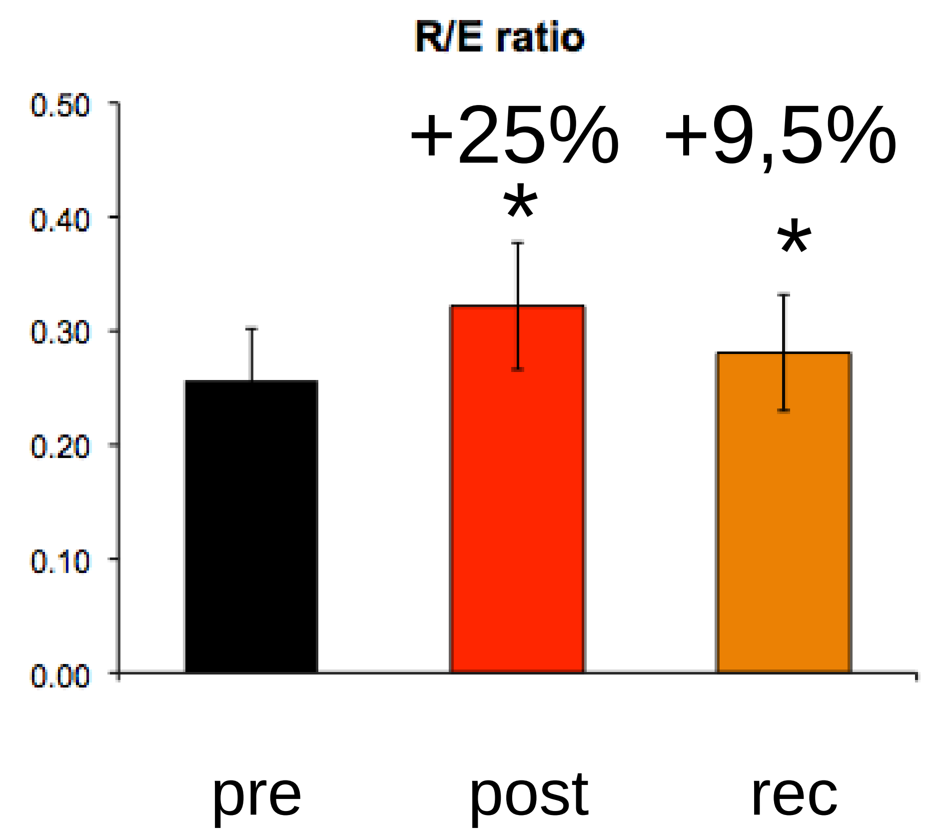
Blood cells as a surrogate to study mitochondrial function



24 hrs

pre post rec

R/E was increased significantly indicating the influence of massive physical strain and time of recovery on human platelet metabolism



R/E increases due to:

(i) high ATP demand and ADP-stimulated ROUTINE respiration,

(ii) partial uncoupling,

Main results:

- a significant change of the *R/E* ratio indicating changes in platelet basal metabolism;

- **blood cells emerge as indicators of systemic mitochondrial function, including responses to strenuous exercise.**

- **advantages of this approach: non-invasive, enabling multiple measurements in time series.**

Studies on high altitude associated hypoxia are often inconsistent, …altitude achieved, duration of exposure, activity level, gender, metodological approach.

but they indicate that

skeletal muscle oxidative metabolism is lowered by hypoxia exposure

These metabolic changes may precede a loss in mitochondrial density

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