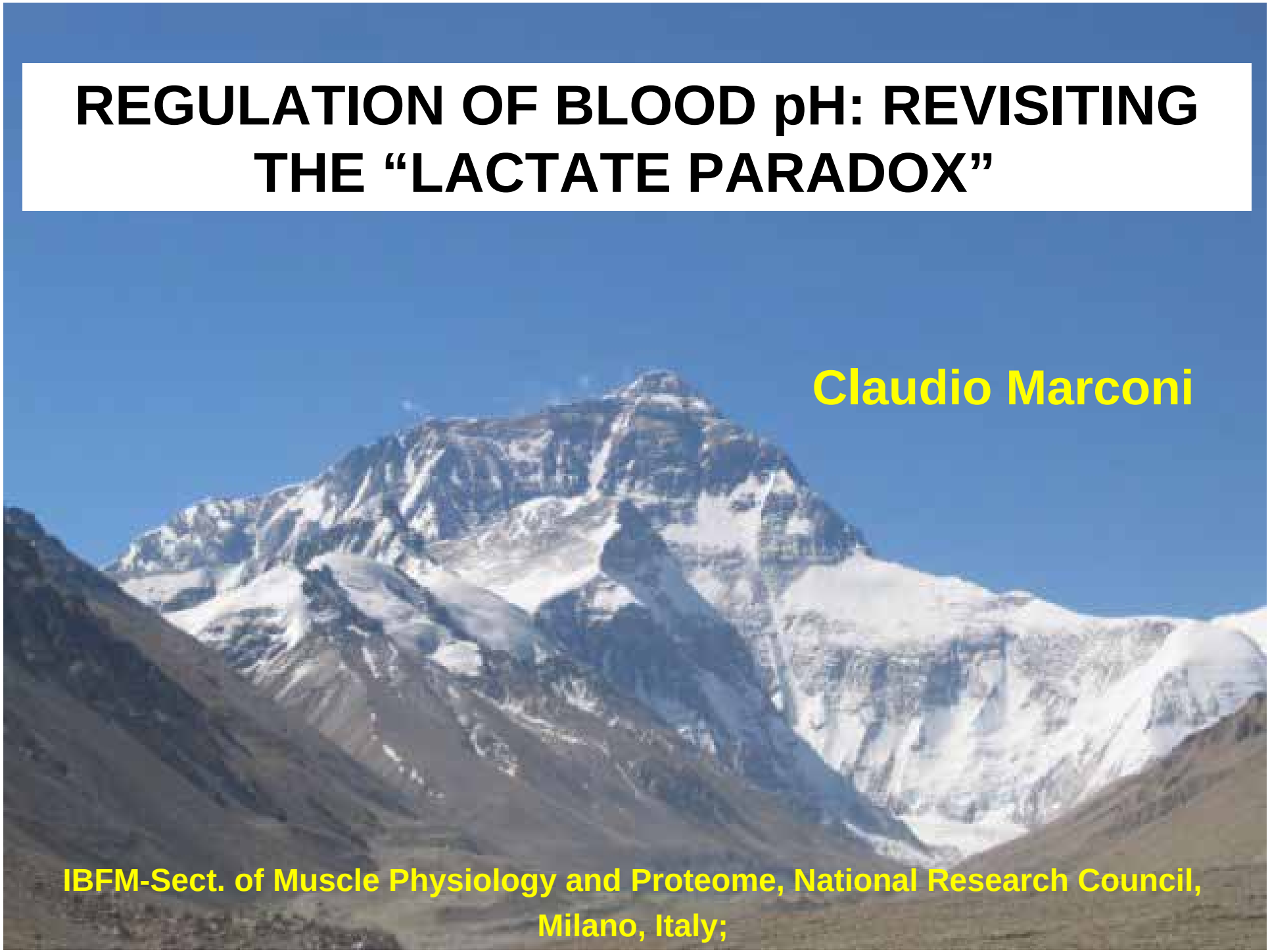
REGULATION OF BLOOD pH: REVISITING THE “LACTATE PARADOX”



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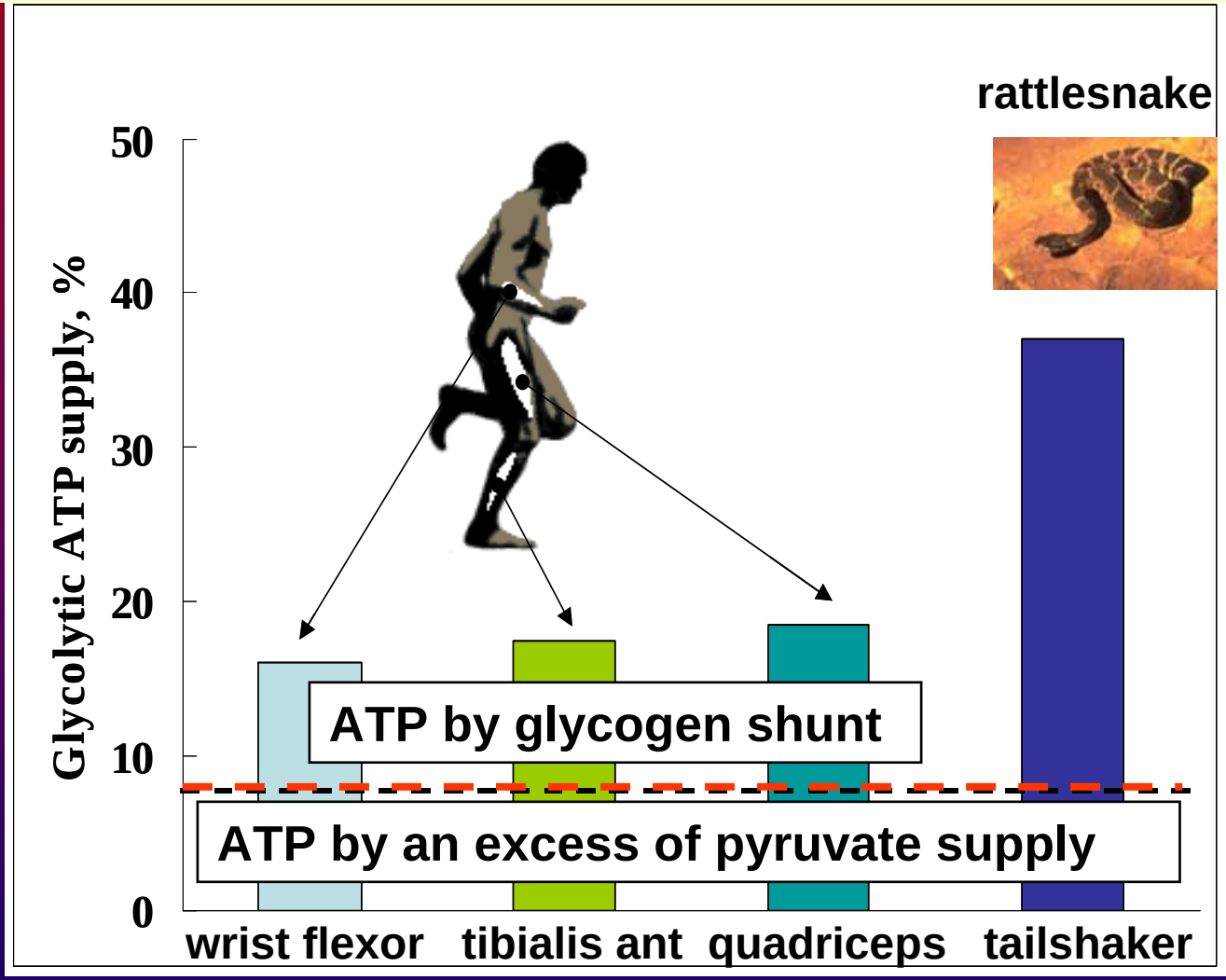
In normoxia, the transition from rest to exercise is characterized by rapid changes in muscle and blood [H^+]

LOHMANN REACTION

$$PCr + ADP + H^+ \xleftrightarrow{CK} ATP + Cr$$

↗ [ADP] ⟷ oxidative phosphorilation ↗

PERCENTAGE OF ATP SUPPLY FROM GLYCOLYSIS (LACTATE GENERATION UNDER AEROBIC CONDITIONS)



The total metabolic proton production increases with time as the rate of PCr breakdown declines and anaerobic glycolysis plays a progressively greater role.

In hypoxia, the mechanism involved in proton generation are the same as in normoxia, but anaerobic glycolysis appears to be regulated differently.

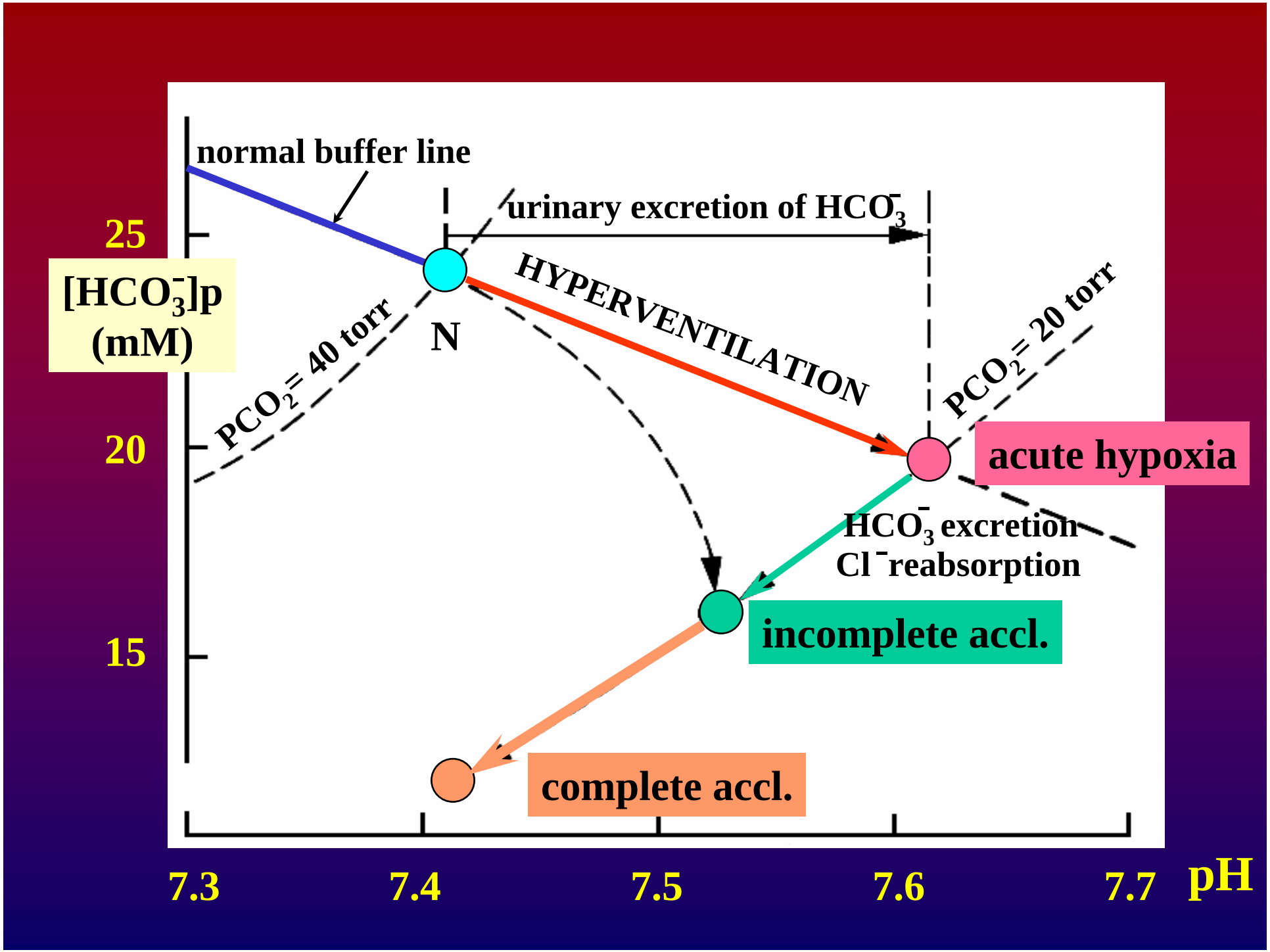
CO_2 HYDRATION

$$CO_2 + H_2O \longleftrightarrow [H_2CO_3] \longleftrightarrow H^+ + HCO_3^-$$

Henderson-Hasselbalch

$$pH = pK + \log \frac{[HCO_3^-]}{0.03 \cdot PCO_2}$$

pK = 6.12


normal buffer line
urinary excretion of HCO_3^-
HYPERVENTILATION
PCO_2 = 40 torr
N
PCO_2 = 20 torr
acute hypoxia
HCO_3^- excretion
Cl^- reabsorption
incomplete accl.
complete accl.
25
20
15
$[HCO_3^-]p$ (mM)
7.3
7.4
7.5
7.6
7.7
pH

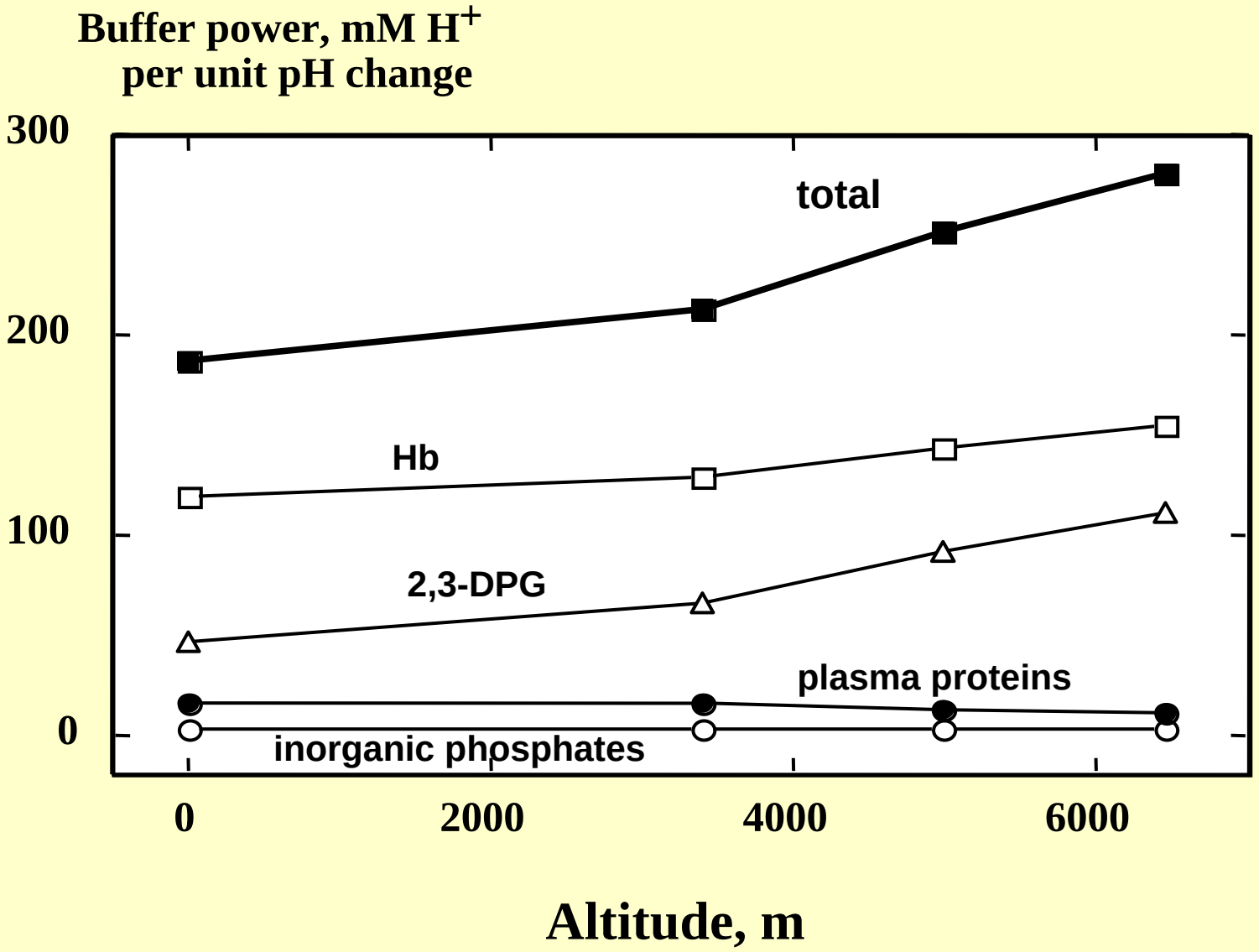
BUFFER POWER IN BLOOD

$$\beta = \Delta [H^+]/\Delta pH$$

β	At 5,000 m	
-plasma proteins	-19%	(due to Ht >)
-hemoglobin	+20%	
-phosphate ions	=	
-2,3 DPG	+97%	(due to Hb >, DPG/Hb>)

TOTAL NON BICARBONATES +35%

TOTAL NON-BICARBONATE BUFFER



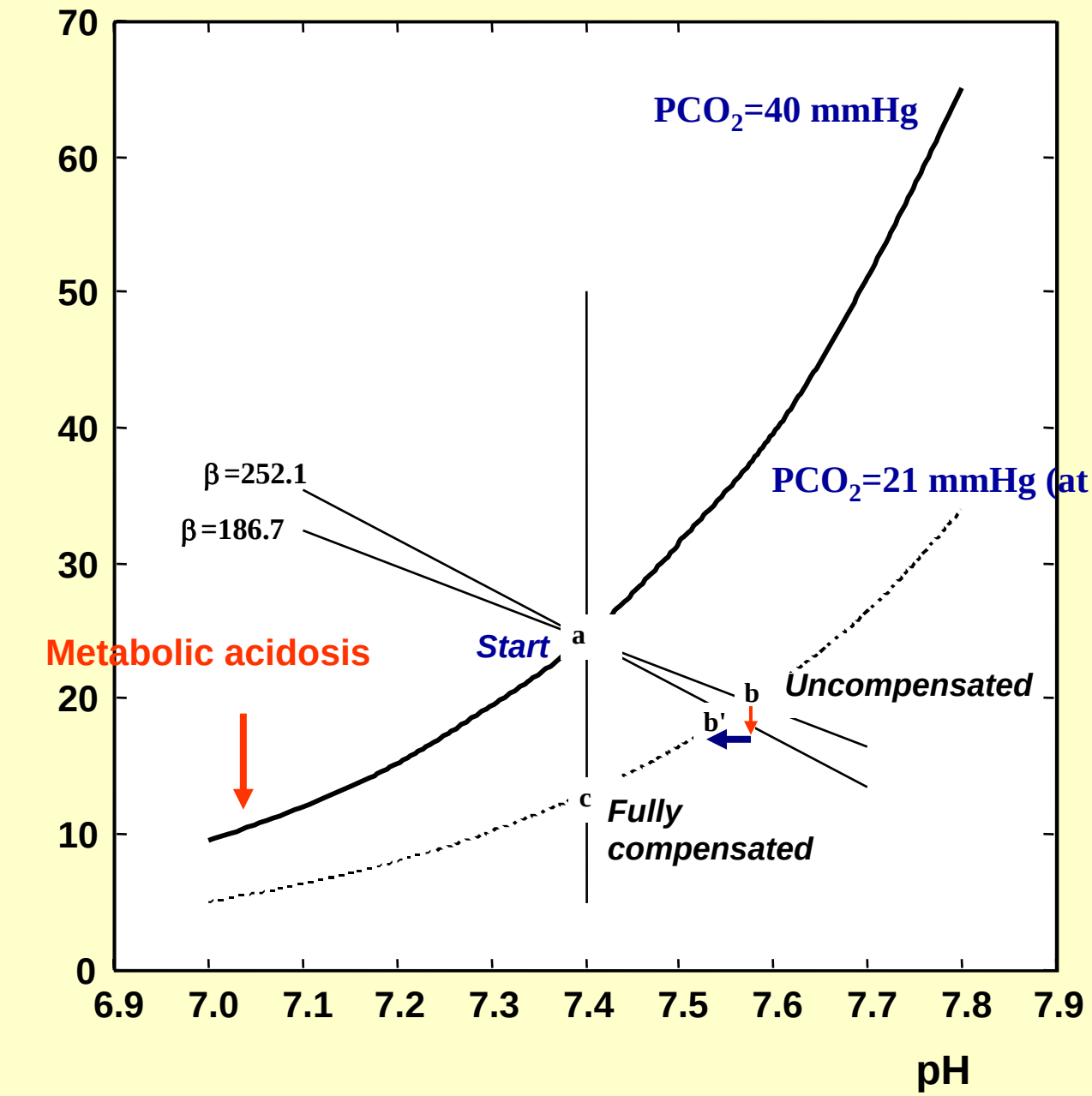
INCREASING NON-BICARBONATE BUFFER POWER HAS TWO CONTRASTING EFFECTS:

The pH shift secondary to a given change in the acid-base balance is less

The amount of acid or base needed to compensate that change is increased

The two corrections may not be equivalent

EVALUATION OF THE EFFECTS OF AN INCREASED NON-BICARBONATE BUFFER POWER ON THE BICARBONATE β



Increased non-bicarbonate β at altitude contributes to decrease alkalosis derived from hyperventilation

As the main producer and consumer of large amounts of lactic acid, muscle plays a key role in the body acid-base balance

During heavy exercise lactic acid accounts for 85-95% of the total H^+ load

Muscle buffer capacity depends on the concentration of:

- **proteins (imidazol groups of histidine residues)**
- **inorganic phosphates and bicarbonate**

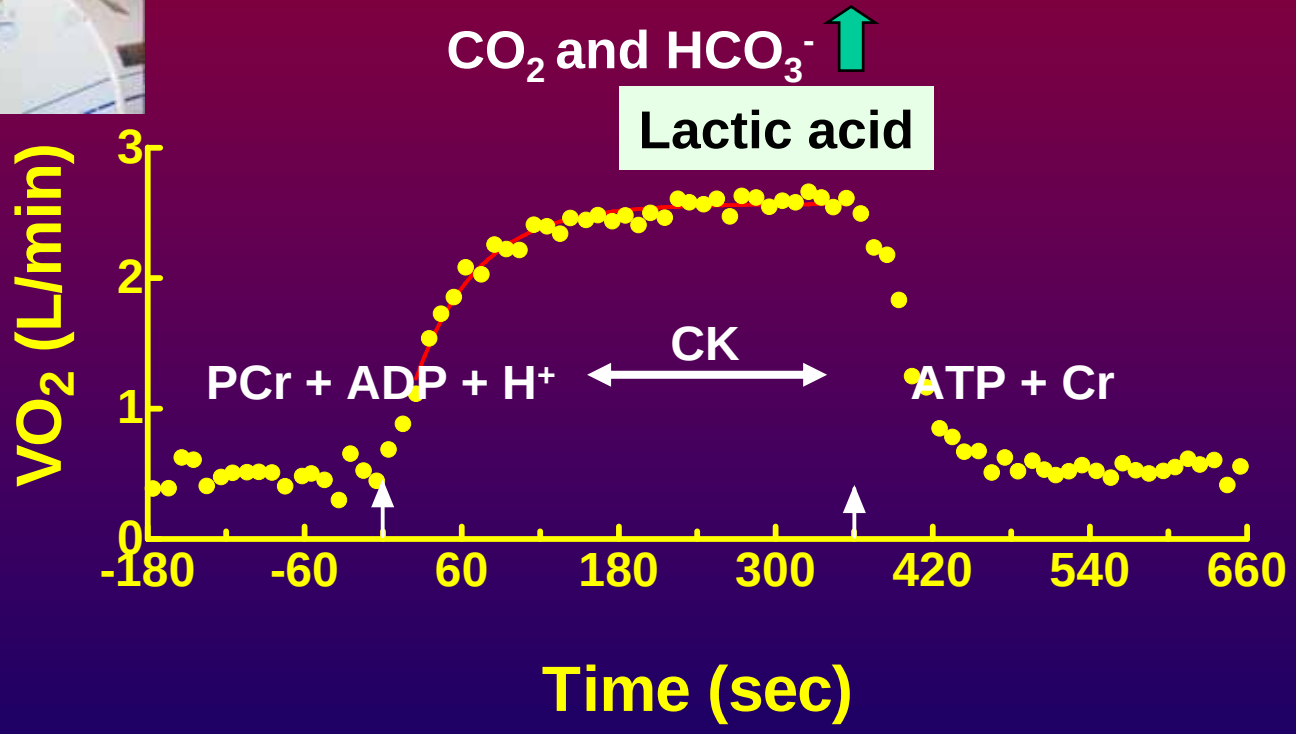
Muscle buffer capacity ranges from 25 to 40 mmol $H^+ \cdot l^{-1}$ $H_2O \cdot pH^{-1}$ and depends on: type, intensity, time course of muscle activity, and training.

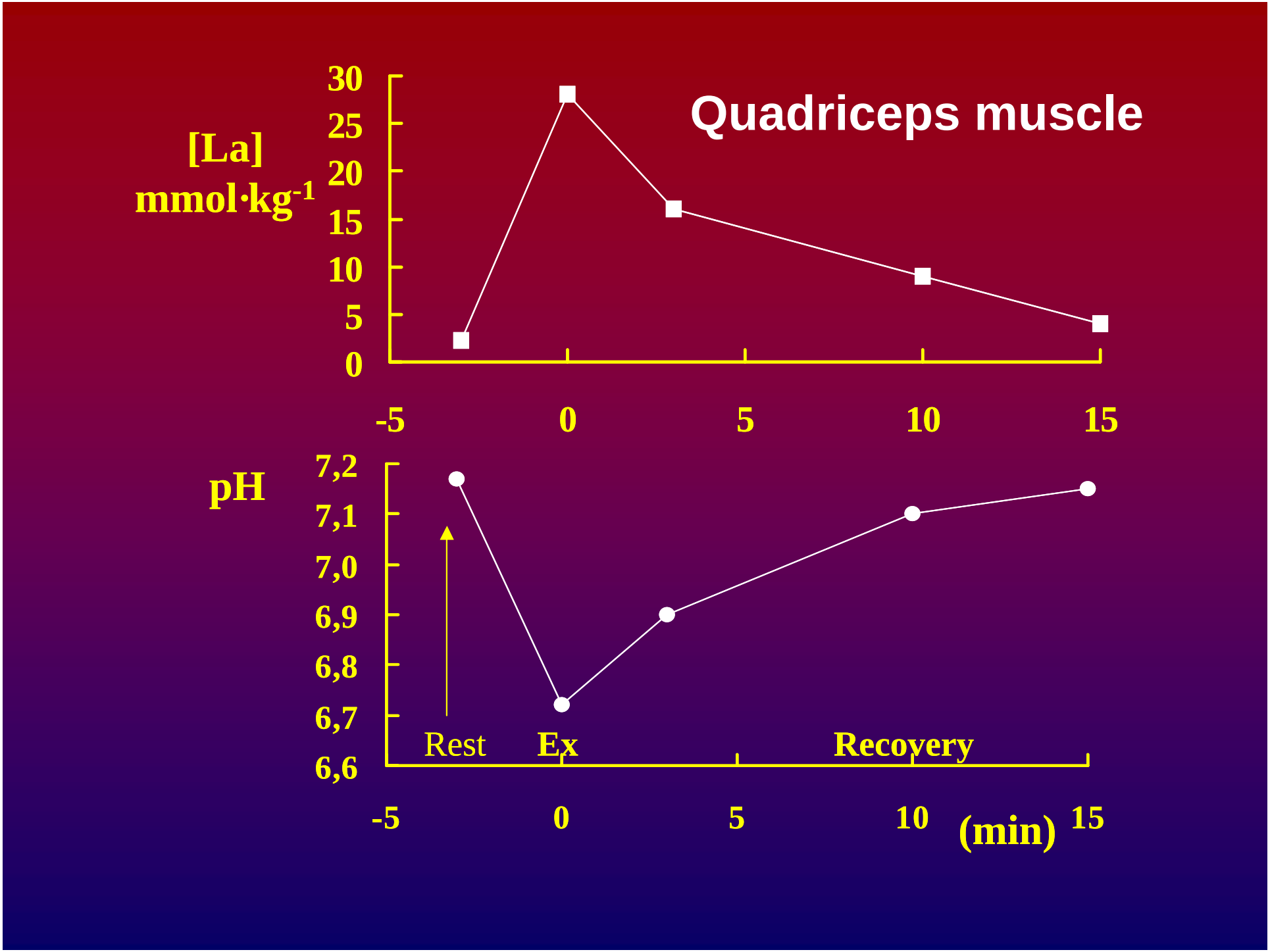
- **8 weeks of sprint training increases β by 38% (likely as a consequence of increased levels of dipeptides such as carnosine, which is mainly present in white muscle)**
- **Endurance training has no effect on β**
- **Altitude acclimatization alters β, mainly because of changes in muscle protein concentration.**

Regulation of muscle pH at rest

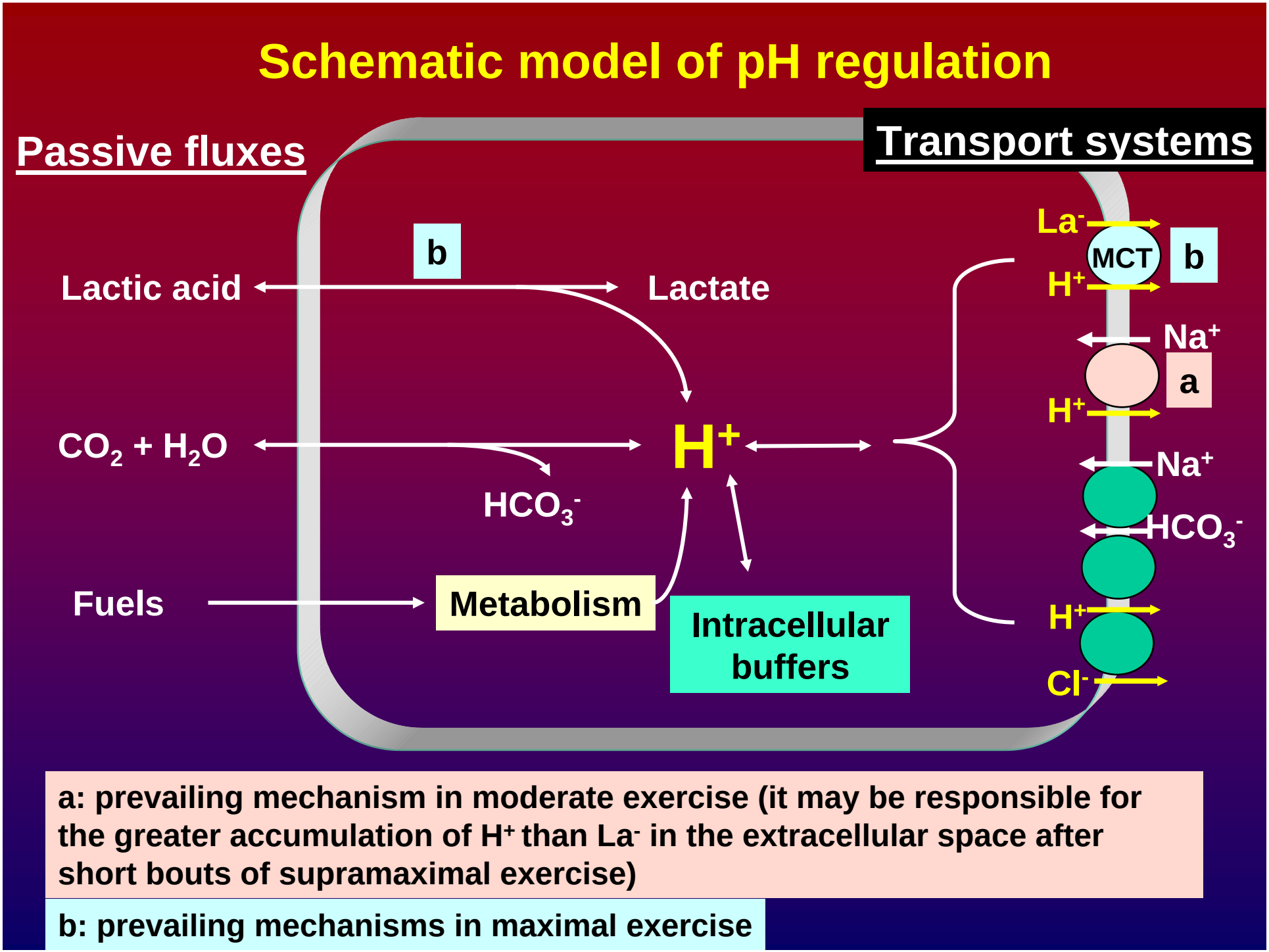
- At rest pH ranges from 7.10 to 7.15
- It depends on the balance between:
  - ⇨ H^+ metabolic production and H^+ inflow,
  - ⇨ Transport of H^+ out (Na^+/H^+ exchange) or HCO_3^- in (HCO_3^-/Cl^- exchange)

Regulation of muscle pH at exercise




Quadriceps muscle
[La]
mmol·kg-1
30
25
20
15
10
5
0
-5
0
5
10
15
pH
7,2
7,1
7,0
6,9
6,8
6,7
6,6
Rest
Ex
Recovery
-5
0
5
10
(min)
15

Schematic model of pH regulation



a: prevailing mechanism in moderate exercise (it may be responsible for the greater accumulation of H^+ than La^- in the extracellular space after short bouts of supramaximal exercise)

b: prevailing mechanisms in maximal exercise

ACID-BALANCE DURING SUPRAMAXIMAL EXERCISE

$[La_b]$ = 25 mM

pH_b < 7.0

HCO_3^- buffers ~75% of protons

Non-bicarbonate buffer system plays an increasing role for $[La_b]$ > 15 mM

$[La_m]$ = 40 mM

pH_m = 6.6

MCT : a family of monocarboxylate La^-/H^+ transporters

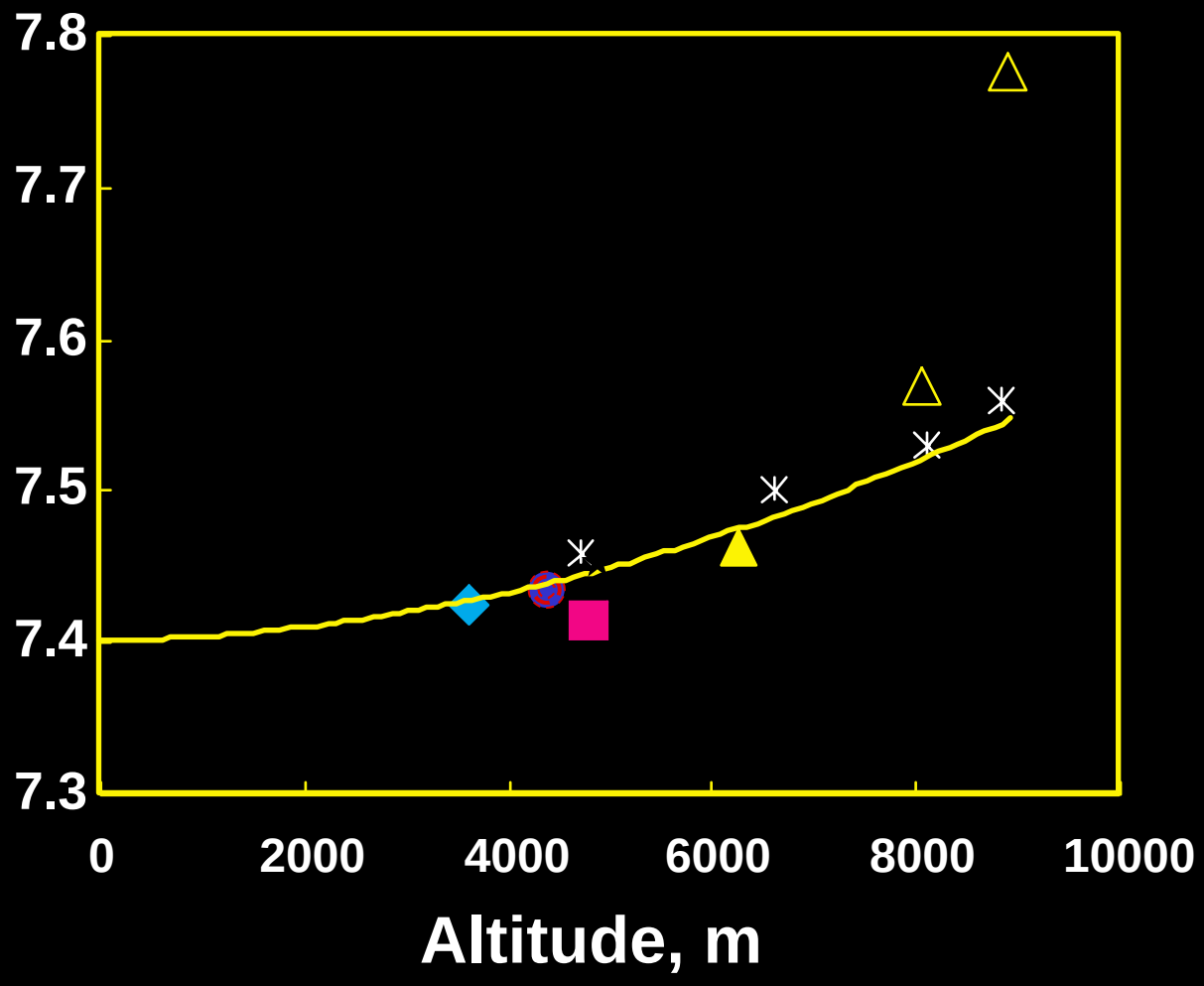
- MCT are membrane proteins and are **pH sensitive**
- MCT1 is more expressed in **slow-twitch fibers** (they need a fast MCT transport because they produce La^- for long time periods) and myocardial fibers than in fast-twitch fibers.
- MCT4 is not correlated to fiber type
- It is suggested that MCT1 is specialized for uptake, whereas MCT4 is specialized for efflux.

MCT and HYPOXIA

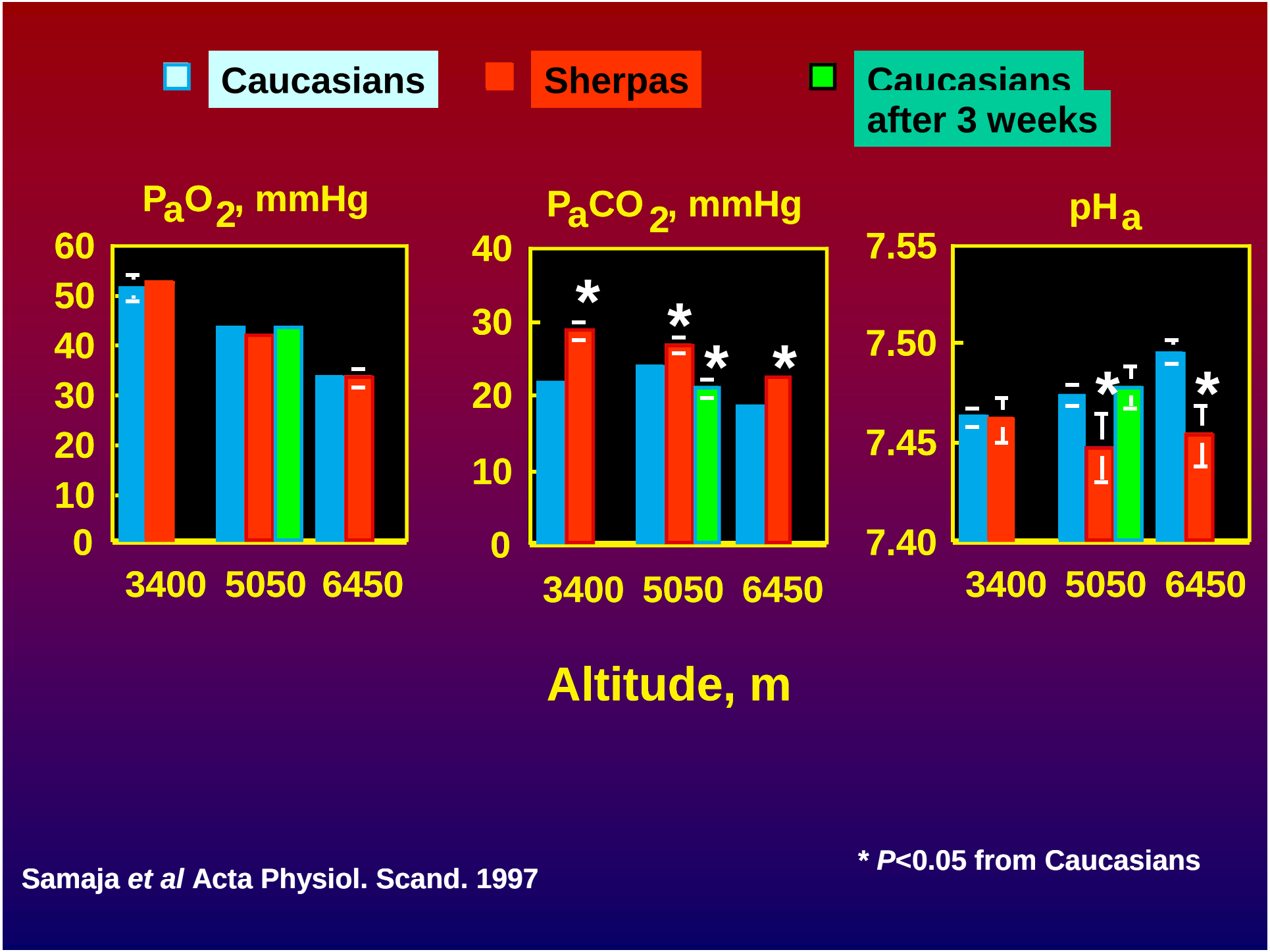
There are relatively few data supporting a role of MCT in regulating the acid-base balance in hypoxia.

ACID-BASE BALANCE AT EXERCISE DURING ALTITUDE ACCLIMATIZATION

pH_a in acclimatized lowlanders: literature survey



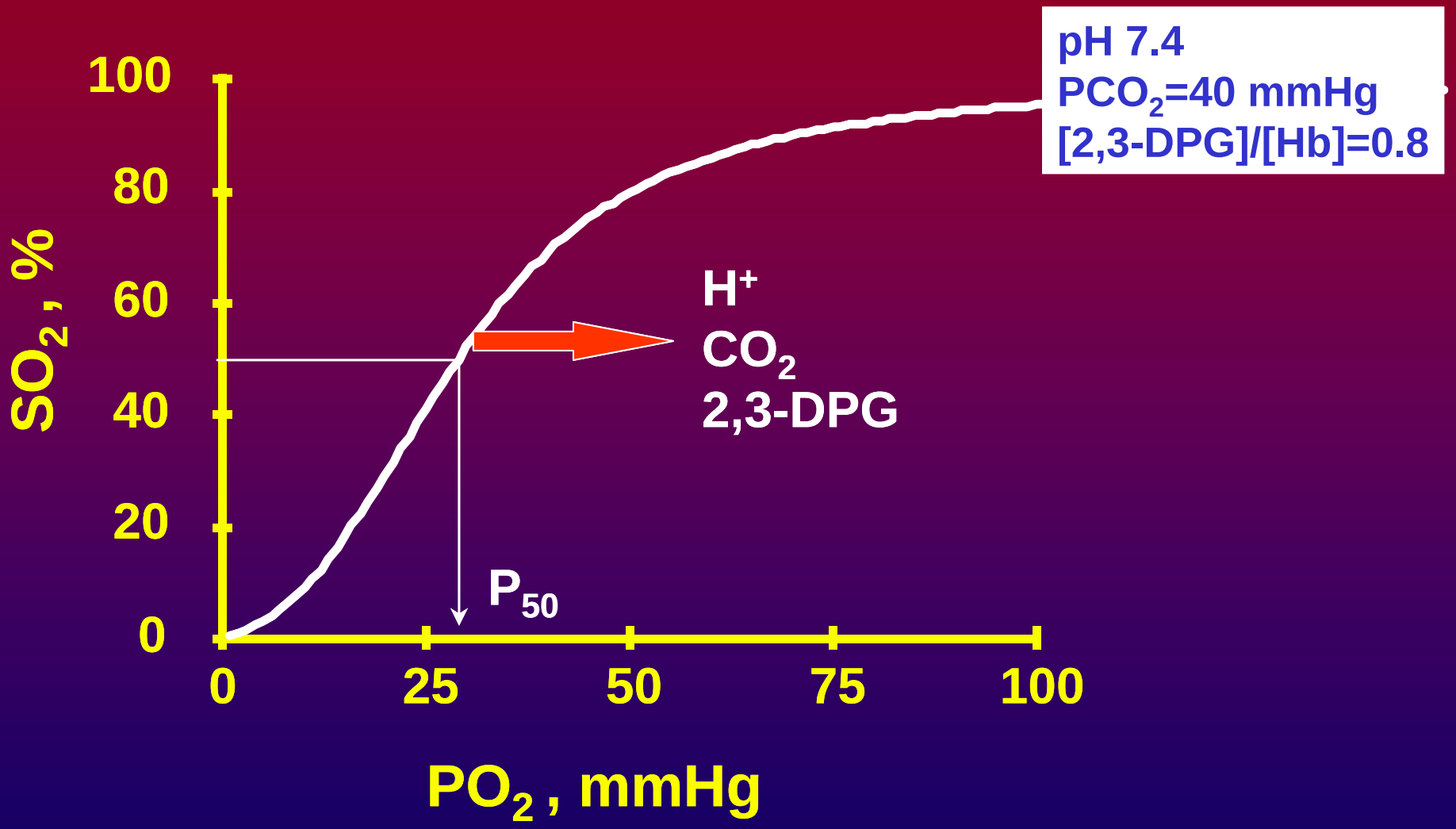
- Cerretelli unpublished
- Lahiri 1967
- Winslow 1984
- Winslow estimated
- Sutton 1988, chamber
- Bender 1989
- Kayser 1993

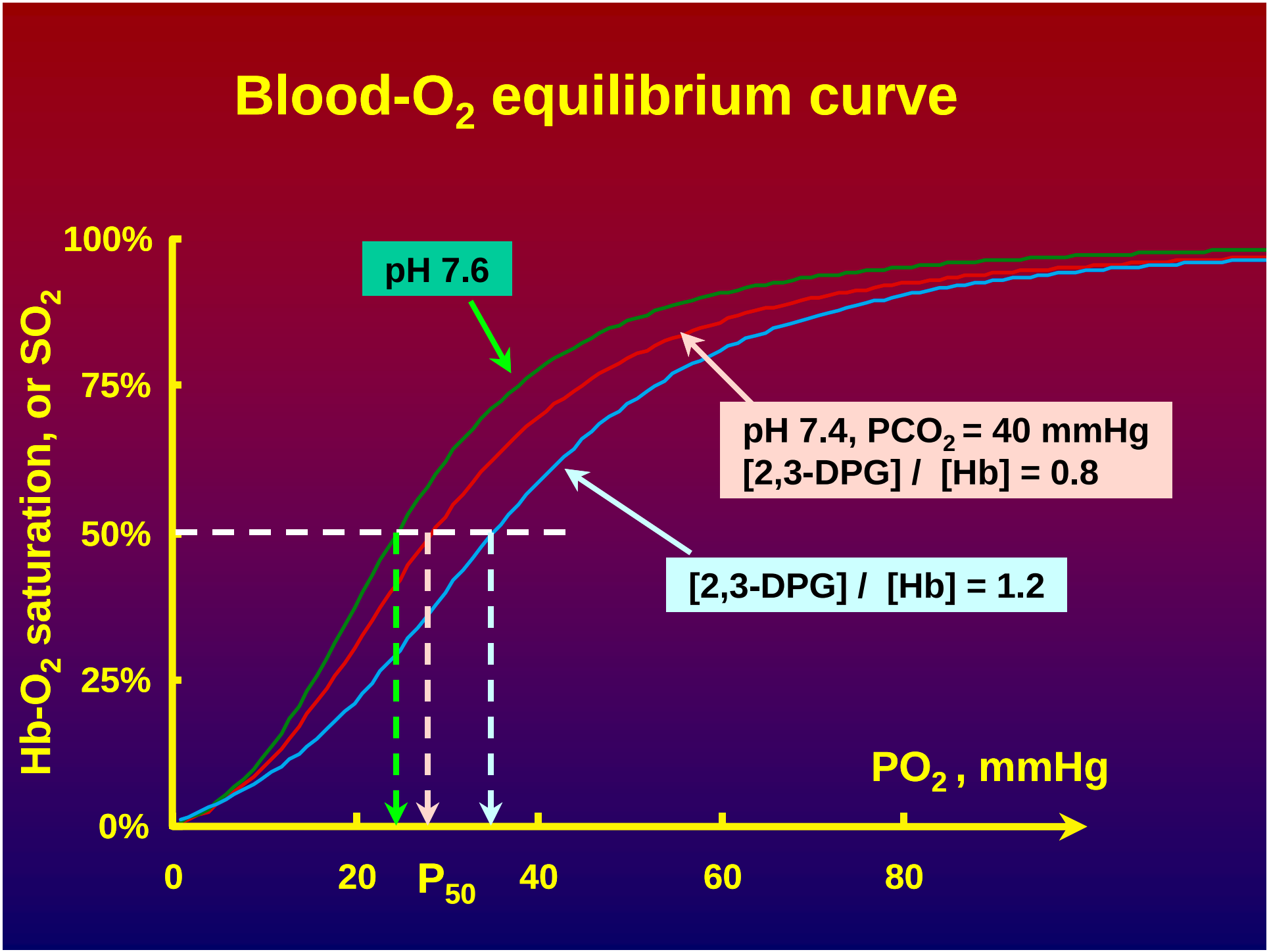


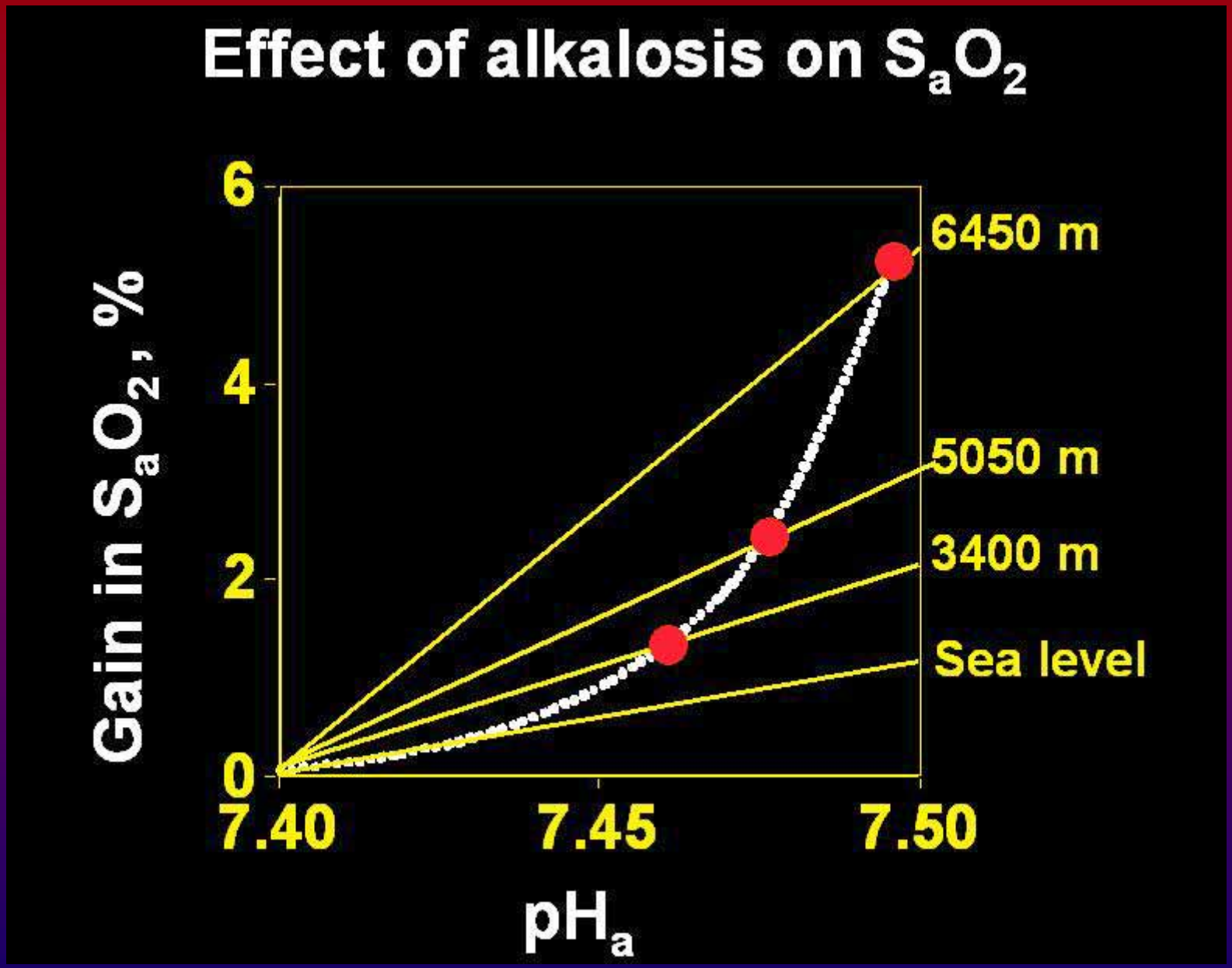
Samaja *et al* Acta Physiol. Scand. 1997

* *P*<0.05 from Caucasians

Hb-O_2 equilibrium curve




Blood-O2 equilibrium curve
100%
75%
50%
25%
0%
Hb-O2 saturation, or SO2
pH 7.6
pH 7.4, PCO2 = 40 mmHg
[2,3-DPG] / [Hb] = 0.8
[2,3-DPG] / [Hb] = 1.2
PO2 , mmHg
0
20
P50
40
60
80

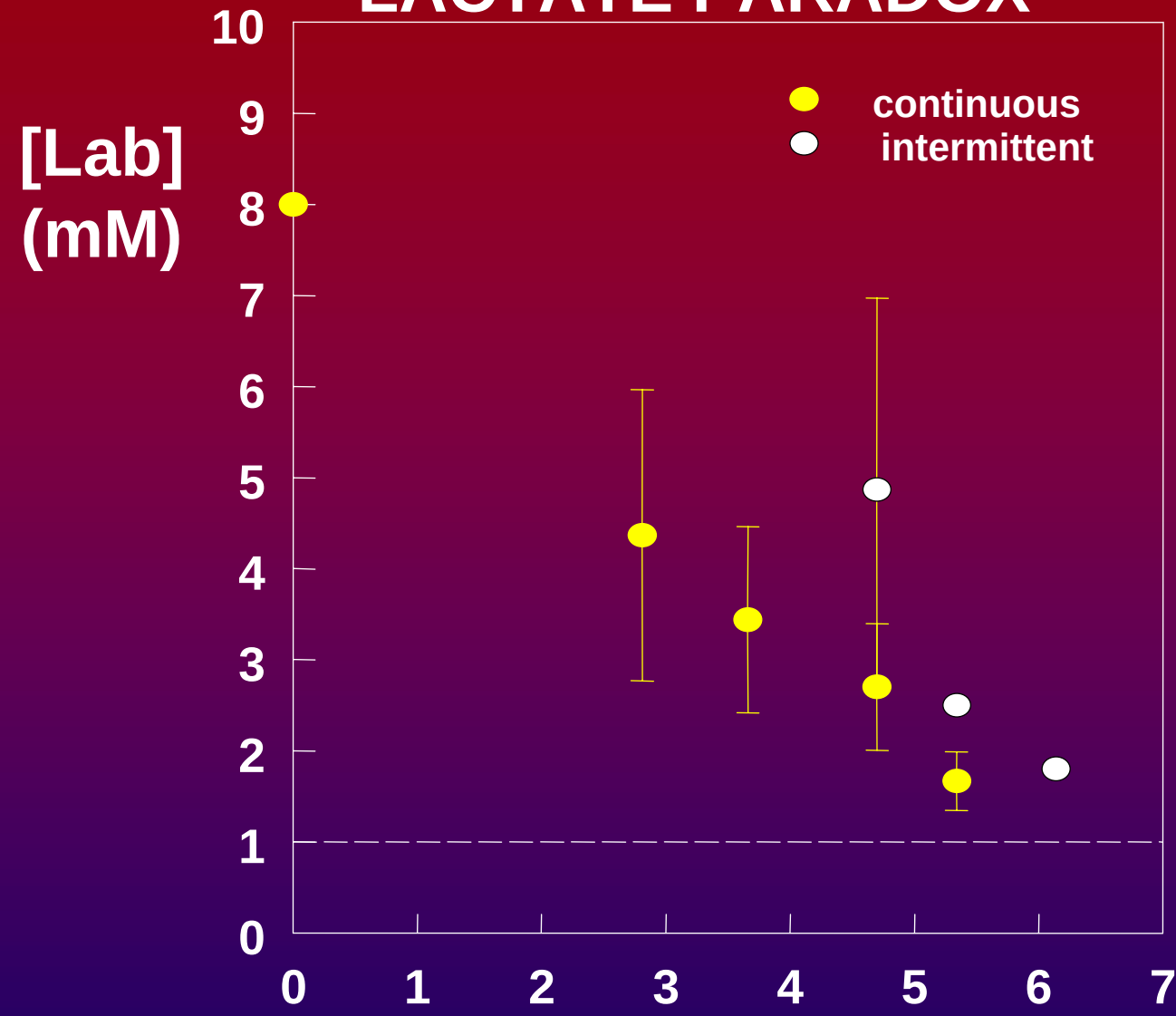

Effect of alkalosis on S_aO_2
Gain in S_aO_2, %
6
4
2
0
7.40
7.45
7.50
pH_a
6450 m
5050 m
3400 m
Sea level

AT REST, THE NEED TO OXYGENATE TISSUES CONFLICTS WITH THE NEED TO MAINTAIN H^+ HOMEOSTASIS

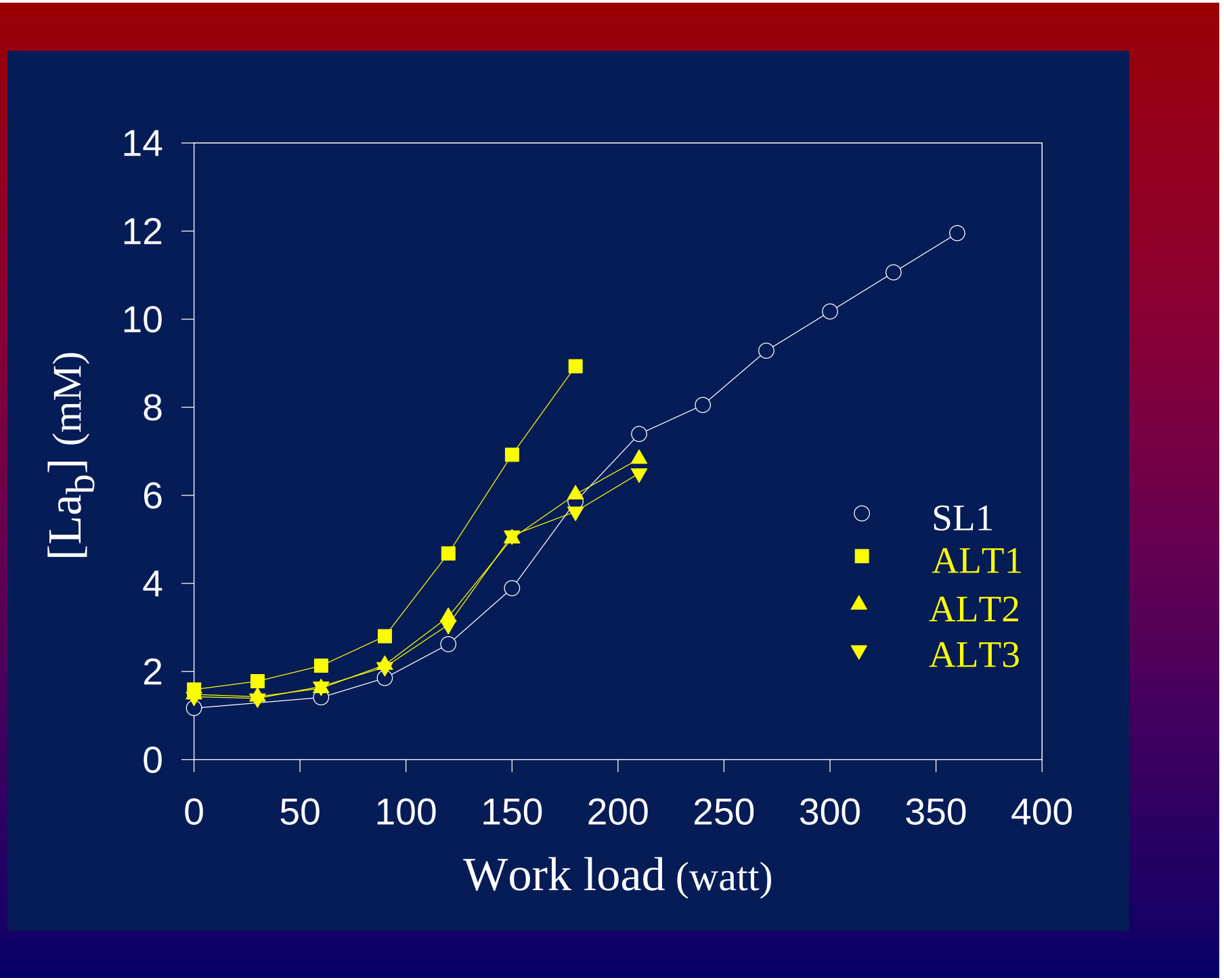
PROLONGED ALKALOSIS IS NOT COMPATIBLE WITH NORMAL BODY HOMEOSTATSIS

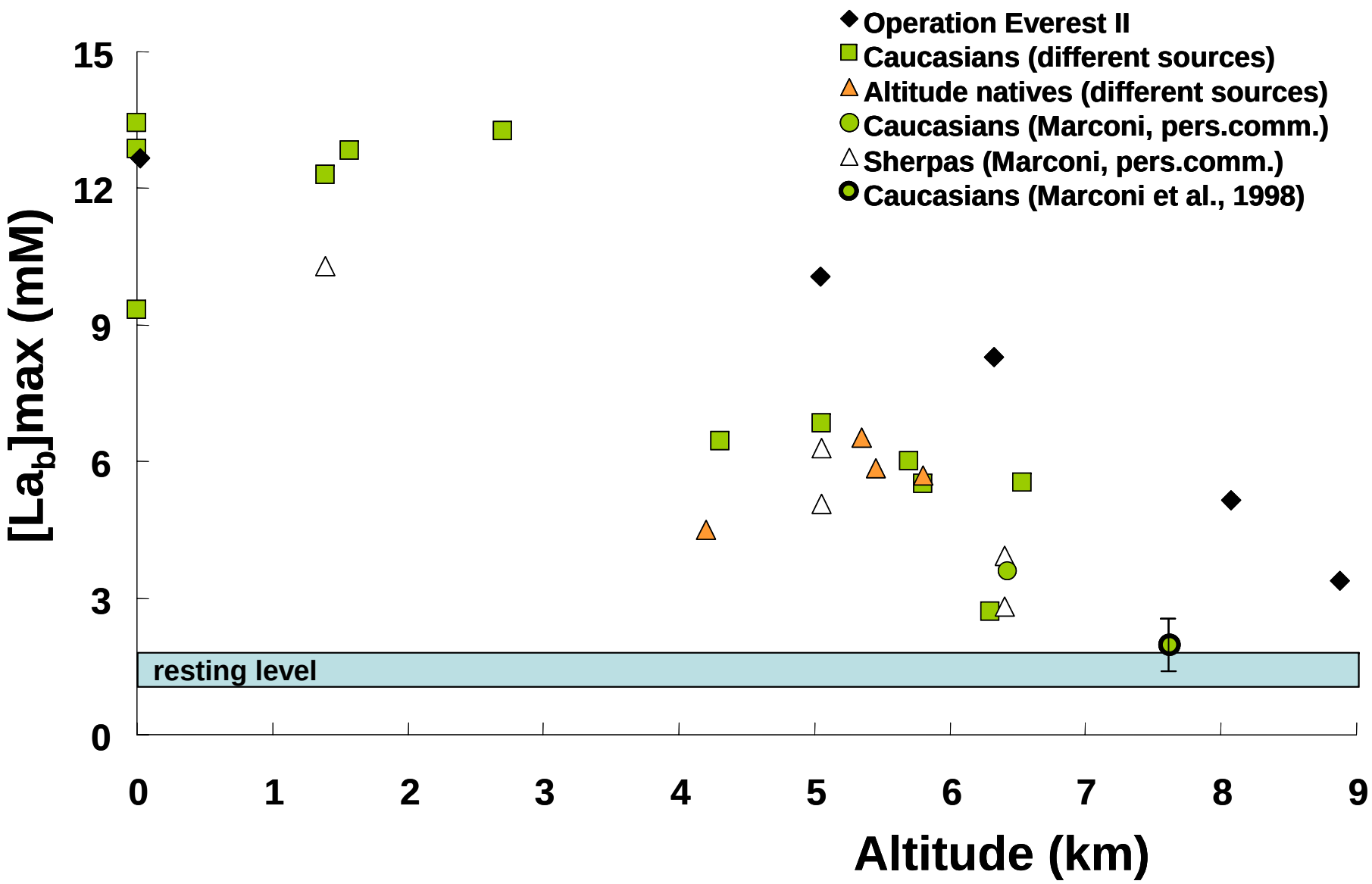
DURING EXERCISE, THE OVERALL BENEFICIAL EFFECT OF ALKALOSIS IS QUESTIONABLE

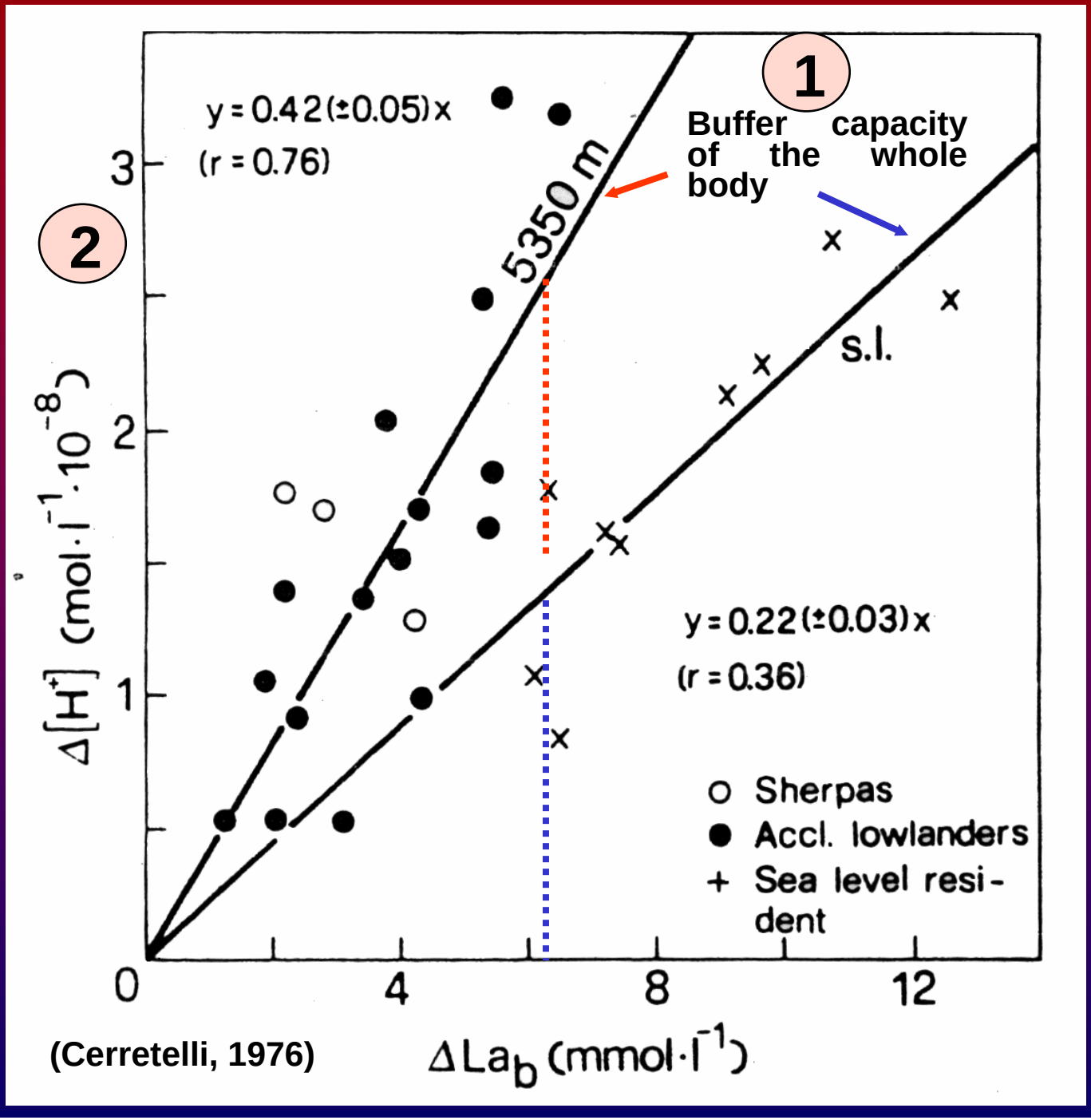
LACTATE PARADOX



(Edwards,1936)


14
12
10
8
6
4
2
0
[La$_b$] (mM)
0
50
100
150
200
250
300
350
400
Work load (watt)
SL1
ALT1
ALT2
ALT3


Operation Everest II
Caucasians (different sources)
Altitude natives (different sources)
Caucasians (Marconi, pers.comm.)
Sherpas (Marconi, pers.comm.)
Caucasians (Marconi et al., 1998)
[La$_b$]max (mM)
15
12
9
6
3
0
resting level
0
1
2
3
4
5
6
7
8
9
Altitude (km)



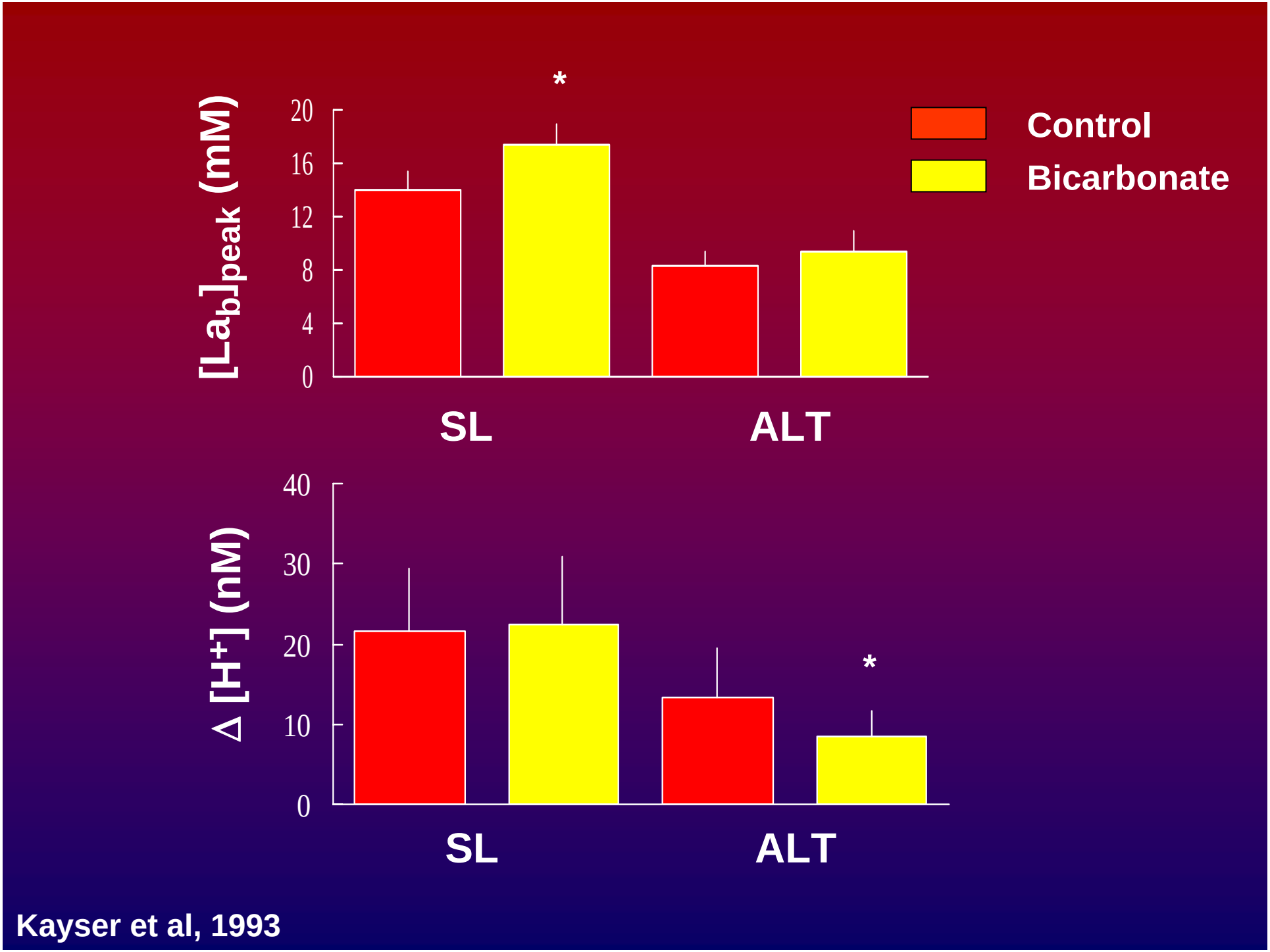
(Cerretelli, 1976)

1) At altitude, the buffer capacity of acclimatized lowlanders is lower than at sea level

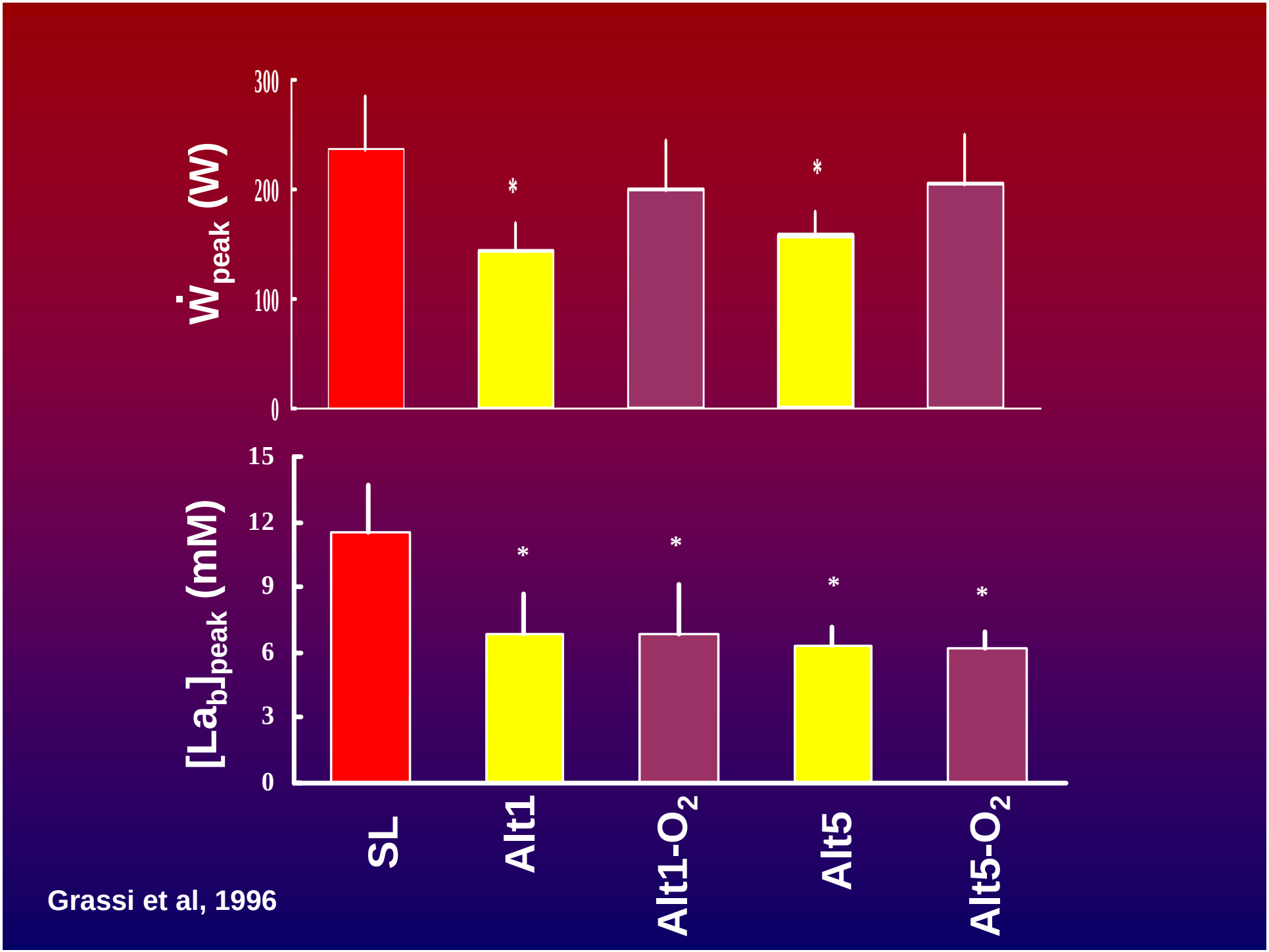
2) The highest $\Delta[H^+]$ is similar at altitude and at sea level, and is independent of [Lab]

Simultaneous measurements of arterial pH and [La] in a group of acclimatized lowlanders after 9 weeks at 5,260 m did not show any significant difference in total body buffer capacity, compared to sea level, despite the reduction in bicarbonate buffer. (Van Halle et al, 2001; Wagner et al, 2002)

This implies that only non-bicarbonate buffers play a substantial role in the regulation of acid-base balance during anaerobic exercise at altitude

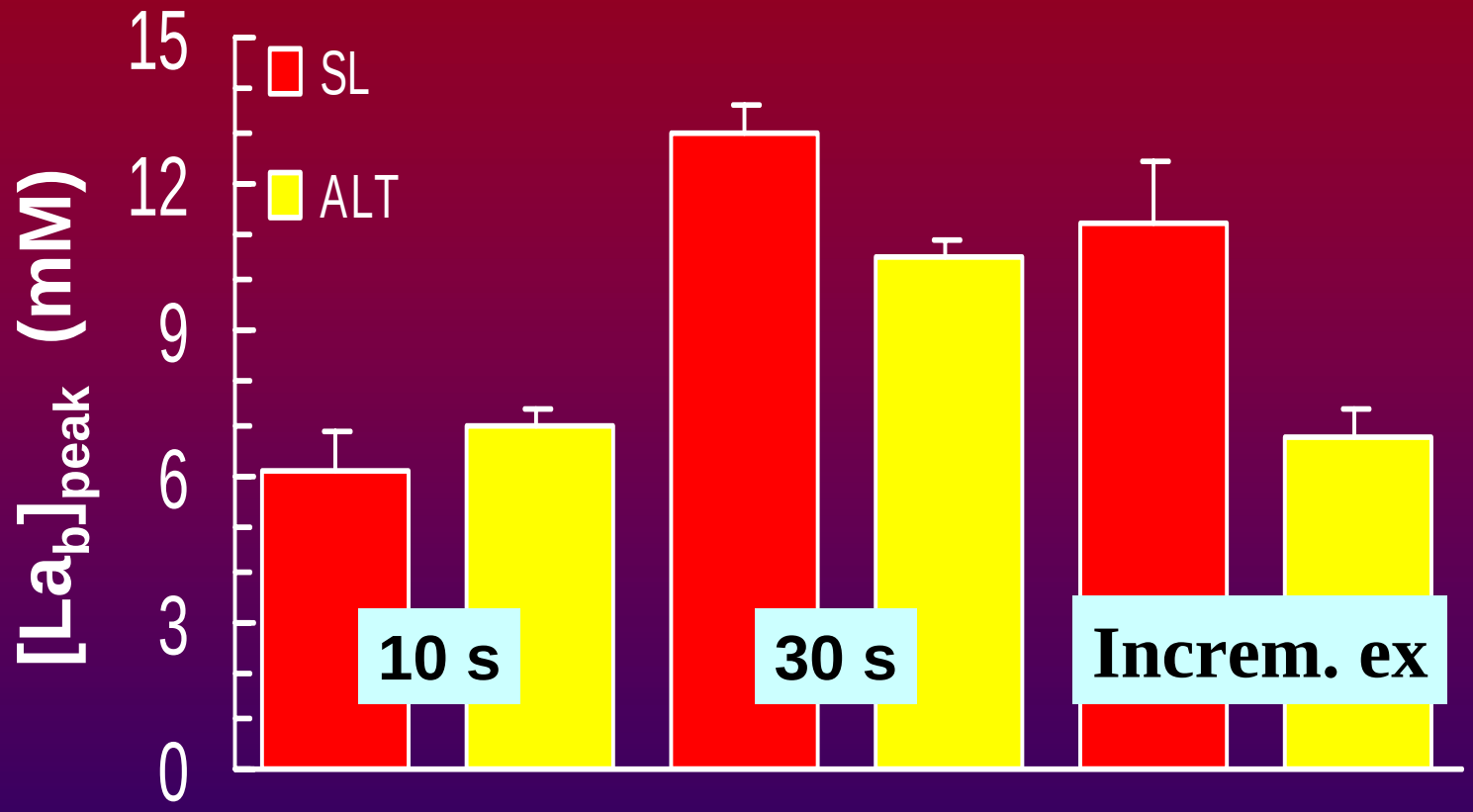


Kayser et al, 1993



Grassi et al, 1996

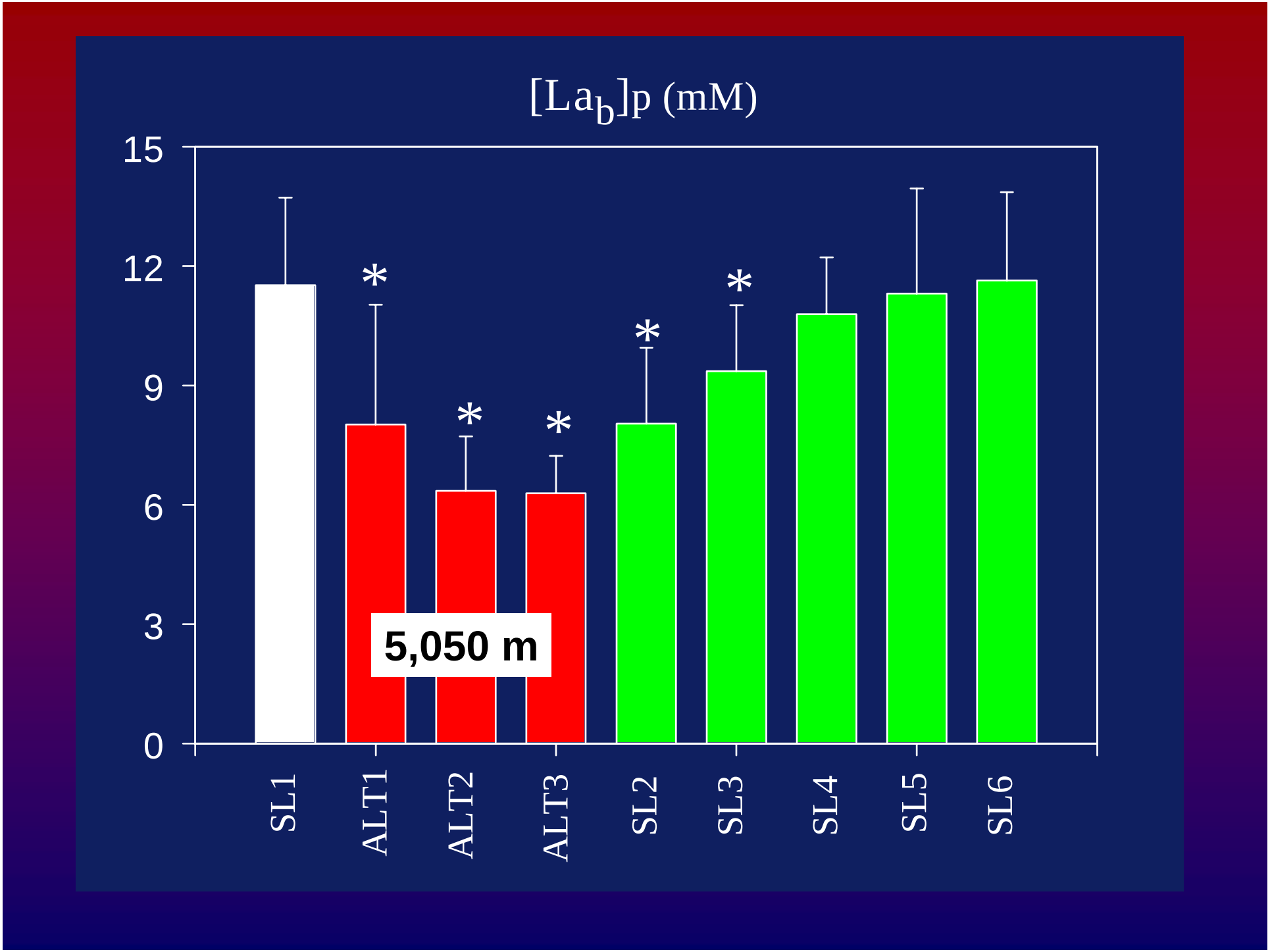
Lactate paradox is at least in part consequence of transient reduced working capacity and/or exercise mode



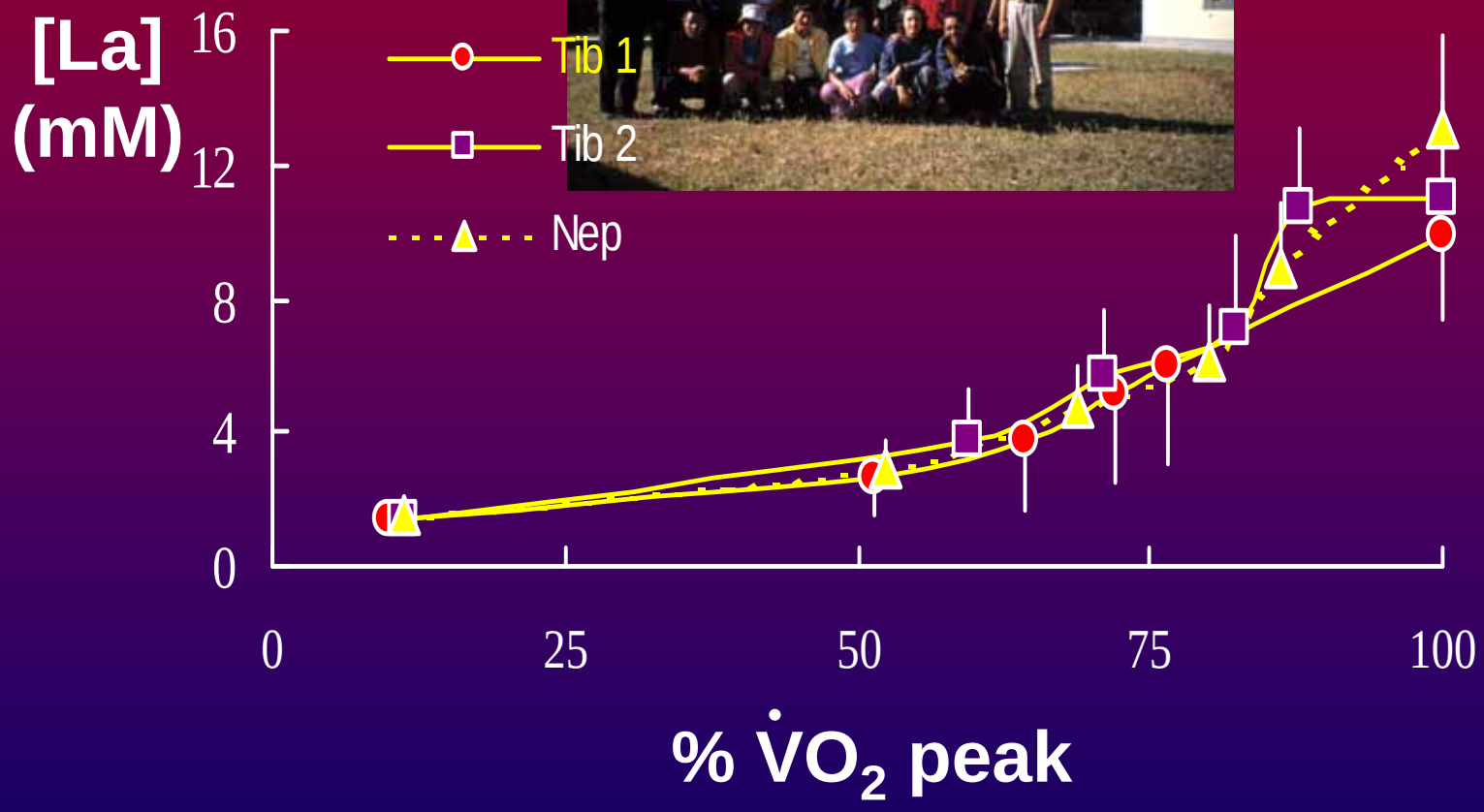
Grassi et al, 2001

Until year 2000 there was consensus on the occurrence and persistence of a lactate paradox, even though the origin of the phenomenon was poorly understood.

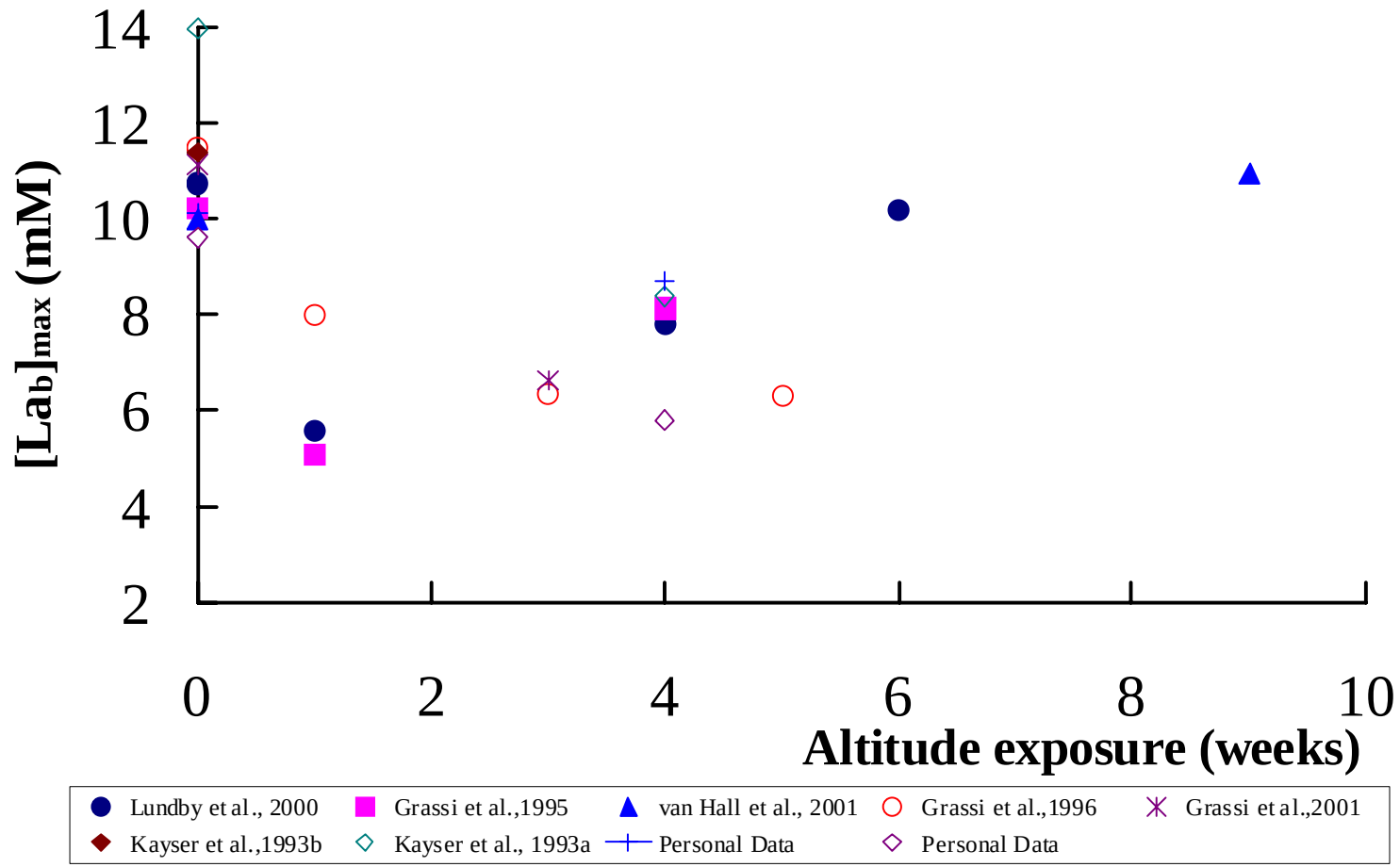
An interesting feature of lactate paradox was its slow reversal upon restoring normoxia


[La$_b$]p (mM)
15
12
9
6
3
0
*
*
*
*
*
5,050 m
SL1
ALT1
ALT2
ALT3
SL2
SL3
SL4
SL5
SL6

Hochachka et al (1991) hypothesized that lactate paradox is permanent in Quechuas transferred to sea level.



Evolution of the “lactate paradox” as a function of exposure duration at altitudes ranging from 5,000 to 5,500 m. There is a fast drop of [La]max within 2-5 weeks from the onset of hypoxia and a progressive recovery thereafter to pre-exposure levels



- It is assumed that a better coupling between ATP supply and demand may be responsible for lactate paradox.
- The progressive disappearance of lactate paradox during prolonged acclimatization means a loss of an acquired adaptive feature, as a consequence of a progressive impairment of muscle function.
- Lactate paradox may underlie a complex gene-based “reorganization” of muscle metabolism occurring in hypoxia.

Proposed time courses of the main events that occur during a period of hypoxia and after return to sea level (from Cerretelli and Samaja, EJAP 2003)