Human Adaptation to High Altitude and Sea Level

Acid-Base Equilibrium, Ventilation and Circulation in Chronic Hypoxia

Copenhagen
55 41'N 12 33'E
Alt: 30 m

Copenhagen
July 2,2007

Season lag

Time lag

Oxygen lag

La Paz
16 30'S 68 9'W
Alt: 3510 m

Background Google Earth

Gustavo Zubieta-Calleja

Visiting Professor at the Panum Institute   &   High Altitude Pathology Institute
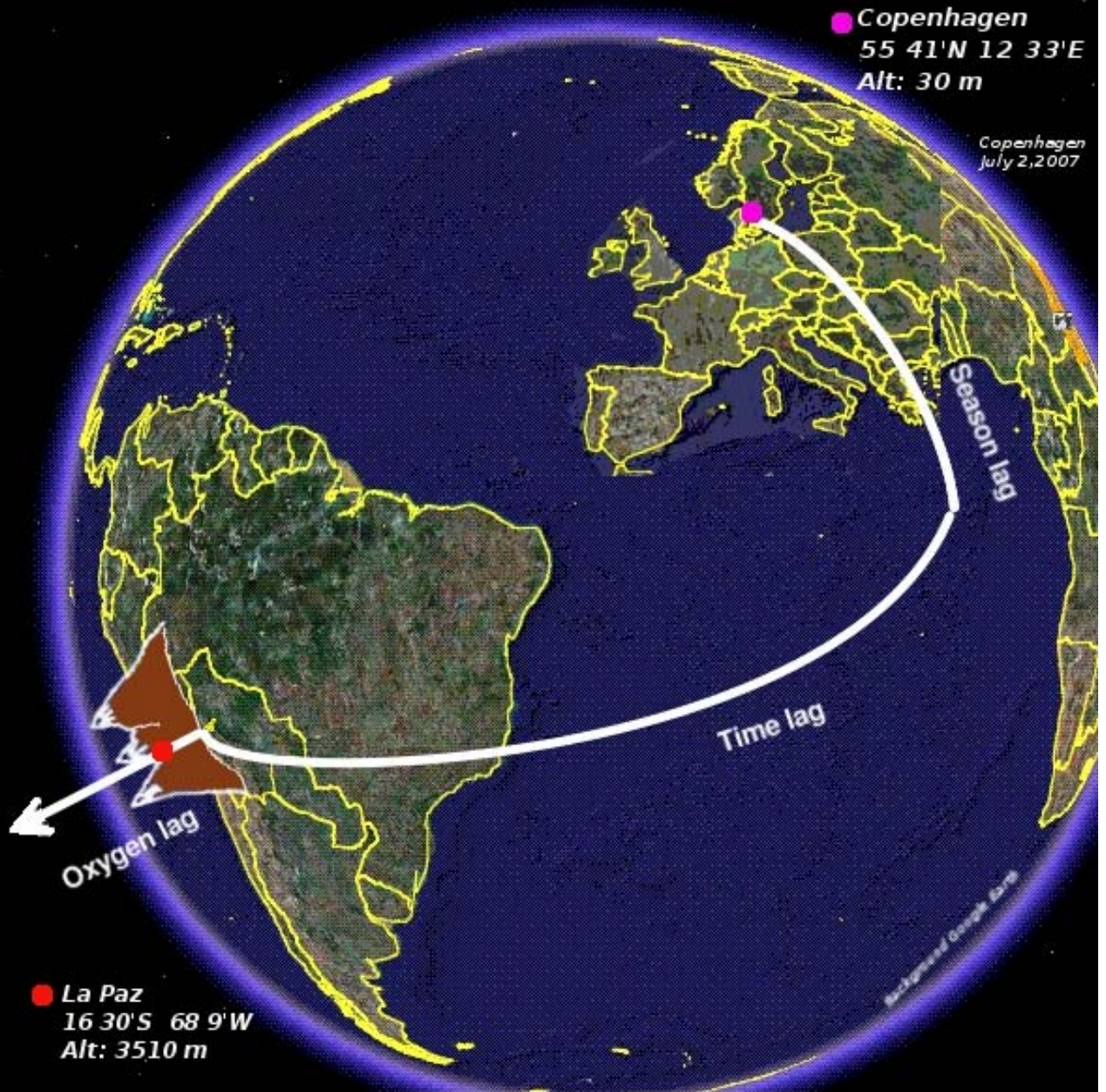University of Copenhagen   Clinica IPPA * La Paz, Bolivia

HUMAN ADAPTATION TO HIGH ALTITUDE AND TO SEA LEVEL

ACID-BASE EQUILIBRIUM, VENTILATION AND CIRCULATION IN CHRONIC HYPOXIA

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CONTENTS

To my beloved wife, Lucrecia De Urioste Limariño,

for her kind and loving support during all these years of

research in Copenhagen

and to my two daughters Natalia and Rafaela,

for their interest, stimulus and with whom we enjoy so much

the "ride in the train of life".

ACKNOWLEDGEMENTS

INTRODUCTION

Twenty three years of medical practice and research at high altitude in the city of La Paz evolved into a dilemma upon arriving to Copenhagen four years ago. The author's wife was sent on mission to the Bolivian Embassy and he had contacted Dr. Poul-Erik Paulev at the Panum Institute of Medical Physiology of the University of Copenhagen. The experience with high altitude medicine and physiology appeared of limited use in a country where the highest point is at 170 meters above sea level. Nevertheless, Dr Paulev showed keen interest in scientific collaboration, immediately upon arrival. We began to work jointly on a paper called "Essentials in the diagnosis of acid-base disorders and its high altitude application". The first section is dedicated to a review and analysis of the historical and transcendental development in Acid-Base physiology born fundamentally here in Copenhagen. The second part is an application of the nomogram developed by Ole Siggaard-Andersen to high altitude, a subject thus far overlooked and important in intensive care life saving therapy. Scientific collaboration further extended to the Glostrup hospital with adaptation studies of the retina with Michael Larsen and football (soccer) at altitude matters at the August Krogh Institute with Jens Bangsbo.

Close to 2 million people live in the city of La Paz, Bolivia, a modern bowl-shaped city, with altitudes ranging from 3100 m to 4100 m above sea level in the heart of the Andes. The airport, located at 4000 m, is enveloped by close to 600,000 inhabitants. The local mean barometric pressure at IPPA, our laboratory, is around 490 Torr (65% that of sea level). The partial pressure of oxygen molecules in the inspired air = 94 Torr is 1/3 less than at sea level. Similarly, the mean arterial partial pressure of oxygen = 60 Torr (*7.99 kPa*) and of carbon dioxide = 30 Torr (*3.99 kPa*) are 1/3 and 1/4 less, respectively.

Given the difficulty of attaining reliable data on altitude related pathologies, Dr. Gustavo Zubieta Castillo (Senior), a highly trained and experienced Bolivian physician, specialized in the field of cardio-respiratory physiology, created in 1970 "Clinica IPPA: del Instituto de Patologia de la Altura", an internationally prestigious medical Institute specialized in high altitude medicine. The author has worked in this

institution during 26 years as a medical doctor, research scientist, pulmonologist and professor.

Travelers arriving to high altitude from sea level can present acute mountain sickness (AMS) and occasionally High Altitude Pulmonary Edema (HAPE) or High Altitude Cerebral Edema (HACE). IPPA also functions as a clinic attending local residents - whose medical test results and clinical problems differ from those at sea level. Residents with chronic pulmonary disease and those with sequelae from previous lung disease frequently suffer from Chronic Mountain Sickness. Most of the equipment and software is developed in the same Institute by the author, making the Institute highly sophisticated with on-line data acquisition. The equipment can be modified in short term, involving software or hardware setup, in order to carry out research.

Until now, medicine in the Bolivian Andean region (and in many mountain areas of the world) is practiced according to sea level standards. Most physicians return from sea-level training, applying their up-to-date knowledge to high altitude residents encountering varied problems in doing so. At the same time, few scientific expeditions from abroad arrive, making only short period observations in basic physiology mostly applied to acute changes due to mountain ascent. However, the problems of permanent residents and the changes they suffer on descent to sea level are broadly overlooked. The "abundance" of oxygen at sea level is taken as a favorable event. For example, difficulties encountered by high altitude soccer players switching to high oxygen pressures at sea level, are disregarded and poorly understood. The complete adaptation times of both changes of altitude (going up or down) are important. A new system to measure full hematological adaptation is required and here presented. A formula of hematological adaptation or acclimatization periods is created giving numeric values to be used when going to any fixed altitude.

The collaboration with Dr. Paulev has given rise to joint publications where high altitude data previously acquired over many years was analyzed applying Danish knowledge and experience in physiology. The following hypotheses were formulated:

A. Are sea level acid-base charts suitable for diagnosis of disorders and their treatment at high altitude?

B. Is it possible to improve the high altitude diving tables?

C. Is there a difference in circulation time between patients with chronic mountain sickness and normal residents at high altitude?

D. Do Chronic Mountain Sickness (CMS) patients save energy by decreasing ventilation and increasing the number of red cells, thereby achieving the most energy efficient mechanism of oxygen transport in order to sustain life?

E. Can CMS be defined as polyerythrocythemia due to a broad spectrum of medical conditions?

F. What is the explanation for acute, sub-acute and chronic mountains sickness at high altitude? What are the physiologic changes of high altitude residents and temporary visitors to high altitude, upon return to sea level?

The following are the peer reviewed and published papers that answer these questions;

A. "ESSENTIALS IN THE DIAGNOSIS OF ACID-BASE DISORDERS AND THEIR HIGH ALTITUDE APPLICATION". P.E. PAULEV, G.R. ZUBIETA-CALLEJA. JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2005, 56, Supp 4, 155-170.

B. "HIGH ALTITUDE DIVING DEPTHS". P.E. PAULEV and G.R. ZUBIETA-CALLEJA. RESEARCH IN SPORTS MEDICINE. Volume 15, Issue 3 July 2007 , pages 213 – 223.

C. "NON-INVASIVE MEASUREMENT OF CIRCULATION TIME USING PULSE OXIMETRY DURING BREATH HOLDING IN CHRONIC HYPOXIA". G.R. ZUBIETA-CALLEJA, G. ZUBIETA-CASTILLO, P-E. PAULEV, L. ZUBIETA-CALLEJA. JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2005, 56, Supp 4, 251-256.

D. "HYPOVENTILATION IN CHRONIC MOUNTAIN SICKNESS: A MECHANISM TO PRESERVE ENERGY". G.R. ZUBIETA-CALLEJA, P-E. PAULEV, L. ZUBIETA-CALLEJA, N. ZUBIETA-CALLEJA, G. ZUBIETA-CASTILLO. JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2006, 57, Supp 4, 425-430.

E. "CHRONIC MOUNTAIN SICKNESS: THE REACTION OF PHYSICAL DISORDERS TO CHRONIC HYPOXIA". G. ZUBIETA-CASTILLO Sr, G.R. ZUBIETA-CALLEJA Jr, L. ZUBIETA-CALLEJA .JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2006, 57, Supp 4, 431-442.

F. "ALTITUDE ADAPTATION THROUGH HEMATOCRIT CHANGES". G.R. ZUBIETA-CALLEJA, P-E. PAULEV, L. ZUBIETA-CALLEJA, & G. ZUBIETA-CASTILLO. JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2007, 58, Suppl 5, 811.818

Please note that reference within the following pages to these articles are enclosed in bold letters and brackets as in {A}. This dissertation is by no means a review of all the scientific literature of every detail presented here, although in some areas there is comparison. The reason is that the material, herein presented, is quite extensive and a resume of original observations of over 36 years at the High Altitude Pathology Institute that has led to the current work at the University of Copenhagen. CMS is only touched briefly and is subject of discussion in other publications [1-6].

CHAPTER A

ACID-BASE DISORDERS AT HIGH ALTITUDE

Normal values of blood gases at different altitudes

As the barometric pressure exponentially decreases with incrementing altitude, the P_aO_2 and P_aCO_2 both decrease as shown in Table 1. These are normal values from our laboratory in La Paz and the three lower rows only come from a few samples drawn under difficult conditions during mountain climbing. This data is shown here for comparison only. The altitude of major importance for this work is at 3510 m in our laboratories in the city of La Paz, a bowl shaped city in the Andes, ranging between 3100 m up to 4100 m.

ALTITUDE m	PB Torr	P_aCO_2 Torr (kPa)	P_aO_2 Torr (kPa)
Sea Level	760	40 (5.33)	100 (13.33)
3510 (La Paz)	495	30 (3.99)	60 (7.99)
6400	344	20.7 (2.76)	38.1 (5.08)
7440	300	15.8 (2.11)	33.7 (4.49)
7830	288	14.3 (1.91)	32.8 (4.37)
8848*	253	7.5 (1.00)	29.5 (3.90)

Table 1. Normal values of blood gases for different altitudes. * The Everest values are calculated [7].

Arterial acid-base distribution curves at high altitude

At the High Altitude Pathology Institute - Clinica IPPA, located at 3510 m above sea level in the city of La Paz [8], a computerized database containing 2431 records of blood gas studies recollected over 10 years, was analyzed. These had been run on a pHmK2 Radiometer Acid-Base Analyzer, properly calibrated according to the company's specifications. These results show the variation of blood acid-base values and blood gases in a high altitude population that lives a normal life that include all activities of a metropolis in spite of the chronic hypoxia. After excluding all the tests performed using supplementary oxygen, a total of 1865 records that included both sexes, with a mean

weight of 64.52 ± 17.21 (SD) kg and a mean hemoglobin concentration of 10.4 ± 2.17 mM (16.85 ± 3.45 g%) gave the following results. Note that this refers to data taken from a medical center in order to observe a distribution pattern of patients at high altitude and is not to be taken as normal values.

	pH	P_aCO_2 Torr (*kPa*)	P_aO_2 Torr (*kPa*)
Mean =	7.38	29.4 (*3.91*)	52.4 (*6.98*)
S.D. =	0.19	6.9 (*0.91*)	9.8 (*1.30*)

Table 2. The mean and standard deviation of the arterial blood gases of the IPPA database of 1865 patients.
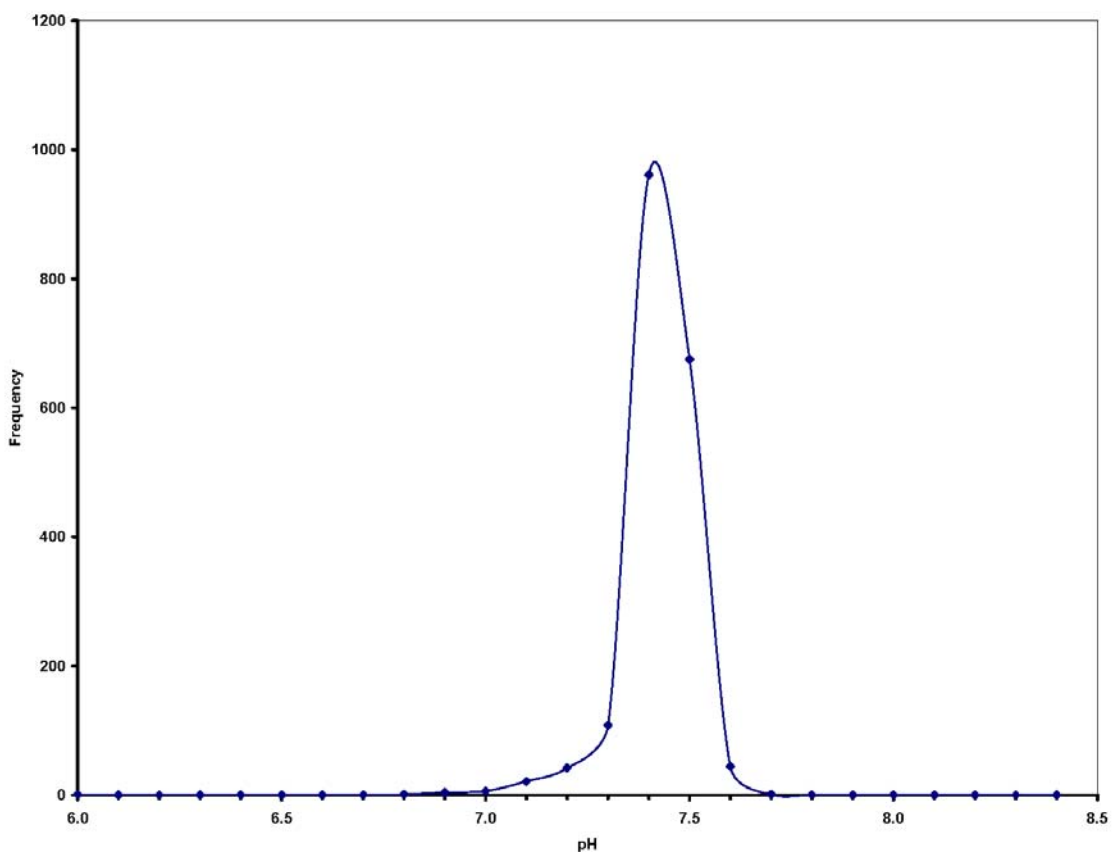
Fig. 1. Frequency pH distribution of arterial blood of 1865 patients at high altitude 3510 m.

The high kurtosis curve in Fig. 1, shows that most patients had a normal pH of 7.4. This is because many were suffering from disease that did not compromise the acid-

base status of blood. However, the incidence of a pH of 7.5 is also important since at high altitude hyperventilation is one of the fundamental compensation mechanisms for acute hypoxia. Metabolic (or rarely respiratory) acidosis is present and a result of disease that is of the same characteristics as at sea level.
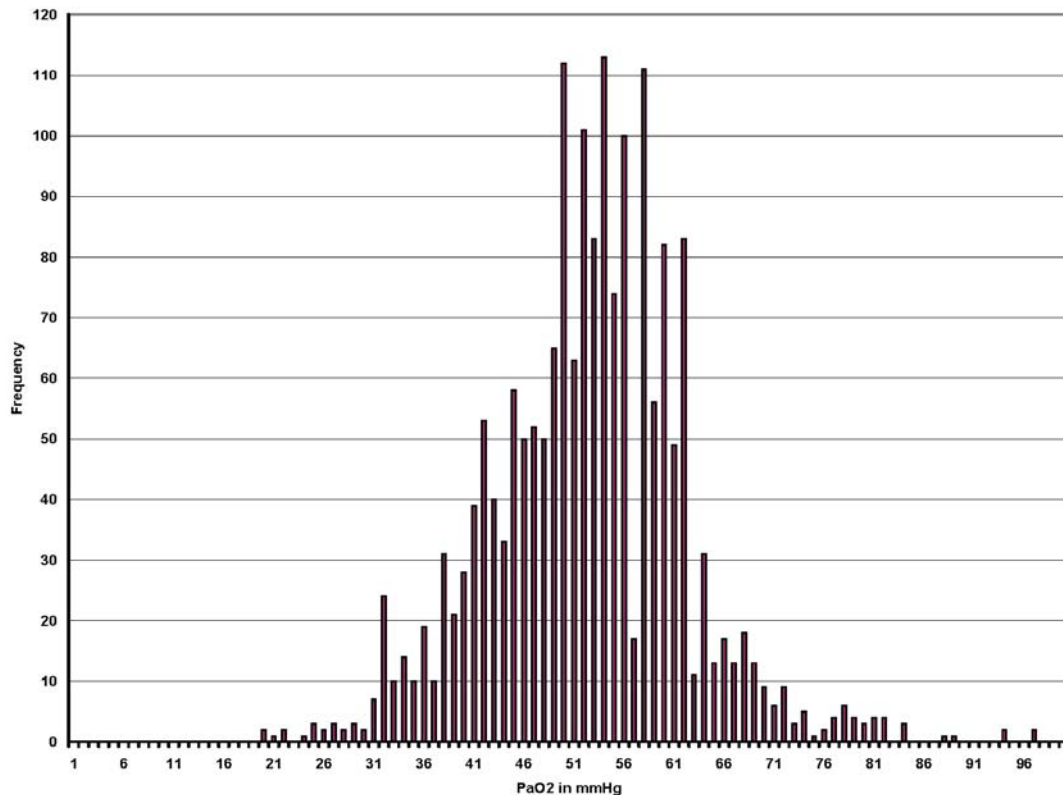
Fig 2. P_aO_2 frequency distribution of 1865 patients examined at our laboratory in La Paz.

The normal P_aO_2 is 60 Torr (7.99 kPa) in the capital of La Paz (Table 1). Fig. 2 shows a negatively skewed curve as the patients at high altitude with cardio-respiratory disease tend to have a decrease in the P_aO_2. On the far left there are some subjects that had a very low P_aO_2. These unusual cases led to further investigation and the description of the Triple Hypoxia Syndrome by Gustavo Zubieta-Castillo (Sr.) not detailed in this dissertation [9, 10]. These tolerance to low P_aO_2 values also led to the proposal of a new theory by Gustavo Zubieta-Castillo (Sr.) of human adaptation to the hypoxic levels of the summit of Mt. Everest [11, 12].
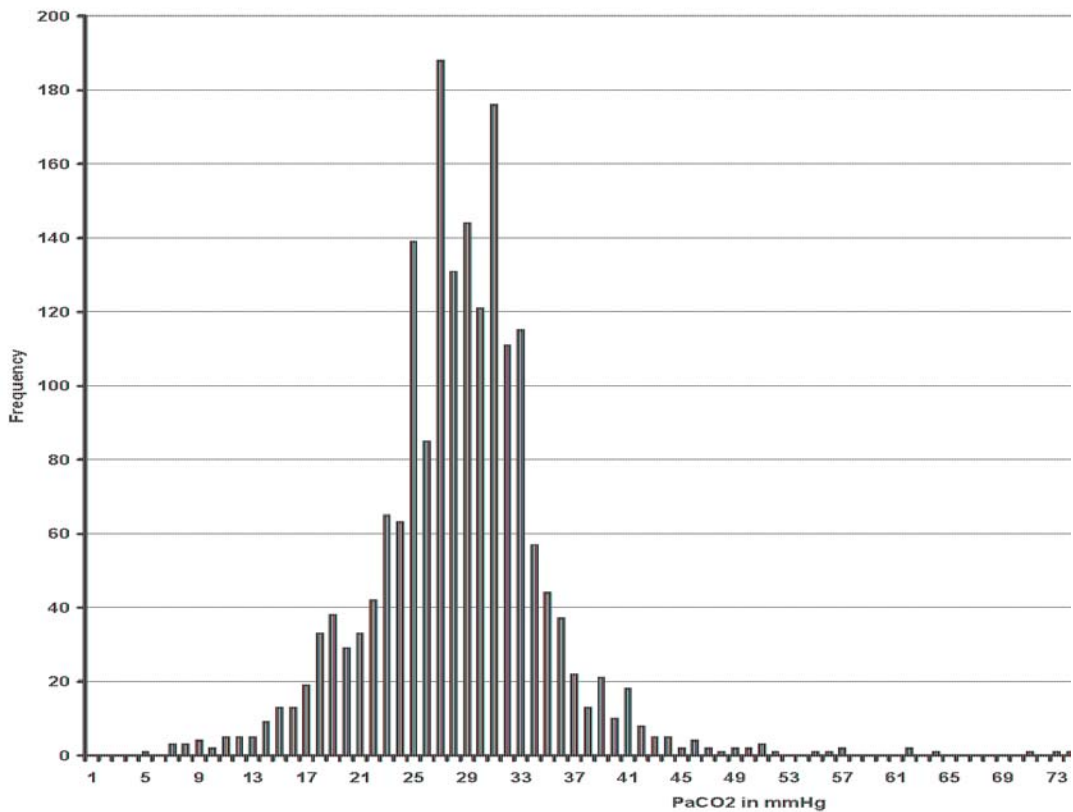
Fig 3. Distribution curve of the P_aCO_2 in 1865 patients including both sexes at 3510 m.

Above 90 % of the patients have a P_aCO_2 below 40 Torr (*5.33 kPa*) (Fig. 3). The average is at 29.4 as seen in Table 2, happens to be the same as the value of normal at 3510 shown on Table 2. This implies that although the average P_aO_2 can be lower at high altitude during disease, the average P_aCO_2 remains within the normal limits. It also shows that the highest values reached are around 57 and in some extreme but very isolated and serious cases up to 73 Torr (*9.73 kPa*). At high altitude it is not possible to tolerate a high P_aCO_2.

All medical centers in the world working above 2500 m of altitude are using sea level tables and nomograms to make acid-base corrections in critically ill patients. If the Siggaard-Andersen nomogram is observed in the city of La Paz (3510 m), where the normal P_aCO_2 = 30 Torr (*3.99 kPa*), the base deficit (currently renamed Titratable Hydrogen Ion Concentration) by its original author [13] and Titratable Hydrogen Ion concentration Difference from normal (THID) by us [14]) is found to be −5. However, the acid-base correction, is made to 0. A critically ill patient from diverse conditions,

such as post-operative, acute metabolic acidosis like in diabetes will be corrected to sea level values. This implies regulating the optimal cellular equilibrium to a different environment, where P_aCO_2 would be 40 Torr (*5.33 kPa*) at a pH of 7.4. Clearly this is not the way to correct acid base disorders at any altitude as the Base Deficit increases exponentially with altitude following the barometric change (Fig. 4).

Plot showing Base Deficit in mEq/l on the y-axis (0 to 9) versus PB in Torr on the x-axis (400 to 800). Data points are labeled 4500 m (at ~8), 3500 m (at ~5), 2500 m (at ~3), and a point near 760. The equation shown is:

$$y = 8E\text{-}05x^2 - 0.1141x + 43.095$$
$$R^2 = 0.9979$$
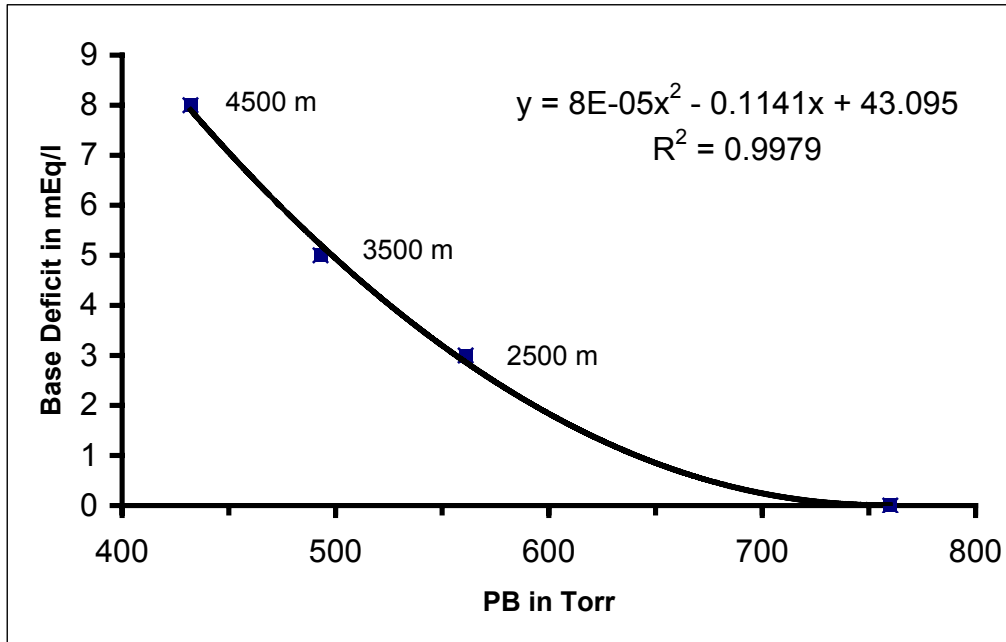
Fig. 4. Shown here is the old Base deficit terminology and the actual high altitude values plotted against the barometric pressure with the current sea level Van Slyke formula. The equation corresponds to the best fit curve.

In our report **{A}**, three tables are presented for different altitudes. These were developed based on the calculated value of P_aCO_2 at different altitudes and setting the 0 point of THID to these values. P_aCO_2 versus altitude was analyzed from data provided by different authors as explained in **{A}**.

Correction factors in {A}

The development of the corrected Van Slyke formula for high altitudes **{A}**, is herein developed and explained.

We initiate the application to high altitude by modifying the original Van Slyke formula.:

$$THID = -0.93 * \Delta(HCO3-) + 14.6 * (pH-7.40) \tag{1}$$

where Δ (HCO3-) = (actual bicarbonate) - 24.5 mM, for a hemoglobin concentration of 3 mM in eECF. This is due to the fact that the normal hemoglobin (at sea level) taken to be around 9.18 mM is divided by 3 as originally suggested by Ole Siggaard-Andersen, as he considers this to be the buffering capacity in the extended extra cellular fluid volume (eECF). Note that extended includes the extra-cellular fluid plus the red blood cell volume.

The first constant factor 0.93 and the second constant factor 14.6 depend upon the hemoglobin concentration [15].

The following formula shows the formula above (1) in detail:

$$THID \text{ in } eECF = (1 - ((Hb) / 43)) * (\Delta (HCO3-) + \beta B * (pH-7.4)) \tag{2}$$

Where (Hb) = (Hb in mM)/3 in the eECF and

Δ (HCO3-) = (actual HCO3-) - (Altitude HCO3-)

$$(Altitude\ HCO3-) = -1.8 \text{ x (altitude in km)} + 24.32 \tag{3}$$

The calculated mean altitude HCO3- values for the chosen altitudes (2500 m, 3500 m, and 4500 m) are ***19.8, 18 and 16.2 mM***, respectively. These go into the altitude formulas described below and shown in ***bold italic*** characters.

The 43 factor above is an empirical constant accounting for plasma-erythrocyte bicarbonate distribution [15].

Additionally the buffering capacity of a normally increased hemoglobin concentration at high altitude must be taken into account in order to be precise. The first term in the Van Slyke equation ((Hb) factor 1) is calculated based on the data from our aboratory:

$$(Altitude\ Hb) = (Hb) + 0.2 * (altitude \text{ in km}) \tag{4}$$

where (Hb) is the normal eECF sea level value of 3.

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which results in **0.93, 0.92 and 0.91** at the three altitudes, respectively. The buffer value

of non-bicarbonate buffers in blood (βB) is calculated using these altitude Hb

values and the formula:

$$\beta B = 2.3 * (Hb) + 7.7 \text{ mM} \quad [15] \tag{5}$$

being *14.9, 15.1, and 16.7* mM at the 3 altitudes, respectively.

Furthermore, one fundamental observation that is borne from this analysis is that the much lower bicarbonate buffer concentration at high altitude minimizes its buffer capacity, whereas the non-bicarbonate buffer capacity increases somewhat.

These same calculations (equations 3 and 4 above) can be performed using the barometric pressure:

$$(\text{Altitude HCO3-}) = 0.0256 \text{ x (PB in Torr)} + 5.15 \tag{6}$$

$$(\text{Altitude Hb}) = (Hb) + (2.25 - 0.003 * (\text{PB in Torr})). \tag{7}$$

Barometric pressure is taken into account, since most acid-base analyzers now have barometers included. Accordingly, the formulas for each level shown in the graphs in **{A}** are:

At sea level:

THID in eECF = **-0.93** * (Δ (HCO3-) + *14.6* * ΔpH)

where Δ (HCO3-) = (actual bicarbonate) - *24.5 mM*.

At 2500 m:

THID in eECF = **-0.93** * (Δ (HCO3-) + *14.9* * ΔpH)

where Δ (HCO3-) = (actual bicarbonate) - *19.8 mM*

At 3500 m:

THID in eECF = **-0.92** * (Δ (HCO3-) + *15.1* * ΔpH)

where Δ (HCO3-) = (actual bicarbonate) - *18.0 mM*.

At 4500 m:

THID in eECF = **-0.91** * (Δ (HCO3-) + *16.7* * ΔpH)

where Δ (HCO3-) = (actual bicarbonate) - *16.2 mM*.

If the bicarbonate high altitude levels are used in the sea level equation, then the result will give a false THID. This is the reason for creating 3 tables for the altitudes (2000-2999, 3000-3999 and 4000-5000 m) in **{A}**.

CHAPTER B

SPORTS AT HIGH ALTITUDE

The practice of sports at high altitude is a subject of growing interest worldwide. The practice of mountain climbing increases and brings forth further goals and challenges. The understanding of the physiology helps improve the quality and reduce the risks of these sports.

High altitude diving depths

Diving at high altitude carries a higher risk as noted by Prof. Paulev upon a visit to the Bolivian Navy high altitude diving school, located on Lake Titicaca at 3600m. Several years back the US Navy visited the lake and brought along several divers, scientists and even pressure chambers. The deepest dive under controlled conditions was made to 15 meters. They developed tables with barometric corrections, but these were not complete and overlooked some aspects. We have introduced the Standard Equivalent Sea Depth (SESD) which allows conversion of the Actual Lake Diving Depth (ALDD) to an equivalent sea dive depth.

SESD is defined as the sea depth in meters or feet for a standardized sea dive

equivalent to a mountain lake dive at any altitude, such that:

$$SESD = ALDD * [\textit{Nitrogen Ratio}] * [\textit{Water density ratio}]$$

$$SESD = ALDD * [(760 - 47)/(P_B - 47)] * [1000/1033]$$

$$SESD = ALDD * [SESD\ factor]$$

For this reason, it was found convenient to re-analyze the data following calculation of the SESD factor, we recommended the use of our diving table with 2 guidelines:

1) The classical decompression stages (30,20, and 10 feet or 9,6, and 3 m) are corrected to the altitude lake level, dividing the stage depth by the SESD factor, including the water vapor pressure factor and the nitrogen ratio in **{B}.**

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2) The lake ascent rate during diving is equal to the Sea Ascent rate divided by the SESD factor.

The new diving table was presented at the 1ˢᵗ Symposium on the Effect of Chronic Hypoxia on Diseases at High Altitude. It is a contribution to safer diving at high altitude thereby reducing the risk of decompression sickness at the altitude of Lake Titicaca. The tables are now under evaluation at the naval diving school.

Another study looked at the decompression sickness following seawater hunting using underwater scooters. (Hans Christian Møller Thorsen, Gustavo Zubieta-Calleja Jr. and Poul-Erik Paulev. In print at *Research in Sports Medicine*).

Exercise at high altitude

The metabolic carbon dioxide production divided by the simultaneous oxygen consumption equals the metabolic respiratory quotient (RQ) for all cells of the body.

The ventilatory exchange ratio (*R*) equals the carbon dioxide elimination from the lungs divided by the simultaneous oxygen input.

RQ equals *R* at respiratory steady state but otherwise not (see the section "The RQ is often different from *R*").

The accumulative sub-maximal work capacity of 17 male Aymara natives of La Paz, as evaluated and compared in three conditions: 1) La Paz (LP) 3510 m, PB = 495 Torr *(66.0 kPa)*, PIO_2 = 94 Torr *(12.5 kPa)*. 2) Simulating Chacaltaya (SC) at the same altitude in the hyperoxic/hypoxic adaptation chamber with a PIO_2 = 77 Torr *(10.3 kPa)* and 3) in the Chacaltaya Glass Pyramid Laboratory (CH), at 5200 m, PB = 398 Torr *(53 kPa)* and PIO_2 = 74 Torr *(9.8 kPa)* [16],[17, 18]. ECG, V_E, PEO_2, P_ECO_2 and SaO_2 (pulse oximetry) were measured on-line in a computerized system that calculated VO_2, VCO_2 and the ventilatory exchange ratio (*R*). The USAFM exercise treadmill protocol was utilized with 0/0, 2/0, 3/0, 3/5, 3/10, 4/10 (mph/Degrees) 3 minutes each stage. Expired air samples were taken near the end of each stage with automatic calibration software taking into account the barometric changes. Data analysis (mean ± SEM) at rest (standing on a treadmill) and at sub-maximal exercise was performed during the final minute of the 5ᵗʰ level of exercise (Table 3).

Rest

R	VO$_2$ L/min	VCO$_2$ L/min	*R*	SaO$_2$ %	Pulse /min
LP	0.46 ± 0.12	0.50 ± 0.12	1.07 ± 0.14	90.4 ± 1.7	72.5 ± 6.0
SC	0.37 ± 0.20	0.51 ± 0.17	1.35 ± 0.31	84.4 ± 3.4	84.9 ± 13.7
CH	0.17 ± .08	0.22 ± .07	1.25 ± 0.15	82.1 ± 5.0	92.0 ± 11.4

Sub-maximal Exercise

E	VO$_2$ L/min	VCO$_2$ L/min	*R*	SaO$_2$ %	Pulse /min
LP	3.76 ± 0.50	4.29 ± 0.71	1.14 ± 0.15	86.5 ± 1.8	142.3 ± 11.9
SC	3.16 ± 0.68	4.29 ± 0.53	1.35 ± 0.33	76.2 ± 3.3	151.2 ± 13.9
CH	1.37 ± 0.49	1.83 ± 0.27	1.33 ± 0.17	76.2 ± 6.1	152.4 ± 11.5

Table 3. Gas exchange, *R,* SaO$_2$ and pulse as measured in 17 Aymara natives both at rest and at the end of a sub-maximal exercise.

The Table 3 material is shown in detail graphically in Fig. 5 and Fig. 6.
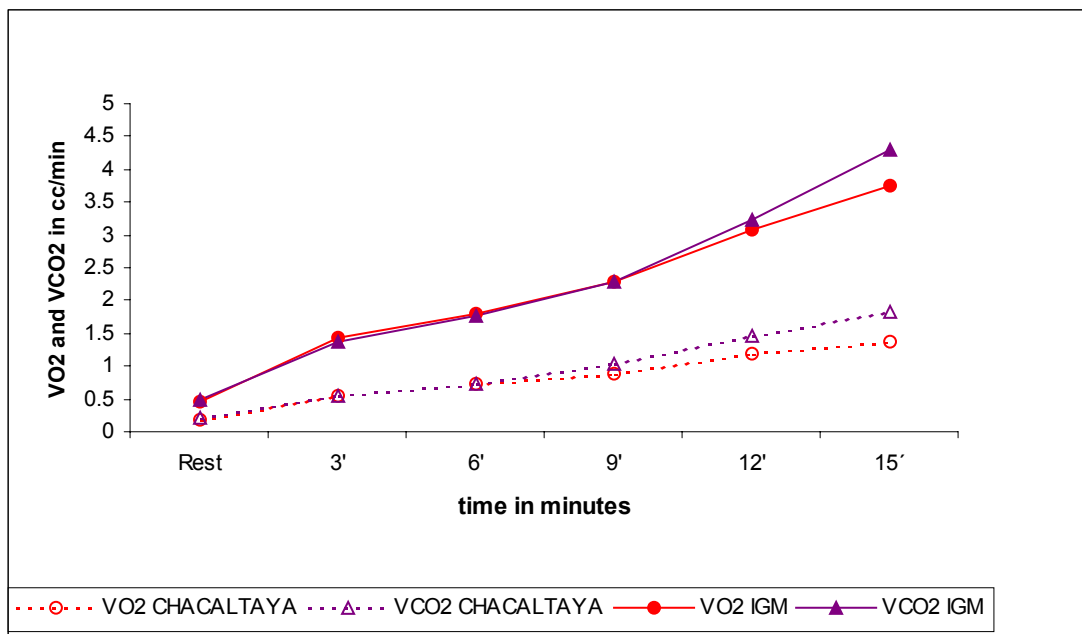
Fig 5. VO$_2$ and VCO$_2$ at rest and different stages of exercise in La Paz 3510 m. solid lines (shown here as IGM, which stands for Instituto Geografico Militar) and at Chacaltaya 5230 m in doted lines.
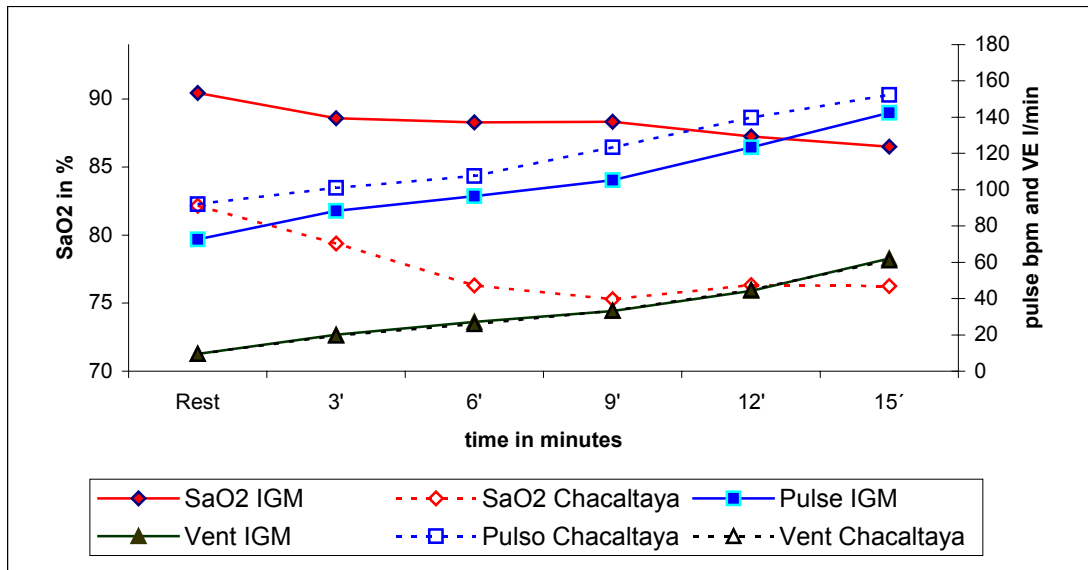
Fig. 6. Saturation, pulse and ventilation measured in La Paz (shown as IGM) and in Chacaltaya at rest and during the different stages of exercise (data From Table 6).

The accumulative sub-maximal work capacity is essentially the same during the 3 different conditions at both altitudes in spite of a lower oxygen consumption and carbon dioxide production at high altitude.

Football at high altitude

Two groups were tested for a football adventure. The Sajama Group (SG) were 7 healthy male Aymara natives (Age: 32.2 ± 5.7) born and living in the Sajama village at 4200 m at the base of the Sajama Mountain (6542 m), that work as guides and porters at the mountain Sajama and other high mountains in Bolivia. The La Paz group (LP) were 17 healthy Aymara male natives (Age: 21.3 ± 6.5) of the Bolivian army Instituto Geografico Militar (IGM), born and living in La Paz (3500 m), constantly in physical exercise. The USAFM exercise protocol described above was used once more.

The SG maintains the SaO_2 at rest and during the first 3 stages of exercise, and drops in the last two stages. In the LP group the SaO_2 drops immediately at the start of exercise (Fig. 7).
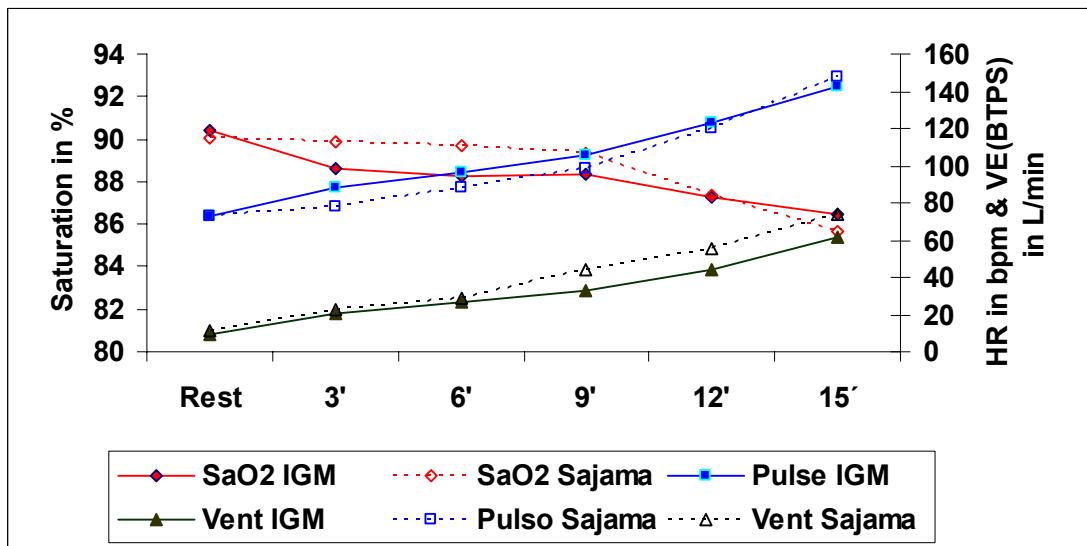
Fig. 7. Comparison of the two groups Sajama (SG) and IGM normal residents both at La Paz (LP) during a sub-maximal treadmill exercise test.

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The SG ascended in 7 hours from the Sajama Village at 4200 m to the summit at 6542 m, prepared the soccer field, played 40 minutes intensely and returned to celebrate to the Sajama Village, all in 16 hours. This traduces a remarkable capacity to perform accumulative sub-maximal exercise at extreme altitudes. The football game played by the Bolivian Aymara on the summit of Mount Sajama at 6542 m in August 2nd, 2001, shows that even at that altitude, football is possible. One player vomited but continued to play. We have the video recording showing the game that lasted 20 minutes per side.

Football (soccer) at high altitude is a subject of constant controversy in the Fédération Internationale de Football Association (FIFA). In 2001 they vetoed world cup games in the city of La Paz. There was a social outcry and a defense of the practice of sports at high altitude. Now in June, 2007, the FIFA once more has proposed the same veto. Immediately after, the President of Bolivia, Evo Morales played a soccer game at 6000 m on Mount Sajama to prove that it is possible without AMS and no cases were reported. The BBC reported both events (2001 and 2007). Highland football players going to sea level can suffer the effects of "relative hyperoxia lag" (Table 11).

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CHAPTER C

BREATH-HOLDING AND CIRCULATION TIME AT HIGH ALTITUDE

Breath-holding at high altitude

Breath holding produces respiratory and cardiac changes well documented at sea level [19-21]. The great variations in the low pulse oximetry saturation in normal residents at La Paz were observed with a new breath-holding (BH) technique. A computer was set up to display on-line, ventilation by pneumotachograph, infra-red capnography, and pulse oximetry (finger probe). The seated subject using a nose-clip and breathing in steady state through a mouthpiece during 2.5 minutes (1 screen), was asked to hold his breath at total lung capacity (TLC) up to the breaking point (beyond no-respiratory sensation).

A typical graph of the saturation response is plotted, where two peaks are shown, one after deep inspiration and the other following the compensatory hyperventilation, with a low saturation in-between (Fig. 8). In fourteen non-trained normal native males (mean age 28.2 ± 7.81 S.D.) the average breath-holding time (BHt) was 65.2 ± 20.08 S.D. seconds. The resting saturation ($x = 90.4\% \pm 1.34$) rose to a peak saturation (SATmax) $x = 97.1\% \pm 1.29$ (p<0.0001), similar to sea level values, following maximum inspiration prior to BH at $x = 34.9 \pm 9.93$ seconds (maxSATt), an unexpected long blood transit time. In spite of individual variations, saturation decreased after BH to an average of $78.0\% \pm 5.70$.

The first deep inspiration followed by hyperventilation induced at breaking point gave a second peak of saturation at 36.4 ± 10.59 seconds with a correlation of r=0.93 with respect to maxSATt. The end-tidal CO_2 ($ETCO_2$) remained constant with resting respiration ($x = 29.0 \pm 1.53$ Torr) (*3.87 ± 0.20 kPa*) and increased to $x = 33.6 \pm 1.90$ Torr (*4.48 ± 0.25 kPa*) (BH- $ETCO_2$) at breaking point expiration (p <0.0001). The correlation between BHt and BH- $ETCO_2$ was $r = 0.66$.
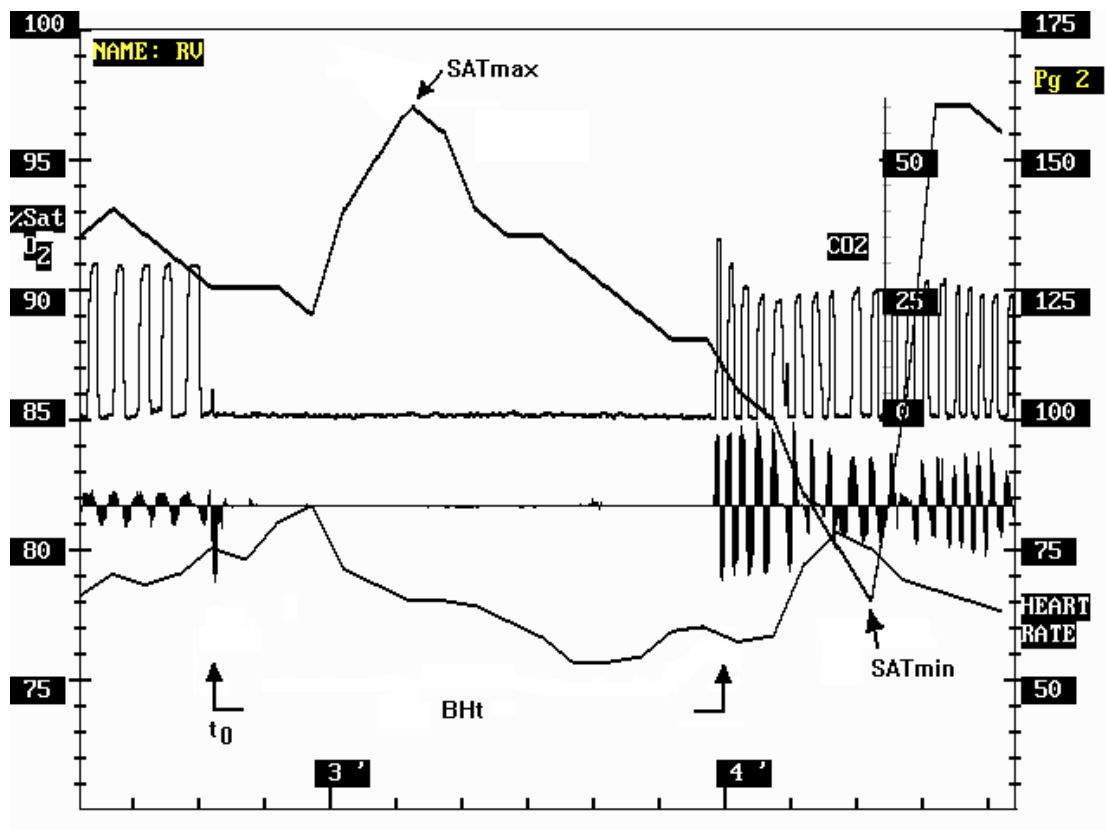
Fig. 8. Breath holding and pulse oximetry graph at 3510 m, showing the saturation changes, $ETCO_2$, pneumotachograph and pulse (shown in order starting at the left side and top of the screen). The left y-axis is SaO_2 in %. The right y-axis is the HR. The upper right short axis is the $ETCO_2$ in Torr.

These young normal high altitude residents have a BHt of 65.2 seconds and reach a SATmax of 97.1%, showing no shunts or diffusion alterations. The average maxSATt (time from peak inspiration to peak saturation in the finger) reached in normal subjects is 34.9 sec. These changes can be observed only in chronic hypoxic conditions at high altitude in which the resting pulse oximetry saturation is low (x = 90.4%).

Voluntary hyperventilation and breath-holding at high altitude

Normal breath holding (BH) was compared with voluntary hyperventilation breathing ambient air (HAA) and hyperventilation breathing 90 % oxygen (HO) in the same subject. The first 2.5 minutes the subject hyperventilated voluntarily maintaining a PCO_2 of around 25 Torr (*3.33 kPa*) and a saturation of approximately 95 % (Normal

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for this altitude 91 %). Then he took a deep breath and held his breath for as long as possible, beyond the respiratory breaking point. The procedure was repeated breathing 90 % oxygen from a Douglas bag, using a one way valve system.

Results were as follows:

	ETCO$_2$ before BH Torr (*kPa*)	BHt sec	ETCO$_2$ after BH Torr (*kPa*)	Satmin %
Normal	30 (*3.99*)	66	35 (*4.66*)	84
HAA	23 (*3.07*)	138	34 (*4.53*)	78
HO	22 (*2.93*)	235	37 (*4.93*)	NO

Table 4. Breath-holding breathing ambient air (Normal) during Hyperventilation in ambient air (HAA) and hyperventilation with oxygen (HO), ETCO$_2$ before BH = end tidal CO$_2$ prior to BH. BHt = breath-holding time in seconds. ETCO$_2$ after BH = breaking point expiration end-tidal CO$_2$.SATmin = minimal saturation reached during breath-holding.

Voluntary hyperventilation in La Paz for 2.5 minutes extends breath-holding time about twice, reaching a lower minimal saturation but with the same end-tidal CO$_2$ as in normal BH (Table 4). In hyperventilation with hyperoxia, BHt is increased four times, with no decrease in saturation and a slight increase in ETCO$_2$, that became the driving stimulus to resume ventilation. The ETCO$_2$ at 37 Torr (*4.93 kPa*) is below the sea level value.

Defining circulation in relation to gravity

One of the effects of space flight is anemia. This has to do with circulatory changes due to the no gravity environment. This is discussed in the article **{F}.** It is fundamental to define a 0 gravity re-definition of the circulatory system.

If a subject is suddenly exposed to a Trendelenburg tilting maneuver of – 6 ° gradient, the increase in thickness of the dermis of the forehead is greater than that of the tibial dermis. These measurements are performed with a dermatology instrument modified by me as a contribution to the PhD student Thilo Noack of the Zentrum Fur Weltraummedizin in Berlin, Germany on Dec 8, 2005.

The difference between the greater and sudden increase in volume in the dermis of the forehead with respect to the tibial dermis immediately following the tilting maneuver, may be due to the following.:

As well known, the human body has two circulatory systems:

1) The systemic high pressure system and

2) The pulmonary low pressure system.

But it likewise has an interesting gravity dependent division:

1) The top circulatory system, located above the heart and

2) The bottom circulatory system located below the heart.

These two differ in that the return of blood from the top is aided by gravity. Hence there is only one valve in the lower part of the internal jugular vein and no further valves are necessary in the venous return system from the head. But this valve is a semilunar valve that avoids reflux to the veins in the head. However, the external jugular vein has no valves and it can of course give rise to a reflux in the tilt of -6 degrees.

The bottom 3/4 of the length of the body has a complex and admirable venous return system. Blood has to return against gravity for over 1.4 meters (roughly, in a person 170 cm tall) and due to a slightly higher density of blood it amounts to approximately 114 Torr *(15.2 kPa)* of pressure difference. It is extraordinary for blood to return through large vessels in the standing position against gravity and not using a micro-capillary circulation system as in plants.

One of the mechanisms that allow for this is the presence of valves in the venous system. When these become insufficient, edema and dilatation ensues as in the case of varicose veins. The venous return is aided by muscular contraction in what the late and extraordinary Brazilian Physician Mario Rigatto termed "The five hearts of the body", where he expressed that the four limbs during contraction of movement were acting as pumps. That is why a long flight trip in the sitting position can give rise to swelling in the feet and circulatory problems, such as pulmonary thrombo-embolism. The valves are still there, but since there is no movement, the "muscular venous pumps" of the lower limbs are not acting.

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The dermatology test, here described shows a thickening of the dermis in the forehead and not in the tibial region. This could possibly be explained by a circulatory re-flow to venous capillaries in the forehead in the Trendelenburg position. This phenomenon would not be so evident in the tibial dermis, because the valve system in the venous return system does not allow for a sudden reflux in the standing position.

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CHAPTER D

HYPO- AND HYPERVENTILATION AT HIGH ALTITUDE

Hypoventilation in CMS: an energy saving mechanism

CMS patients have a lower ventilation than normal [22]. This is believed by many authors, to be the cause of a low P_aO_2 and hence the polyerythrocythemia. It was necessary to question this point of view and this is the subject of the article **{D}**.

At high altitude, patients with polyerythrocythemia hypoventilate at rest. They show a significant decrease of SaO_2. During exercise, they also have a significant decrease of SaO_2 although their ventilation and cardiac frequency is higher in the first 4 stages of exercise compared to normal. The low SaO_2 during exercise shows that even though the pneumo-dynamic and hemo-dynamic pumps are working well above that of the normal control group, there is a deficiency in the pneumo-dynamic pump which is due to pulmonary insufficiency (veno-arterial shunts and uneven ventilation). Hence it is inferred that hypoventilation with low arterial oxygen content at rest is an energy saving mechanism. This is possible thanks to an increase in the number of red blood cells, that allows the involved cardio-respiratory muscles to consume the least amount of oxygen required.

Relativity applied to hyperventilation at high altitude

The shortfall of inspired oxygen tension (PIO_2) due to an ascent to high altitude is compensated by hyperventilation that brings about hypocapnia and respiratory alkalosis.

Ventilation is defined as the renewal of air in the lungs and oxygenation of blood in the capillaries of the lungs. To hyperventilate then would mean that there is a greater renewal of air in the lungs than necessary. Hyperventilation at sea level implies a greater renewal of air. More molecules of air are moved within the lungs and hence P_aO_2 rises. Therefore, at sea level hyperventilation increases the number of oxygen molecules exposed to the lung capillaries. By using the Ideal Gas equation: **PV=nRT**

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Where P = pressure, V = volume, n = # of moles, R = gas constant and T = temperature. If R and T remain constant, the volume increases as a result of lowering the pressure.

Provided the mean ventilation (BTPS) in L/min/m2 at sea level is 4.82, then in order to ventilate the lungs with the same # of molecules at 3600 m above sea level, at the same temperature, it is necessary to increase the ventilation in accordance to the following calculation: **P$_1$ V$_1$ = P$_2$ V$_2$**

$$\textbf{(760 Torr) (4.82) = (495 Torr) V}_2$$

$$\textbf{V}_2 \textbf{ = 7.40 L/min/m2 of air}$$

Where P$_1$ is the barometric pressure at sea level, V$_1$ is the V$_E$ (BTPS) at sea level, P$_2$ is the barometric pressure at 3600 m and V$_2$ is the expected V$_E$ (BTPS) at 3600 m. The hypothetical hyperventilation of 7.40 L/min/m2 with a Gas R value higher than 0.8, implies an important rise in $P_A O_2$, a lesser fall in $P_A CO_2$ and small fall in PAN2 as seen in Fig. 9 for a higher altitude in the Andes.
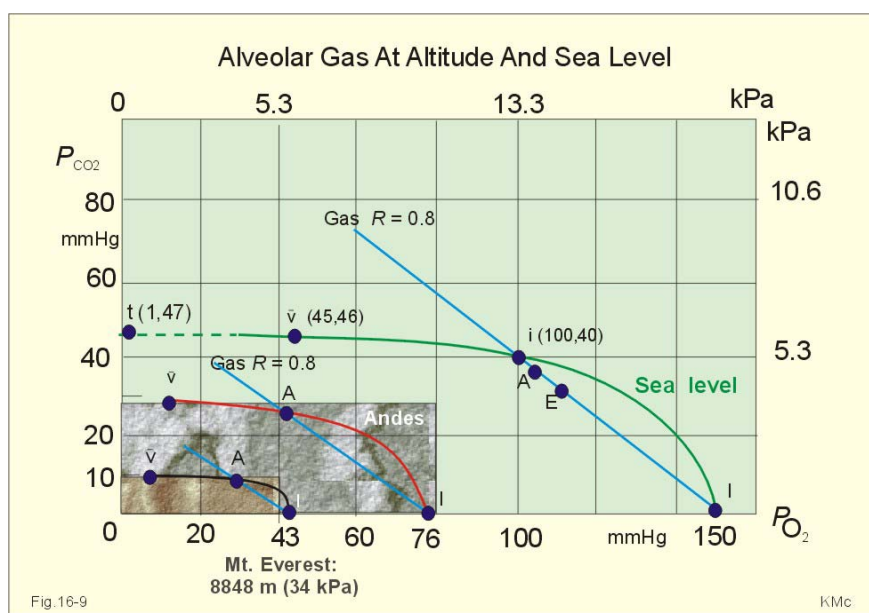
Fig. 9. PO$_2$-PCO$_2$ diagram from Textbook of Medical Physiology, Paulev, with permission from the author [23].

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In reality, the mean ventilation for chronically adapted individuals at 3600 m is around 5.07 L/min/m2 or actually 31 % less than the hypothetical value. This is why the $P_A O_2$ is only 60 Torr (*7.99 kPa*) in La Paz and 45 Torr (*5.99 kPa*) at a higher altitude in the Andes (Fig 9). But energy expenditure would be too great and the organism has less expensive means of adaptation.

The increase of $p_a o_2$ through deep inspirations

One fundamental question is why does a deep inspiration increase the oxygen tension of arterial blood, if the later is regulated solely by pressure gradients?

The Pressure gradient is indeed driving the diffusion of oxygen through the alveolo-capillary barrier; on a down gradient passive diffusion as clearly stated by August Krogh back in the beginning of the previous century when he affirmed that oxygen transport from the alveoli to the capillaries is by diffusion and by diffusion alone. This was an audacious affirmation that brought an ongoing discussion to a stop.

At 3600 m the PIO$_2$ is 94 Torr. The (TV- V$_D$) is 350 cc (500-150), therefore the $P_A O_2$ is around 60 Torr (*7.99 kPa*). Here the ratio V$_D$ /TV is 150/500 or 1/3. Whereas if we make a deep inspiration to TLC with an IRV of 3500 cc The ratio V$_D$ /TV max (maximal inspiration) becomes 150/4000 or 1/27 and the alveolar PO$_2$ rises to approx. 80 Torr (*10.66 kPa*). This decreased ratio explains the rise in $P_a O_2$ following a deep breath or hyperventilation. This is the only biological mechanism that allows an increase in the $P_A O_2$ and therefore a greater diffusion of oxygen through the alveolo-capillary wall. This explains why a deep breath at high altitude allows an elevation of saturation from 91% (normal at 3510 m) to 98 % (Fig. 8).

The RQ is often different from R

Twelve native soldiers (average age = 18.7 ± 0.86, weight = 61.4 ± 4.66 Kg, height = 164.5 cm ± 6.36, hematocrit = 54.5% ± 2.95), residents of El Alto at 4100 m were examined, in a mobile unit equipped with a computerized cardio-ventilatory apparatus. After 15 minutes of rest, the sitting subjects were connected via mouthpiece to a one way flow valve during 12 minutes. Expired gas samples were collected in Douglas bags every 3 minutes, and sampled in 60 cc plastic syringes.

Triplicate samples from different bags, were analyzed in a well calibrated Radiometer PhmK2 Acid-Base analyzer, at 3510 m, a couple of hours later. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) in STPD were calculated.

Average ± S.D. results were:

VO_2 = 138.25 ml/min ± 34.90, VCO_2 = 255.50 ml/min ± 52.90 and R = 1.88 ± 0.21.

In a second study [24], 15 soldiers of El Alto (4100 m), with R = 1.56 ± 0.16, when taken 1000 meters lower to Aranjuez, reduced their R to 0.82 ± 0.06 (p<.001). As an average this group was probably close to respiratory steady state, since R was found to be 0.82 - the value for RQ on a mixed diet.

In a third study, twelve subjects (3 women and 9 men) with an age x = 21.5 ± 4.96 SD, weight x = 58 ± 6.27 SD in resting conditions were studied. Ventilation during 12 minutes was initially measured inside the chamber, via mouthpiece to a one way flow valve, while breathing ambient air (PIO_2 =94 Torr) in steady state. Oxygen consumption and carbon dioxide production in STPD was calculated from analyzed expired gases using standard techniques. Doors of the chamber and the airlock were closed and the oxygen concentration was increased to a PIO_2 = 150 Torr, corresponding to sea level, maintaining the same barometric pressure (PB = 494 Torr). Statistical analysis using paired t-students' was performed.

	Ambient Air **PIO_2 = 94 Torr**	**Hyperoxia** **PIO_2 = 150 Torr**	**p**
SaO_2 in %	90.5% ± 1.55	97.0% ± 1.63	< 0.001
V_E in l/min (BTPS)	9815.1 ml/min ± 2230.1	10543.6 ml/min ± 2694.7	NS
HR in beats/min	68.42 bpm ± 10.32	60.58 ± 10.29 SD	< 0.001
VO_2 in cc/min (STPD)	146.1 ml/min ± 44.64	284.6 ml/min ± 122.51	< 0.001
VCO_2 in cc/min (STPD)	181.9 ml/min ± 49.83	186.5 ml/min ± 59.73	NS
R	1.27 ± 0.30	0.76 ± 0.38	

Table 5. Results from the Hyperoxic/Hypoxic Adaptation Chamber.

The average ventilatory exchange ratio (R) diminished by 0.40 and reached the normal sea level values (0.76 ± 0.38). Note that ventilation slightly increased (Table 5). The resting normal P_aCO_2 at 3600 m is 30 Torr (*3.99 kPa*) and the respiratory center has a tendency to maintain the P_aCO_2 at this level upon immediate exposure to hyperoxia.

The following quote from Paulev and Siggaard-Andersen [25]:

"For a patient in steady state, an R-value between 0.7 and 1.0 provides information on the composition of the diet. If the patient is not in a steady state, the R-value may be lower than 0.7 indicating retention of CO_2 in the body, for example due to hypoventilation or developing metabolic alkalosis. A value above 1.0 indicates excessive elimination of CO_2, for example due to hyperventilation or developing metabolic acidosis", clearly explains the repetitive finding of a high R at high altitude and its value below 1.0 upon return to sea level or during hyperoxia at high altitude.

Acute exposure of high altitude native residents from La Paz to a sea level PIO_2 of 150 Torr *(20 kPa)* at the same barometric pressure, 495 Torr *(66 kPa)*, in the Hyperoxic/Hypoxic Adaptation Chamber, produces an expected increase of oxygen saturation, a decreased heart rate, greatly increased oxygen consumption and maintained carbon dioxide production at the cellular level, thereby decreasing the ventilatory exchange ratio R.

CHAPTER E

CHRONIC MOUNTAIN SICKNESS

High altitude increased polyerythrocythemia, known as chronic mountain sickness (CMS) is frequent and still creates much confusion. Patients are bled periodically, given all kinds of treatment with different teas and even toxic drugs [26]. The institution IPPA practices extensive testing in these patients, with blood tests, urine tests, chest X-rays, blood gases, spirometry, electrocardiogram, cardio- pulmonary stress tests, nitrogen washout, ventilation studies, oxygen dissociation curves, and others. The gained experience helps managing increased polyerythrocythemia and all cardio-pulmonary diseases at high altitude. The core research work in this area has been done by Prof. Gustavo Zubieta-Castillo (Sr.), and his son, the author of this dissertation. They both participated in worldwide discussion forums on the definition of disease at high altitude. They jointly organized the First World Congress on High Altitude Medicine and Physiology, that has gone through Peru, Japan, Chile, Barcelona, China, Tibet and now this year in Scotland. They also have organized the First Symposium on the effect of Chronic Hypoxia on Diseases at High Altitude in 2005 and the next one will be in 2008.

High altitude hematological terminology

Whereas, the sea level physician considers the hematocrit of high altitude residents as increased (by sea level standards), the high altitude physician interprets this as normal for the population. In the case of chronic mountain sickness (CMS), where hematocrit is above that of the normal altitude population, the sea level physician classifies it as increased polycythemia, while at high altitude it is simply called polycythemia (Table 6). Furthermore, when sea level studies are performed in highlanders and oxygen breathing concentrations are increased to sea level these are referred to as normoxia. For the highlander and for the physician in the high lands, this would actually be hyperoxia (i.e. an abnormal increased oxygen concentration). The organism of the highlander is adapted to the reduced partial pressure and this is his normal condition. This is the theory of relativity applied to high altitude medicine.

Physician's point of view	Hematocrit values measured in La Paz	
	50 to 58 %	> 58 %
Sea Level Physicians	Polycythemia	Increased Polycythemia
High Altitude Physicians	Normal	Polyerythrocythemia (CMS)

Table 6. Comparison of the hematocrit values measured at high altitude.

The importance of this observation lies in the fact of defining high altitude residents as "normal" humans in their own environment. Although this is apparently obvious there is a tendency to consider the medical observations only from the sea level perspective. This is why, the acid-base status of blood continues to be adjusted to sea level standards and a subject of one of the articles **{A}.** With the same focus another report **{F}** regards the high altitude dweller as normal in his environment and the descent to sea level a condition of relative hyperoxia, to which he gradually adapts thus defining the term "adaptation of highlanders to sea level".

The inadequate use of term "excessive polycythemia"

Patients with CMS have also been referred to as suffering from "excessive polycythemia". This concept is born from the belief that above a certain level of hematocrit, the increment is "excessive" and hence "needless". This is based on the belief of many authors that man was only fit to live at sea level and that the erythropoyetic response at high altitude is useless.

Analogously, if a sedentary subject's maximal oxygen uptake is compared to an athletes then it cannot be affirmed that the later has an "excessive" oxygen uptake. In reality the athlete has developed an optimal oxygen uptake during maximal exercise through an adaptation process.

Low oxyhemoglobin saturation in CMS patients during exercise

Accumulative submaximal work capacity and arterial oxygen saturation (SaO_2) in 12 CMS male patients and 1 CMS female patient with polyerythrocythemia (Table 7) were compared with that of 17 normal males (N), in our laboratory at 3510 m using the USAF Modified treadmill exercise protocol (0/0, 2/0, 3/0, 3/5, 3/10, 4/10 mph/Degrees). The following variables (ECG, V_E, PEO2, and PECO2) were measured on-line in a computerized system that calculated VO_2, VCO_2 and *R*.

	Normal Control	Polyerythrocythemia
n =	17	13
Age =	19.7 ± 1.7	54.8 ± 11.7
Weight =	65.1 ± 5.9 Kg	73.6 ± 13.1 Kg
Ht =	50 ± 2.1 %	72.1 ± 5.3 %

Table 7. Biometric results from the two groups.

:

Resting	SaO_2 %	Pulse /min	V_E l/min
N	90.4 ± 1.7	72.5 ± 6.0	9.54 ± 1.8
CMS	87.2 ± 2.9	80.1 ± 10.6	8.73 ± 2.3
Exercise	SaO_2 %	Pulse /min	V_E l/min
N	86.5 ± 1.8	142.3 ± 11.9	61.9 ± 10.1
CMS	76.5 ± 23.4	121.1 ± 41.7	58.6 ± 30.19

Table 8. Resting and sub-maximal exercise results in normal and CMS. (V_E in BTPS*)*

The resting SaO_2 in CMS was lower than N (p <0.003) and decreased from 87.2 to 76.5 % at sub-maximal exercise (Table 8). Ventilation and pulse were not significantly different from N at sub-maximal exercise. The accumulative submaximal work capacity remained unchanged, traducing that the oxygen transport mechanism was effective even during polyerythrocythemia with low arterial oxygen tension. The

fall of SaO_2 in CMS during exercise, shows that there is pulmonary insufficiency due to uneven ventilation and/or veno-arterial shunting that increases during exercise and increased cardio-respiratory function is unable to sustain the oxygen saturation. This observation gave rise to article **{D}**, discussed above.
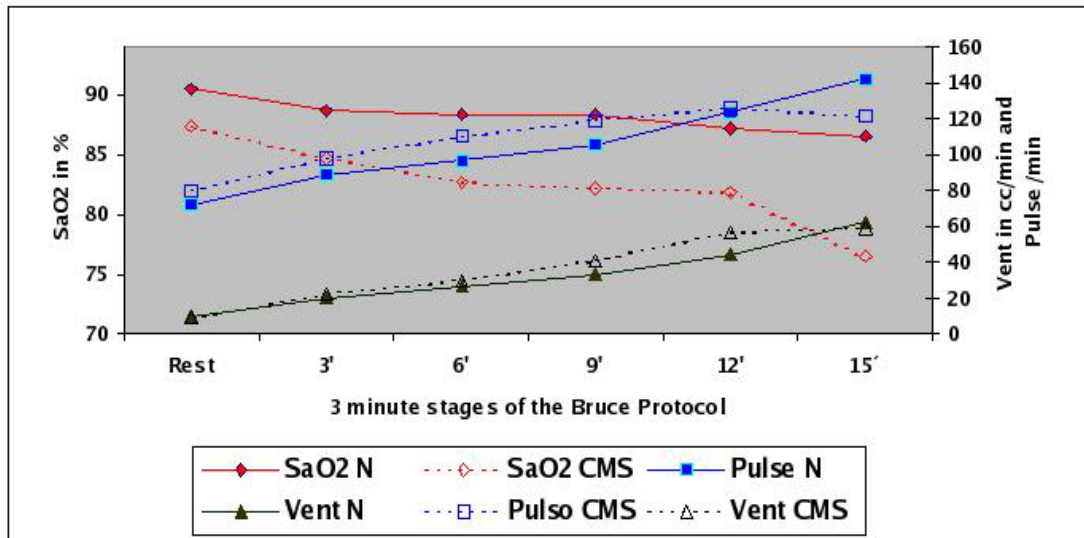
Fig 10. SaO_2 (primary y-axis) ventilation and pulse (secondary y-axis) during submaximal exercise in 13 CMS patients with hematocrit = 72 %, compared to 17 normal subjects (N) with hematocrit = 50 % at 3510 m.

Oxygen transport is efficient during exercise in patients with CMS, who compensate ventilatory and respiratory deficiencies with polyerythrocythemia by increasing oxygen content.

The fall of SaO_2 in CMS during exercise, shows that there is pulmonary insufficiency due to uneven ventilation and/or veno-arterial shunting that increases during exercise and is unable to sustain the oxygen saturation.

Concepts regarding CMS should not be generalized, but correspond to a great percentage of these patients and their current condition depends on the *ethiopathogenesis*, that is multiple, of different grades; and related to their sedentary habits [1, 4].

Pulse oximetry in CMS

Variations in pulse oximetry at high altitude can confuse the observer. Large fluctuations are seen during breath-holding in high altitude residents (3510 m) as we previously described [27]. Pulse oximetry together with fast O_2 and CO_2 analyzers and a pneumotachograph along with the adequate software, shows the changes on-line during breath holding. A "typical graph" of the saturation response is plotted (Fig 8), where two peaks are shown, one after deep inspiration and the other following the compensatory hyperventilation, with a low saturation in-between. Results were as follows:

	Age	Ht	Sat	BHt	maxSATt	SATmin	otms
Normals n = 14	28.2 ±7.81	50.0 ±3.00	90.4 ±1.34	65.2 ±20.08	34.9 ±9.93	78.0 ±5.70	2.5 ±6.43
CMS n = 12	52.8 ±10.79	68.4 ±6.11	85.0 ±4.63	105.1 ±37.17	38.9 ±13.21	64.9 ±7.95	39.0 ±34.45
p <	0.0001	0.001	0.0001	0.001	NS	0.0001	0.001

Table 9. Breath holding test results in normal and CMS at 3510 m.

Where Ht = Hematocrit in %, Sat= average resting saturation in % prior to BH, BHt = breath holding time, maxSATt = peak saturation time following inhalation to TLC, SATmin = minimal saturation reached following BH, otms = oscillation time at minimal saturation.

Patients with high hematocrit values had nearly twice as long breath-holding times as normal and were able to sustain extreme desaturation at very low levels. This is further proof of the remarkable adaptation process in chronic hypoxia.

Patients with stable CMS have shown to tolerate breath-holding almost twice as long as young normal residents at high altitude (3510 m), and to have oscillations at minimal oxygen saturations, during an average of 39 seconds [28].

CHAPTER F

ADAPTATION TO HIGH ALTITUDE AND SEA LEVEL

Human presence on planet Earth is possible due to the presence of water, oxygen, Sodium, Potassium, Chlorine, Calcium and adequate temperature. The complex biosphere where plants, animals, bacteria, viruses, minerals render him with the proteins, carbohydrates and fat along with vitamins and salts, are also necessary for survival. Oxygen as the catalyst of biochemical reactions is essential in adequate amounts. Up to the altitude of Mount Everest, the highest point of planet Earth, oxygen pressure decreases exponentially.

The human body can regulate the amount of water required through thirst, taking only what is necessary. The same happens with sodium chloride, the amount of proteins, carbohydrates and fats. The feedback mechanisms of satiation produce an unpleasant sensation after the stomach is filled with nutrients. In other words, in spite of the great abundance of nutrients surrounding man, he will only take what he needs. Conversely, pulmonary respiration, the mechanism through which oxygen is transported through the lungs and exposed to blood at the alveolo-capillary barrier, is mainly limited by a pressure factor, not a volume factor. In other words, on our planet it is not possible to increase essentially the amount of oxygen entering the organism except through a deep inspiration or hyperventilation, particularly evident at high altitude as shown here. It likewise is a permanent process unable to stop. The two biological macro-systemic pumps: the hemo-dynamic (circulation) and the pneumo-dynamic (ventilation) have functional similarities. Both have a frequency: cardiac frequency and respiratory frequency. Both have a volume: stroke volume and tidal volume, respectively. These two factors multiplied together make the cardiac output and the ventilation per minute. The difference resides in that one pump works in the liquid media of blood and the other in the air. In other words in two states of matter: liquid and gas. With altitude changes the pneumo-dynamic pump is exposed to different gas pressures.

The hemoglobin concentration increases upon altitude ascent [29]. The initial increase is attributed to a shift of water out of the vascular system, with a decrease in the

plasma volume (PV) up to 20 % and a correlated decrease of blood volume (BV), confirmed by an increase in the concentration of plasma proteins [30]. Atrial natriuretic peptide, released by exposure to hypoxia is believed to be the underlying mechanism [31]. However, red cell volume (RCV) has individual variations with changes both increasing and decreasing between +20 % down to −13%. Iron supplementation in women has been shown to improve the hematocrit increase at high altitude [32]. Adaptation needs a control system that is simple to measure. Periodic trips alternating 3 months in Copenhagen with 1 month and a half in La Paz during the past 4 years has allowed me to observe and study the mechanisms of adaptation going up and down through changes in longitude (time lag), latitude (season lag) and altitude (oxygen lag).

Adaptation versus acclimatization

A biological adaptation is a physiological process or behavioral trait of an organism that has evolved over a short or long period of time by the process of natural selection such that it increases the expected long-term reproductive success of the organism. The term adaptation is also sometimes used as a synonym for natural selection, but most biologists discourage this usage. Organisms that are adapted to their environment are able to: obtain air, water, food and nutrients, cope with physical conditions such as temperature, light and heat, defend themselves from their natural enemies, reproduce and respond to changes around them.

Adaptations enable living organisms to cope with environmental stresses and pressures. One common form of physical adaptation is acclimatization. Acclimatization allows the organism to survive in a new environment.

Acclimatization is defined as: The physiological adaptation of an animal or plant to changes in climate or environment, such as light, temperature, or altitude.

Etymology: French *acclimater,* from *a-* (from Latin *ad-*) + *climat* climate.

The use of these two terms, adaptation and acclimatization creates some confusion. Geneticists prefer to use both terms in order to distinguish changes at the genetic level in adaptation from physiological changes in acclimatization. Furthermore, sports medicine physiologist use the term adaptation to refer to training with exercise [33]. Since acclimatization is a form of adaptation, it seems permissible to use the later as we have done over many years in high altitude studies. Medical terminology is not

always adequate according to the latin etymology. The word anemia should more adequately be called hypoemia, since there is no absolute loss of blood. But history and tradition remain. Consequently we prefer the use of the term adaptation and sometimes we are forced to refer to it as acclimatization, acclimate, or acclimation (from the www.freedictionary.com).

Effects of high altitude acclimatization

Altitude acclimatization and physiological adaptations to altitude, can have many acute (immediate) and chronic (long term) effects (Table 10).

Acute	*Chronic*
Hyperventilation	Regular ventilatory rate
Increase in heart rate	Normal cardiac output and heart frequency
Normal or slightly increased hematocrit	Normalized arterial blood pH (7.4)
Pulmonary hypertension	Increased hematocrit (Polycythemia)
Fluid loss	Increase in myoglobin
Slightly lowered stroke volume	Increase in mitochondria
	Increased capillary density
Increased NO output	Increase in aerobic enzyme concentration
	Increase in DPG
ODC right shift	Chronic pulmonary hypertension
	Right ventricular hyperthrophy
No immediate P50 change	
	Lower lactate production
Respiratory alkalosis	Compensatory alkali loss in urine
	Decrease in plasma volume
	Increase in RBC mass
	Higher concentration of capillaries in striated muscle tissue
	P-50 increased ODC left shift or normal.

Table 10. Acute and Chronic physiologic response to high altitude. This table is presented here as a comparative reference to Table 11.

The increase in hematocrit during high altitude adaptation

Adaptation is altitude and time dependent following the equation:

$$Adaptation = \frac{Time}{Altitude}$$

This is the simplified version analogous to Ohm´s Law. Each concept stands for:

High altitude adaptation factor = Time at altitude (days) / Altitude in kilometers (km).

For a fixed altitude the only variable that changes is Time {F}. Immediately upon ascent the organism senses the lowering of the oxygen partial pressure due to a diminished barometric pressure. The initial acute phase usually lasts up to 3 days, varying on the health conditions of the subject and if he has previously been exposed to high altitude, and learned how to "handle" it in complex macro-systemic and micro-systemic mechanisms. The first implies cardio-respiratory compensation and the later adaptation processes at the cellular and molecular level. The macro-systemic mechanisms attempt to raise the P_aO_2 to "sea level values" through increased ventilation and higher cardiac frequency, never being able to achieve it (see the discussion above on hyperventilation at high altitude), thereby reducing the P_aCO_2 and producing respiratory alkalosis, a negative action at the cellular level. The micro-systemic mechanisms return the pH to normal, through kidney function, reducing the negative symptoms of acute mountain sickness through adequate cellular function. However, a permanent and stable adaptation to 3600 m is only achieved at around 4 weeks when the hematocrit reaches the optimal level for the altitude. CMS subjects increase the hematocrit to levels above that of normal individuals due to cardio-pulmonary deficiencies as referred to above.
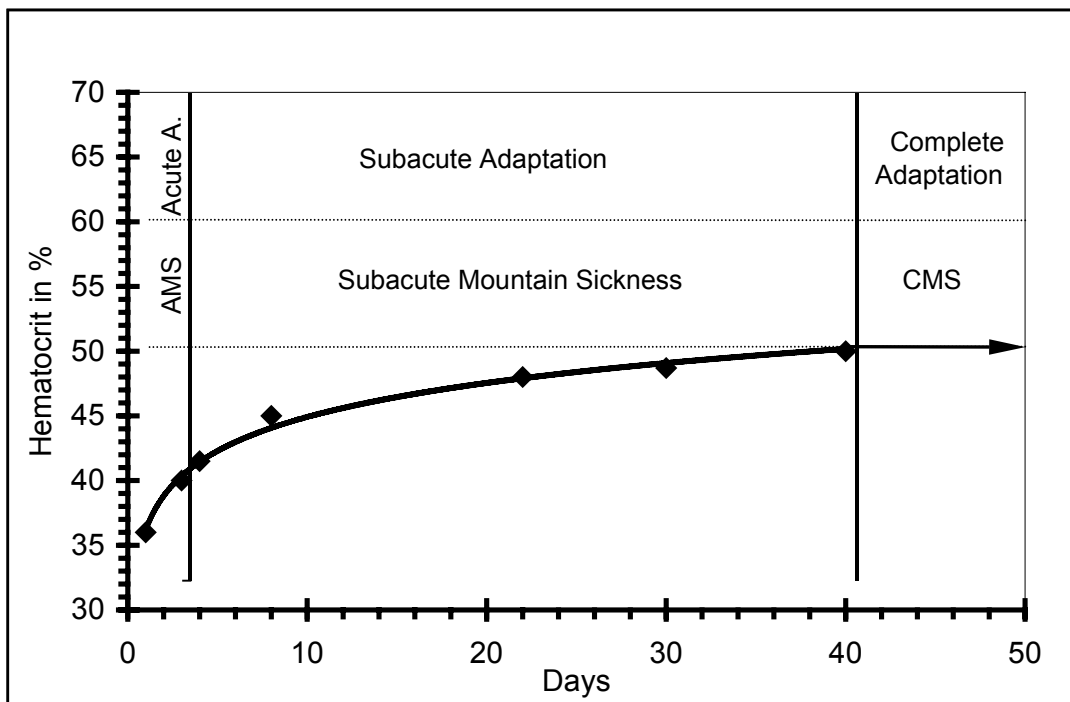
Fig. 11. The three hematocrit adaptation stages after ascent from sea level to high altitude.

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The three hematocrit stages after arrival to 3600 m: A) Acute adaptation (from the time of arrival up to 3 days) where acute mountain sickness can occur. B) Sub acute adaptation where subacute mountain sickness such as High Altitude Sub-acute Heart Disease occurs. C) Chronic Adaptation or complete hematologic adaptation, where CMS can be observed.

The hematocrit is taken as an indicator of adaptation, because the author feels that it is a simple method that is easy to perform. It is true that the most dramatic symptoms of AMS, HAPE or HACE are evident during the acute adaptation stage. And after these symptoms subside, it is believed that adaptation is achieved. However, one aspect that is overlooked is the capacity to perform physical activity. The shortness of breath upon low physical exercise is evident during all the sub-acute adaptation stage. Not so after the full adaptation or chronic stage is reached when the hematocrit reaches a plateau. This full adaptation stage may be questioned when studies pertaining to maximal exercise pulmonary gas exchange show that lowlanders do not reach highlanders levels even after 8 weeks at 4100 m of altitude [34]. It is difficult to compare the exercise performance in different altitude groups depending on their place of birth. The high altitude dwellers, can possibly handle the adaptation process in a more efficient way as this may compromise not only functional characteristics but also cerebral memory of adaptation handling. Some subjects exposed to hypoxia present neurogenic and humoral ventilatory responses (fast and slow), but others only humoral [35, 36].

The gradual right heart hypertrophy as a response to sustained pulmonary hypertension is evident in highlanders. This hypertrophy (just as exercise increase striated muscles in any physical activity) takes time to develop.

Complete hematocrit adaptation to 3500 m was achieved after 40 days (Fig. 11). Hence, using the adaptation formula above: 40 days/3.5 km = 11.4 days/km for the altitude of La Paz.

The high altitude adaptation factor is assumed to be a constant and thus applicable at any altitude. We can calculate the number of days necessary to achieve a complete adaptation to other fixed altitudes, when ascending from sea level.

Time at altitude (days) = 11.4 * Altitude in kilometers (km).

As a first example of the use of this high altitude adaptation factor, we can calculate

the length of time required to adapt to any altitude. For example order to adapt to 2500 m: 2.5 * 11.4 = 28.5 days are required. This is a practical use of the adaptation formula based on simplified methods following physics laws. It is true that more complex formulas could be searched but these have not been successful and only complicate the observations due to the existence of multiple variables that create confusion and false interpretation [37].

This investigation is useful in understanding space travel anemia. The astronauts in zero gravity suffer from anemia. The international space station has a normal 21 % oxygen concentration with a sea level barometric pressure.

High altitude residents suffer acute sea level sickness

The greater part of the 600,000 inhabitants of the plateau of El Alto (4000 m) in the city of La Paz, are born there and have no idea what sea level is. They don't know that they live in a hypoxic environment, and hence this is their natural and normal habitat, the world being mostly mountainous to them. If high altitude residents go to sea level, their organism is facing a "relative hyperoxia" and hence, an aggression of an abnormal environment (disregarding the other factors such as temperature and humidity, food, lodging and so on). The aggressor happens to be oxygen, a combustion accelerator. Automobiles well tuned for high altitude when taken to sea level loose strength and valves rattle. They need a retune, changing the gasoline enrichment and the explosion timing. Even tires need more air pressure.

In order to observe the ventilatory response on descent to sea level, in 1975, 6 young men born and living in La Paz (3600 M), were taken to Puerto Villarroel (500 m above sea level), a small tropical town in Chapare, Bolivia . Ventilation was measured using a Wright Respirometer, the day after arrival, and the average decreased from 13128 ml/min (BTPS) the resting value in La Paz to 2300 ml/min (BTPS). Soldier residents in the same location had an average ventilation of 4063 ml/min (BTPS). One of the high altitude subjects decreased his ventilation to such a degree that the Wright Respirometer was unable to measure, forcing us to check if it was in working condition.

This big decrease in ventilation is probably a defense mechanism for a hyperoxic environment, that the body assumes is toxic at the cellular level. The adaptation mechanism acquired over long term high altitude residence, is essentially the high

hematocrit, The high altitude normal adaptive erythrocythemia would in the presence of excess oxygen, increase the oxygen content of blood and produce hyperoxemia. Resultant hypoventilation, in turn diminishes water loss and gives rise to water retention and is particularly evident to people suffering from inadequate adaptation to sea level. High altitude residents that go to sea level, often feel their shoes are tight. This due to edema during the first days in some and persisting several days in others, particularly if kidney function is not 100 % effective. Furthermore, some feel drowsy, tired and sleepy, for a few days, others complain of headaches. Urine carries urobilinogen and stools tend to be darker due to iron loss. Upon descent, the circulation in the retina has been shown to increase through a vessel dilatation (primarily on the venous side) as reported by preliminary data in a study currently performed by Michael Larsen, Peter Kofoed and the author at Glostrup Hospital on 15 Bolivian students that arrived from the city of La Paz 3510 m to Copenhagen for a two and a half month stay. As the hematocrit decreases, in the adaptation process, the blood flow in the retina increases at sea level. This is probably a natural compensation for a diminished oxygen carrying capacity in the relatively reduced hematocrit, after over 1 month of residence at sea level.

Furthermore, on immediate descent of CMS patients there is bright red color in the cheeks, simulating the face of the Pink Puffer but without the shortness of breath. The full oxygen saturation of a blood with a very high hematocrit is the explanation. As the hematocrit decreases, the color of the skin changes to become more pale along with the conjunctivae and the mucosa.

Effects of low Altitude acclimatization (for highlanders)

Low altitude physiological acclimatization and adaptations, can have acute (immediate) and chronic (long term) effects (Table 11). Again the acute stage is limited generally to 3 days. The full hematocrit adaptation from the city of La Paz to sea level takes between 18 and 23 days **{F}.** Future research should be oriented to further physiologic observation of the neurological response time of reflexes, nuclear magnetic resonance in search of mild cerebral edema, kidney function, pulmonary artery pressure, reduction time of right ventricular hypertrophy through echocardiography and metabolic changes.

ACUTE	CHRONIC
"relative hyperoxia lag"	
Hypoventilation	Anemia*
Excessive somnolence	Somnolence
Lower limb edema	Gradual increase of fatigue if sedentary
Diminished urine output	
Urobilinogen	Pale fascies
Dark stools due to iron loss	Reduction in retinal blood flow
Diminished reflexes	Normal sea level ventilation
Inadequate coordination of fine movements	Normalized arterial blood pH (7.4)
Pink fascies (a result of an oversaturated high hematocrit in CMS)	Normal R
	Normal PAP
Respiratory acidosis	
Increased oxygen consumption VO_2	
Normalized R	

Table 11. Acute and Chronic physiologic response of highlander's adaptation to sea level. *The anemia is relative to high altitude but an overshoot below normal sea level values is possible.

Bloodletting

Bloodletting *(venosection or phlebotomy)* increases cardiac and respiratory frequency and this is interpreted as being favorable for patients with polyerythrocythemia. Upon arriving to high altitude there is evident shortness of breath on medium exercise, in relation to the same amount of exercise at sea level, prior to departure. This "shortness of breath" gradually disappears with adaptation and is apparently closely related to the hematocrit level {F}. Conversely, a patient that had his polyerythrocythemia reduced through the use of a hemolytic drug Phenylhidrazine (WHO proscribed by law), presented an intense cyanosis following a regular USAFM exercise protocol, remaining with a great oxygen debt [26]. This can be interpreted as insufficient oxygen "transporters" in a patient that had lung disease and compensatory polyerythrocythemia.

The author and Gustavo Zubieta-Castillo (Sr.) oppose bloodletting in CMS patients at high altitude, as it reduces the oxygen carrying capacity of the human organism that has reached that level through a process of adaptation that is most efficient [38]. Bloodletting increases respiratory and cardiac frequency, local muscular blood flow and vascular conductance. This is an unstable condition. The organism will re-initiate

the adaptation process towards the most energy efficient state **{D}**. Bloodletting, actually reduces the altitude of residence and the subject has to once again adapt to the current altitude.

Muscular local blood flow to the muscle and vascular conductance increased when Hb was reduced [39]. This shows yet another mechanism to improve oxygenation, which probably consumes more energy as compared to solely the hemoglobin increase.

With further understanding of the adaptation time lapses for high altitude, residents going to sea level (where neocytolisis along with no renewed red cell production is encountered **{F})**, it would seem suitable that bloodletting be performed. This facilitates the adaptation to relative oxygen rich environments, but only in healthy high altitude residents going to sea level where they will remain at least 20 days (provided they come from 3600 m of altitude).

Bloodletting for space travel

Astronauts in the micro-gravity environment of space suffer many changes such as loss of body weight, orthostatic intolerance, hemo-dynamic changes, fluid shift to the head (explained by the section on circulation in space above), loss of exercise capacity, loss of bone calcium, loss of muscle nitrogen, muscle atrophy and anemia [40]. However, the anemia is not fully understood, but neocytolisis has been described as the underlying mechanism [41, 42]. The adaptation to micro-gravity involves less use of muscle work and changes in ventilation perfusion at lung level that the organism finds convenient to reduce the hematocrit following the least energy expenditure described in **{D}**. The knowledge and understanding of polycythemia and anemia resulting from altitude changes in the present study, allows for a logical proposal to bloodletting of astronauts when going into space. The logic is that they would economize energy avoiding the destructive phase of adaptation. However, upon return to sea level, re-infusion of the phlebotomized blood could return the hematocrit to normal levels. Erythropoyetine administration is also a possibility but artificial and more complicated.

Hypoxic environment in the space vehicles

Original space flights were in a pure oxygen environment and one third the sea level pressure until serious fire accidents were encountered. Currently, the cabin pressure is normal sea level pressure at 760 Torr with 20 % oxygen and 80 % nitrogen [43].

An alternative to the complication of anemia would be to reduce the ambient oxygen tension within space vehicles, down to 2/3 the sea level pressure, in order to maintain a hypoxic stimulus and sustain the number of red blood cells for re-entry to Earth. Furthermore, the weightlessness space conditions require less oxygen consumption as there is less muscular use and hence tolerance to hypoxia can be increased. Likewise the **Extravehicular Mobility Unit** could benefit from a lower oxygen tension, less pressure difference with the space capsule and additionally more autonomy. The return to the hyperoxic environment of sea level, would ease adaptation, as there would have been no reduction of the hematocrit.

CONCLUSIONS

Chapter A. This project focused on the acid-base correction of critical care patients at high altitude, post-surgery, diabetes, cardiac disease, pulmonary embolism and others. Some of these patients can also suffer Chronic Mountain Sickness (CMS). Three tables were developed, based on the Siggaard-Andersen nomogram that allow for rapid interpretation of acid-base correction factors developed for high altitude habitats. Each nomogram is specific to each altitude: 2000 to 2999, 3000 to 3999 and 4000 to 5000 m.

Chapter B. This article carries essential advice on high altitude diving tables. The tables apply the physics of pressure differences to all variables, thereby making them the most precise for diving sports at high altitude lakes. The tables are evaluated at the Naval Diving School at the Titicaca lake, Bolivia.

Chapter C. CMS is defined as polyerythrocythemia with underlying disease. Polyerythrocythemia is defined as a too high relative blood cell volume (ie. Hematocrit value in %) measured with a centrifuge. Pulse oximetry during breath-holding in normal residents at high altitude (3510 m) shows a typical graph pattern. Following a deep inspiration to total lung capacity and subsequent breath-holding, a fall in oxyhemoglobin saturation (SaO_2) is observed at around 16 sec. The down-pointed peak in SaO_2 corresponds to the blood circulation time from the alveoli to the finger, where the pulse oximeter probe is placed. In the normal group all altitude residents have a hematocrit value below 58 %, and in the CMS group all had a value above 58 %. No significant difference was found circulation time between these two groups. Although the viscosity of blood is greater in the CMS group since viscosity increases with an increasing hematocrit value, it does not slow down circulation time in this study.

Chapter D. Chronic Mountain Sickness (CMS) patients often hypoventilate. Low saturation in CMS is typically related to hypoventilation. However, this report shows - through an indirect analysis that hypoventilation at rest is an energy saving mechanism of the pneumo-dynamic and hemo-dynamic pumps. Increased ventilation

would achieve an unnecessary high SaO$_2$ at rest. Polyerythrocythemia with low ventilation at rest is the mechanism through which these patients have a reserve of oxygen transport for exercise. Hypoventilation found in CMS patients is probably a consequence of the disorder – hardly the cause of polyerythrocythemia.

Chapter E. The High Altitude Pathology Institute "Clinica IPPA" database in La Paz, Bolivia, has been reviewed in order to study and analyze the incidence and diagnosis of polyerythrocythemia. Among 1823 hemograms performed, 240 had a hematocrit value above 58% - the threshold level established as normal for 3600 m of altitude. This is the basis for the definition of polyerythrocythemia as a disorder with a hematocrit above 58 %. CMS, is shown to be an adaptation of the blood transport system to a deficient organ function due to diverse disease processes; the adaptation aimed at sustaining normoxia at the cellular level in the hypoxic environment at high altitude.

Chapter F. High altitude adaptation is defined as having three time stages: A) Acute, first 72 hours, where acute mountain sickness can occur; B) Sub-acute, from 72 hours until the slope of increase of the hematocrit value with time is zero; here mountain sickness can occur as high altitude subacute heart disease and C) Chronic, where the hematocrit level is constant and the healthy high altitude residents achieve their optimal hematocrit. In the chronic stage patients with chronic mountain sicknesss (CMS or polyerythrocythemia) increase their hematocrit values to levels above that of normal individuals at the same altitude.

High altitude adaptation is altitude and time dependent following the simplified equation:

$$Adaptation = \frac{Time}{Altitude}$$

Where each concepts stands for:

High altitude adaptation factor = Time at altitude (days) / Altitude in kilometers (km).

A complete and optimal hematocrit adaptation is only achieved at around 40 days for a subject going from sea level to 3510 m at the capital city of La Paz, Bolivia. The time in days required to achieve complete hematological adaptation to any altitude, ascending

from sea level, can be calculated by multiplying the adaptation factor 11.4 with the altitude measured in km.

Adaptation takes place not only going to high altitude, as generally accepted, but also going down to sea level. Going from high altitude in La Paz to sea level in Copenhagen the hematocrit response is a fall over 18 to 23 days. Likewise, astronauts develop anemia in micro-gravity because they are exposed to excess oxygen for their muscular oxygen requirement, in a space vehicle sea level pressure (760 Torr) and a breathing mixture of 20 % oxygen and 80 % nitrogen. In order to preserve the hematocrit value for re-entry, bloodletting prior to space travel and re-infusion upon return to Earth is proposed. Alternatively, a hypoxic environment within space vehicles can save transportation energy yet be physiologic.

A practical test that allows for adequate and complete hematological altitude adaptation has been developed through measurements of the hematocrit value - a simple yet effective method.

The author's residence in Copenhagen during the past four years has allowed a productive and critical evaluation process, where high altitude medical physiology has been analyzed, compared and related to sea level physiology.

CONCLUSIONS / SUMMARY in Danish

Kapitel A. Dette projekt fokuserede på syre-base korrektion af alvorligt syge patienter i bjergegne, post-kirurgi, diabetes, hjertesygdom, lunge-emboli og andet. Nogle af disse patienter lider af kronisk bjergsyge ("Chronic Mountain Sickness", CMS). Tre tabeller blev udviklet baseret på Siggaard-Andersens nomogram, som yder hurtig tolkning af syre-base korrektion for patienter ved højde klima. Hvert nomogram er specifikt for højderne: 2000 - 2999, 3000 - 3999 og 4000 - 5000 m.

Kapitel B. Denne rapport rummer væsentligt nyt om dykke- tabeller for højdeklima. Tabellerne anvender de fysiske trykforskelles påvirkning af alle variable, hvilket gør dem til de mest præcise for sportsdykning i bjergsøer. Tabellerne bliver for øjeblikket afprøvet ved "Naval Diving School", Titicaca søen, Bolivia.

Kapitel C.

Sygdommen CMS er defineret som polyerythrocythemia med underliggende sygdom. Polyerythrocythemia er defineret som et for højt relativt blod-celle-volumen (ie. Hæmatokrit-værdi i %) og måles med centrifuge. Puls oximetri under vejr-holdning af normale bjergboere (3510 m) viser et typisk grafisk mønster. Efter en dyb inspiration til total lunge kapacitet og vejrholdning observeres et fald i oxyhemoglobin saturationen (SaO$_2$) efter ca 16 sec. Den nedad pegende spids i SaO$_2$ korresponderer til blodets circulations-tid fra alveoli til fingeren, hvor puls-oximeter detektoren er placeret. I den normale gruppe havde alle bjergboere en hæmatokrit-værdi under 58%, og i CMS-gruppen havde alle en værdi over 58%.

Ingen signifikant forskel blev fundet mellem circulations-tiden for normale og en gruppe af CMS patienter. Skønt blodets viskositet er større i CMS gruppen, da viskositeten stiger med stigende hematokrit-værdi, sænkes circulations-tiden ikke i dette materiale.

Kapitel D.

"Chronic Mountain Sickness"(CMS) patienter hypoventilerer ofte. Lav saturation i CMS henføres sædvanligvis til hypoventilation.

Imidlertid viser denne rapport – gennem en indirekte analyses af ventilation og oxygen saturation under arbejde - at hypoventilation i hvile er en energi-besparende mekanisme i de pneumo-dynamiske og hemo-dynamiske pumper. Øget ventilation ville medføre en unødvendig høj SaO_2 i hvile. Polyerythrocythemia med lav ventilation i hvile er mekanismen, hvorved disse patienter får en reserve af oxygen-transport for arbejde. Hypoventilation fundet hos CMS patienter er sikkert en konsekvens af sygdommen - næppe årsagen til polyerythrocythemia.

Kapitel E.

The High Altitude Pathology Institute´s ("Clinica IPPA") database i La Paz, Bolivia, er blevet studeret og analyseret med henblik på incidens og diagnose af polyerythrocythemia. Blandt 1823 hemogrammer, havde 240 en hematokrit-værdi over 58% - tærskel- niveauet etableret som normalt for 3600 m i La Paz. Dette er basis for definitionen af polyerythrocythemia som en sygdom med hematokrit-værdi over 58%.

CMS vises at være en adaptation af blodets transport system til en defekt organ funktion baseret på diverse sygdoms-processer; adaptationen søger at opnå normoxia på celle-niveau i de hypoxiske omgivelser ved højde-klima.

Kapitel F. Højde- adaptation er defineret i 3 tidsmæssige stadier: A) Akut, de

første 72 timer, hvor akut bjergsyge kan opstå; B) Subakut, fra 72 timer ind til hældningskoeffecienten for stigning af hematokrit-værdien med tid er nul; her kan højdesyge optræde som subakut hjertesygdom; og C) Kronisk, hvor hematokrit-niveauet er konstant og den sunde højde-beboer har sin optimale hematokrit-værdi. I det kroniske stadium øger patienter med polyerythrocythemia deres hematokrit-værdier til et niveau, der overstiger normale individers ved samme højde.

Højde- adaptation er højde- og tids- afhængig som beskrevet i følgende simplificerede ligning:

$$Adaptation = \frac{Tid}{Højde}$$

Hvor hvert begreb står for:

High altitude adaptation factor = Tid (dage) / Højde i kilometer (km).

En komplet og optimal hematokrit- adaptation nås først efter ca 40 dage for en person, der rejser fra hav-niveau til 3510 m i hovedstaden, La Paz, Bolivia. Tidsperioden i dage nødvendig for komplet hematologisk adaptation til enhver højde udgående fra havniveau kan beregnes ved at multiplicere adaptations- faktor 11.4 med højden målt i km.

Adaptation finder sted ikke kun ved rejser til bjergegne (som det er alment accepteret), men også ved rejser fra højde til hav-niveau. Rejser man fra højden i La Paz til havniveau i København, er hematokrit- responset et fald over 18 til 23 dage. Ligeledes vil astronauter udvikle anæmi under microgravitet, fordi de er udsat for overskud af oxygen til deres beskedne oxygen-krav i et rumfartøj med havniveau tryk (760 Torr) og en gas-blanding af 20% oxygen i 80% nitrogen. For at bevare hematokrit-værdien, foreslås åreladning før rumrejser og re-infusion ved tilbagekomsten til jorden. Alternativt kan et lettere hypoxisk miljø i rumfartøjet spare transport-energi og alligevel være fysiologisk.

En praktisk måling af adekvat og komplet hematologisk højde- adaptation er blevet udviklet gennem måling af hematokrit-værdien - en simpel men effektiv metode.

Forfatterens ophold i København i de forløbne 4 år har muliggjort en produktiv og kritisk vurderende proces, hvor medicinsk fysiologi fra højdeklima blev analyseret, sammenlignet og relateret til hav-niveau fysiologi.

SYMBOLS AND UNITS

In the American continent, the pressure unit used is mmHg. In Europe its equivalent is the Torr. 1 mmHg = 1 Torr. The Torr units are also converted to *kPa* shown in italics within brackets.

A	=	Alveolar gas
a	=	arterial
AMS	=	Acute Mountain Sickness
ATPS	=	ambient temperature, pressure, saturated with water vapour

B:		
BB	=	buffer base
BD	=	base deficit
BE	=	base excess
BH	=	Breath holding
BHt	=	Breath holding time
BMR	=	basal metabolic rate
BSA	=	body surface area
BTPS	=	body temperature and ambient pressure, saturated with water vapour

C:		
C	=	concentration of gas in blood. Squared brackets around a substance also denote concentration
CMS	=	Chronic Mountain Sickness
CNS	=	central nervous system
COLD	=	chronic obstructive lung disease

D:		
D	=	diffusion capacity
2,3-DPG	=	diphosphoglycerate

E:		
E	=	Expired

ECG	=	electrocardiogram
ECF	=	extracellular fluid
ECV	=	extracellular fluid volume
EEG	=	electroencephalogram
ERV	=	expiratory reserve volume
ESV	=	end systolic volume
ETCO$_2$	=	End tidal carbon dioxide tension
ETO$_2$	=	End tidal oxygen tension

F:		
F	=	fraction of gas in dry air or force
FRC	=	functional residual capacity (= RV + ERV)

H:		
HACE	=	High altitude cerebral edema
HAPE	=	High altitude pulmonary edema
Hb	=	haemoglobin
Ht	=	hematocrit
HR	=	Heart rate

I:		
I	=	inspired gas
ICV	=	intracellular fluid volume
IPPA	=	High Altitude Pathology Institute (Instituto de Patologia en la Altura) www.altitudeclinic.com
IRV	=	inspiratory reserve volume
ISF	=	intenstitial fluid (tissue fluid)
i.v.	=	intravenous
K:		
K	=	Kelvin degrees of temperature
kPa	=	Kilo Pascal pressure units

M:

MAP	=	mean arterial pressure/mean aortic pressure
MR	=	metabolic rate
min	=	minute

N:

NBB	=	normal buffer base/neutral brush border
NO	=	nitric oxide

P:

P	=	partial pressure of gas in air or blood
PAP	=	Pulmonary artery pressure
PCV	=	packed cell volume
PEF	=	peak expiratory flow
P_B	=	barometric pressure
P_{IO2}	=	partial pressure of O_2 in inspired air in trachea
P_ACO_2	=	Partial pressure of CO_2 in alveolar gas
P_AO_2	=	Partial pressure of O_2 in alverolar gas
P_aCO_2	=	Partial pressure of CO_2 in arterial blood
P_aO_2	=	partial pressure of O_2 in arterial blood

R:

R	=	Gas constant
RBC	=	Red blood cells
RQ	=	respiratory quotient (metabolic)
R	=	Ventilatory exchange ratio (=VCO_2/ VO_2)
RV	=	residual volume

S:

S	=	saturation in blood
sec	=	seconds
SaO_2	=	Arterial oxyhemoglobin saturation

SATmax	=	Maximal SaO_2 during breath holding
SATmin	=	Minimal SaO_2 during breath holding
SB	=	standard bicarbonate concentration
STPD	=	standard temperature and pressure, dry (0^oC, 760 Torr)
sv	=	stroke volume

T:		
T	=	*t*ension (force)
T	=	Temperature
t	=	time
TBV	=	total blood volume
TLC	=	total lung capacity (=RV+VC)
Torr	=	Torricelli pressure units (1 mmHg = 1 Torr at 0°C)
TV	=	tidal volume

V:		
V	=	volume
v	=	venous
V^o_A	=	expired alveolar ventilation ($l\ min^{-1}$)
V_E	=	Expired ventilation (l/min^{-1})
VC	=	vital capacity (=IRV+TV+ERV)
V_D	=	dead space volume
VO_2	=	Oxygen consumption
VCO_2	=	Carbon dioxide production
W	=	external work (with pressure-volume work zero)

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