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Tolerance to hypoxia

People living at sea level have poor tolerance to hypoxia. In striking contrast, humans experiencing hypoxia at high altitude live very well. How is it possible for man to tolerate extreme hypoxia at high altitude? In this article we propose a hypothesis that potentially explains the tolerance to hypoxia at high altitude. Close examination of values of hemoglobin and $PaCO_2$ for an altitude of 3510 m demonstrate that an increase in hemoglobin (Hb) and a decrease in arterial carbon dioxide tension (PaCO2) are two essential changes that occur on high altitude exposure. We propose a formula :

$$Tolerance\ to\ Hypoxia = \frac{Hb}{PaCO2} * 3.01$$

and present evidence that the relationship between Hb and $PaCO_2$ explains the tolerance to hypoxia at high altitude.

INTRODUCTION

People living at high altitude in the city of La Paz 3600m, with diverse types of lung disease exhibit extremely low arterial oxygen tensions (PaO_2). Their arterial oxygen partial pressure of oxygen (PaO_2) can range between 30 and 40 mmHg (Normal values: PaO_2 = 60 ± 2 mmHg, arterial carbon dioxide tension ($PaCO_2$) = 30 ± 2 mmHg and pH = 7.40 ± 0.02, Oxyhemoglobin saturation by pulse oximetry (SpO_2) are 91% ± 1%). The SpO2 oscillates with irregular breathing and taking a deep breath can reach even 98% (like at sea level) provided there is a normal pulmonary function, as previously described [1]. This results from a decrease of the ratio between pulmonary dead space and alveolar ventilation. When the medical reports from people in La Paz were shown to physicians at sea level, they often asked: "Were these people conscious?" This clearly shows that people at sea level can not tolerate such low arterial PO2. A patient presenting a PaO2 below 60 mmHg at the sea level is usually sent to an intensive care unit, as his life could be in peril.

Around one out of four subjects, arriving to La Paz, have some form of Acute Mountain Sickness. Some can present extreme hypoxia. The pathologies associated with extreme hypoxia are: pneumonia upon ascent, pulmonary thrombo-embolism, high altitude pulmonary edema, high altitude cerebral edema and several others.

For example, a 25 years old Frenchman climbed Huayna Potosi at 6088m two days after arriving to La Paz 3600 m, from Paris. On the way down he felt very short of breath and unable to sleep overnight. He came to consultation as an ambulatory patient. Blood gas analyses revealed a PaO_2 = 35 mmHg, $PaCO_2$ = 29 mmHg and a pH = 7.53. This was clearly a case of severe hypoxia with respiratory alkalosis and High Altitude Pulmonary Edema (HAPE). Would he have been alive if at sea level? The purpose of this article is to present potential mechanisms underlying adaptation at high altitude.

High Altitude Adaptation Index.

Adaptation to high altitude is dependent on altitude and the duration of sojourn (time). The relation between altitude and duration as a function of adaptation to altitude can be expressed as the following equation [2]:

$$Adaptation\ to\ high\ altitude = \frac{time}{altitude},$$

where time at altitude is in days and altitude is in kilometers (km).

A complete and optimal hematocrit and hemoglobin adaptation is only achieved at around 40 days for a subject going from sea

level to 3,510m in La Paz. It has been estimated that the time in days required to achieve full adaptation to any altitude, ascending from sea level, can be calculated by multiplying the adaptation factor of 11.4 times the altitude in kilometers. This factor was obtained based on the time of full hematological adaptation to 3510m when arriving from sea level. Conversely, descending from high altitude in La Paz to sea level in Copenhagen (35 m above sea level), the hematocrit response is a linear fall over 18 to 23 days [2,4].

Importance of Arterial PCO_2.

The other variable that can allow for the tolerance to extremely low PaO_2 values is the low $PaCO_2$ values at high altitude relative to sea level. As is well known, oxygen and carbon dioxide partial pressures descend as the altitude increases. In Fig 1, the distribution of $PaCO_2$ in arterial blood gases at the city of La Paz (3510m) shows clearly that the average is around 30 mmHg. Furthermore, it can be noted that the highest $PaCO_2$ reached is 72 mmHg in an isolated critically terminally ill patient. The great majority hardly reach a $PaCO_2$ above 53 mmHg. Fig 2. shows the relationship between $PaCO_2$ and altitude. At high altitude, high $PaCO_2$ levels as those seen at sea level are not compatible with life.

Hypocapnia and the ensuing alkaline pH during high altitude exposure shifts the oxygen dissociation curve to the left, allowing more capture and transport of oxygen. The Acid-Base balance in the human body is calculated by the Van Slyke equation based on sea level measurements. The maintenance of blood pH within a fairly strict range at around pH 7.4, with due consideration of the effect of hyperventilation, is essential for cellular function at any altitude. This is

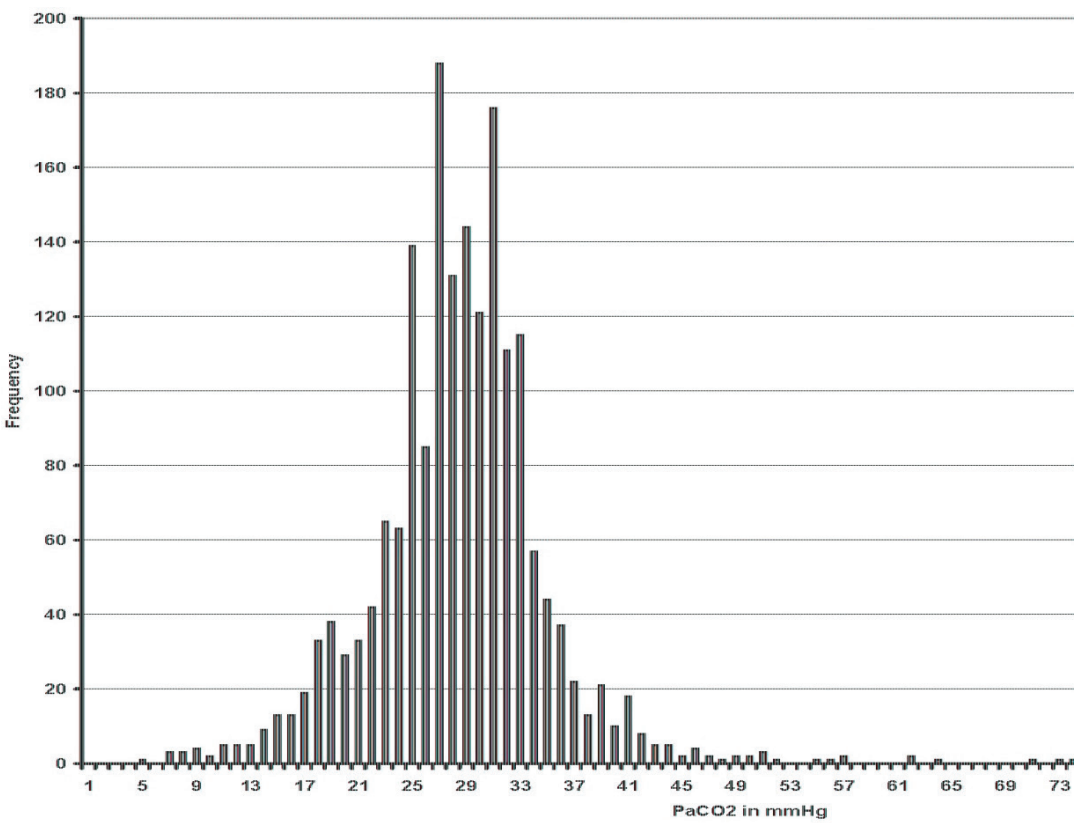

Fig 1. Distribution curve of the P_aCO_2 in 1865 patients including both sexes at 3510 m [4]

because various chemical processes occurring in the body, e.g., those involving proteins and enzymes, are pH-dependent. With chronic low levels of the arterial carbon dioxide partial pressure ($PaCO_2$), the acid-base balance begins to change. Mountaineering physiologists, employed the sea level equation for estimations of acid-base balance in high altitude subjects. without critical appraisal of its validity. The pH effects are inextricably linked critically with hemoglobin and oxygen status that can be crucial at high altitudes. Therefore, for a more precise recalculation of the 'Titratable Hydrogen Ion Difference' (THID), that should use a Hb and HCO_3^- values for a particular altitude, we have derived our modified Van Slyke equation: THID in eECF = (1 - [Hb] / 43) x ($\Delta[HCO_3^-]$ + ßB x (pH-7.4) [5]. An adequate Acid-Base Balance is probably the fundamental metabolic adaptation that allows for mountaineers to tolerate extreme hypoxia and even reach the summit of Mt. Everest [26].

Hemoglobin.

Hemoglobin increases with altitude as shown in Fig.3. This data is from permanent residents at different altitude cities or towns. From the trend curve one can attempt to calculate the optimal hemoglobin value upon the summit of Mt. Everest, if complete adaptation could be achieved.

The Hb values for residents at 2500m, 3600m and 4100m for the Bolivia cities of Cochabamba, La Paz and El Alto, respectively are the normal values in our labs. The Hb values of residents at 4355m, 4660m and 5500m were obtained from bibliographic data [25. 26].

It becomes evident from the observation of a longer breath holding time at high altitude in polyerythrocythemia (PEC) patients with low PaO_2, compared to normal high altitude subjects, that they are more tolerant to hypoxia [6]. The greater oxygen content of blood in PEC, as a result of the increase in Hb, allows for a better tolerance to hypoxia. This is also demonstrated by plotting the oxygen consumption of yeast cells against time after full saturation with 100% oxygen [7]. The resulting oxygen dissociation curve of PEC patients has a much broader oxygen content area when exposed to 100% oxygen as shown in Fig 4.

The above observations on $PaCO_2$ and Hb prompted us to propose the hypothesis that the Tolerance to Hypoxia (TH) formula can be defined as:

$$Tolerance\ to\ Hypoxia = \frac{Hb}{PaCO2} * 3.01$$

The constant factor is obtained by using the Hb and $PaCO_2$ normal sea level values and equating to 1. This way, the tolerance to hypoxia

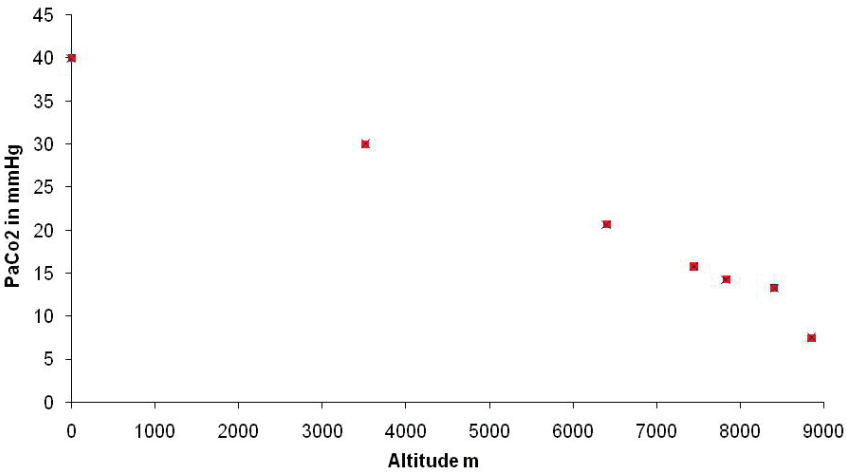

Fig. 2 $PaCO_2$, in its relationship to altitude from data obtained at different altitude sites around the world [4]. At 8400 the PaCO2 is from [8]. The PaCO2 value at 8848 m is obtained from an estimated value [24]

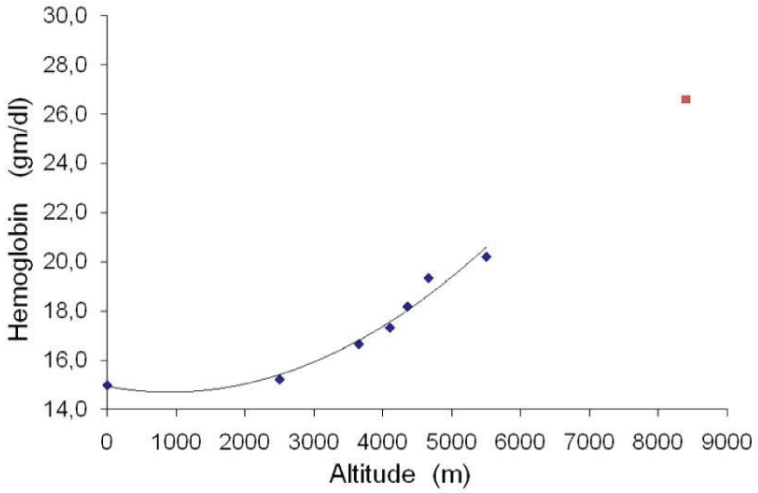

Fig. 3. Hemoglobin values found at different altitudes in resident populations. The red dot is the calculated Hb from the trend equation: $Hb = 2E\text{-}07x^2 - 0{,}0003x + 14, 45$ with an $R = 0.9718$

for comparison purposes becomes 1 at sea level. From then on the values at different altitudes are calculated as shown in table 1.

In this table the Mt. Everest value is obtained from the paper by Grocott et.al[8] taken on the Cauldwell Expedition to Mt. Everest. Blood gases were measured at 8400m and the Hb values were obtained from 4 subjects averaging the measurements at 5300m before and after the climb to the summit. This value should have been measured at higher altitudes and without averaging before and after climb as it reduces the true value. Only the value obtained after the ascent could be a more appropriate measure. However since the subjects were climbing and changing altitudes and the body has a fixed production of red blood cells, there was not enough time for full hematologic adaptation[2]. An optimal hemoglobin value for the summit of Everest is not known. However, based on Fig 2, it is estimated that the optimal hemoglobin for oxygen transport at the summit of Mt. Everest would be around 26 gm%. This roughly corresponds to a hematocrit of 78%. In our medical practice, we have seen patients with PEC even above 80%[9-11]. Hence, although it seems that these are surprising high values, they are within biological limits for humans. It is noteworthy to mention that the maximum possible increase of Hb is double the sea level value, hence the tolerance to hypoxia formula is also is ruled by this.

Our formula links Hb with $PaCO_2$, the hematological and respiratory (including acid-base parameter) responses to hypoxia, respectively. These biological responses to hypoxia in humans will also apply to animals. This is clearly demonstrated when a normal average sea level Hb in males of 13.3 gm% rises to an average of 16.6 gm% in the city of La

Table 1. Tolerance to hypoxia calculated at different altitudes from the Hypoxia Tolerance formula. The values of Hb and PaCO2 obtained from [2, 8].

	Altitude in m	$Hb/PaCO_2$	HT
Sea Level	0	13/40 * 3.01	1
La Paz, Bolivia	3510	16.6/30 * 3.01	1.7
Mt. Everest	8842	21/13 * 3.01	4.86

Paz, Bolivia at 3510m of altitude, for example. The formula also includes the $PaCO_2$ where it is showing the hyperventilatory response to hypoxia. For example, a sea level normal $PaCO_2$ of 40 mmHg upon arrival to high altitude immediately is decreased to a $PaCO_2$ of 30 mmHg, again, in the city of La Paz (3510m). Although this is a tolerance to hypoxia formula, the PIO_2 is not included in the formula as it is directly related to the barometric pressure, as originally described by Paul Bert in 1878[12]. The Barometric Pressure, a physical atmospheric parameter is indirectly included with the $PaCO_2$ which is equal to the $FaCO_2$ * PB –PH_20.

Other factors of adaptation to hypoxia, such as HIF, VEGF, increase in the density of mitochondria, increase in capillary density, increase in pulmonary artery pressure, increase in heart rate and ventilatory rate, etc are not included in this formula, as they would be automatically linked to the two biologic factors included. Adaptation to hypoxia is complex but this formula uses two essential variables and in our criteria sufficient for the adequate interpretation on the concept.

Furthermore, upon initial ascent, the changes in the $PaCO_2$ are immediate, being linked to an increase in the heart rate and hyperventilation. However, as the hemoglobin gradually increases at high altitude, closely linked to the erythropoietin stimulus secondary to hypoxia, the cardio-respiratory initial responses also gradually decrease in search of a less energy consuming adaptation that allows for an efficient and effective energy-cost mechanism such as the increase in hemoglobin [13]. Noteworthy is the fact that the tolerance to hypoxia when first arriving to high altitude is not optimal until the hematocrit reaches its maximum level [2]. Hence it can be appreciated that the numerator is the factor that increases tolerance to hypoxia with time at high altitude. The denominator of the Tolerance to Hypoxia formula is fixed upon arrival to high altitude and will not change during the residence at the same altitude, provided the subject is healthy. So it is not

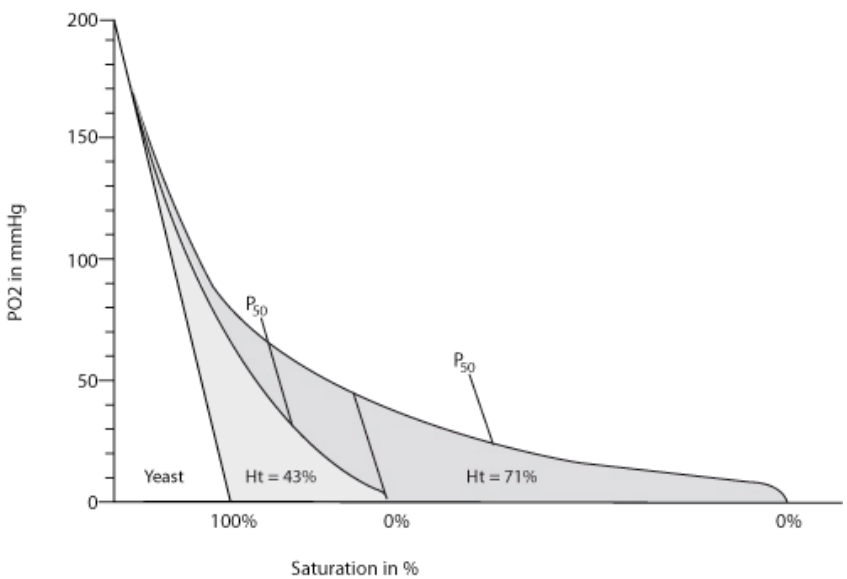

Fig 4. The oxyhemoglobin dissociation curve (ODC) of a normal high altitude resident in La Paz, Bolivia 3510m (Ht = 43%) as compared to a patient with polyerythrocythemia (Ht = 71%) using the Ryan Neville yeast cells oxygen consumption technique [7]. The ODCs can best be viewed by turning the graph 90° clockwise. The Yeast area (on the left) is the oxygen consumed by yeast cells alone. The Ht = 43% area (on the middle in light grey) corresponds to the oxygen content of a normal high altitude resident with a hematocrit of 43%. The Ht = 71% area (on the right in dark grey) plus the middle area, correspond to the total oxygen content in a polyerythrocythemic patient with a hematocrit of 71%

time dependant, but rather barometric pressure and hyperventilation dependant. The initial hyperventilation upon acute exposure to high altitude lowers the $PaCO_2$ however there are minor changes as time allows for the Hb increase and gradual reduction of hyperventilation.

On an autocritical side, tolerance to hypoxia cannot be oversimplified as it is very complex. In Drosophila flies it has been demonstrated that following long term exposure to hypoxia, adaptation through gene expression has allowed for survival even during several hours in anoxia [14]. For improving the tolerance to hypoxia, it has been found that Acetyl Salicylic Acid is neuroprotective against hypoxic hypoxia and chemical hypoxia and delays the decline of intracellular ATP content [15]. Nitrate can be converted to nitrite and nitric oxide, that can improve muscle efficiency and also dilate blood vessels allowing more O_2 to be delivered to active muscle [16]. The ability of cells to tolerate hypoxia is critical to their survival, but varies greatly among different cell types. Pulmonary arterial endothelial cells (PAEC) retain their viability and cellular integrity during hypoxic exposure, whereas renal tubular epithelial cells are extremely hypoxia sensitive and are rapidly and irreversibly damaged. The maintenance of high energy phosphates in hypoxic PAEC suggests that there exists tight regulation of ATP and GTP turnover in these cells and that preservation of these nucleotides may contribute to the tolerance of PAEC to acute and chronic hypoxia [17]. On exposure to hypoxia, biochemical behaviour of skeletal muscles was consistent with lowered reliance on glycolytic contributions to energy supply, thus improving the yield of ATP per mole of carbon fuel utilized. Using glucose in preference to fatty acids, heart adaptations also seemed to rely upon stoichiometric efficiency adjustments, improving the yield of ATP per mole of oxygen consumed [18]. Hemoglobin can also have evolutionary adjustments in Hb–O_2 affinity through alterations of the equilibrium constants of O_2 binding to deoxy- and oxyHb as shown in different vertebrates [19].

Finally, it is well known that in intensive care units (ICU) at sea level some people tolerate hypoxia better than others. This is not clearly understood, but this tolerance to hypoxia formula may contribute significantly. Some ICU could treat selected patients by increasing the Hb level, above the normal expected for sea level. This would increase their tolerance by increasing the numerator of the formula. Of course, this requires a most careful and suitable transfusion and paying attention to the coagulation factors in order to avoid complications. Another interesting possibility would be to use hypobaric chambers in the ICU, thereby reducing the barometric pressure, but of course maintaining the hyperoxia in ventilators. Such a procedure would decrease the $PaCO_2$, the denominator in the formula, further boosting tolerance to hypoxia. Following the same logic, an alternative would be to ventilate subjects trying to achieve a lower $PaCO_2$, but maintaining the pH efficiently. These hypothetical proposals obviously need to be fully and extensively studied before their practical application.

CONCLUSIONS

The importance of presenting this concept of higher tolerance to hypoxia based on the $PaCO_2$ value rather than on the PaO_2 value allows a further understanding of the blunted respiratory drive at high altitude originally observed by S. Lahiri [20]. The gaseous messengers in oxygen sensing have recently gained importance [21]. Focusing the attention not only on the oxygen levels but essentially on the CO_2 levels, can help better understand the observed phenomena. It is also possible that it could contribute in understanding ventilatory drive during hypoxia of the complex neuronal respiratory centers [22]. Nature is wise in allowing for the sustaining of life and giving advantages in hypoxia tolerance, the higher one goes. This new concept of greater tolerance to hypoxia at high altitude further contributes to the understanding of the hypothesis of the extraordinary adaptation of man to extreme hypoxia, including the summit of Mt. Everest [23].

ACKNOWLEDGEMENT:

To Nancy Zubieta, Luis Zubieta, Katia Ardaya and the support team of IPPA that have contributed and collaborated enthusiastically. To Ing. Armando De Urioste who contributed with the mathematical optimization of the formula. To Nanduri Prabhakar for the English correction suggestions and rearrangement of this manuscript.

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СТІЙКІСТЬ ДО ГІПОКСІЇ

Люди, що проживають на рівнині, мають низьку стійкість до гіпоксії. На противагу до цього, люди, що проживають на високогір'ї, почувають себе дуже добре. Як можливо переносити екстремальну гіпоксію на великих висотах? В цій статті ми пропонуємо гіпотезу, що потенційно пояснює стійкість до гіпоксії на висотах. Реєстрація величин концентрації гемоглобіну (Hb) та $PaCO_2$ на висоті 3510 м демонструє, що саме підвищення Hb та зниження $PaCO_2$ є двома суттєвими змінами, що мають місце при підйомі на висоту. Ми пропонуємо формулу: стійкість до гіпоксії = $Hb/PaCO_2 \times 3.01$ і приводимо докази, що залежність між Hb та PaCO2 пояснює стійкість до гіпоксії на висоті. Ключові слова: PaCO2, гемоглобін, високогір'я

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УСТОЙЧИВОСТЬ К ГИПОКСИИ

Люди, проживающие на равнине, имеют низкую устойчивость к гипоксии. В противоположность этому, люди, проживающие высоко в горах, чувствуют себя очень хорошо. Как можно переносить экстремальную гипоксию на больших высотах? В этой статье мы излагаем гипотезу, которая бъясняет устойчивость к гипоксии на высотах. Регистрация величин концентрации гемоглобина (Hb) и $PaCO_2$ на высоте 3510 м показывает, что именно повышение Hb и снижение $PaCO_2$ являются двумя существенными изменениями, которые имеют место при подъеме на высоту. Мы предлагаем формулу: устойчивость к гипоксии = $Hb/PaCO_2 \times 3.01$ и приводим доказательства, что зависимость между Hb и $PaCO_2$ объясняет устойчивость к гипоксии на высоте. Ключевые слова: $PaCO_2$, гемоглобин, высокогорье.

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