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Differences in Poikilocapnic vs Isocapnic Hypoxia in Healthy Adults

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Abstract

For calibration and determining the final accuracy of newly developed pulse oxygen saturation devices, oxygen saturation values measured by this device are paired with arterial blood samples during hypoxia. Arterial oxygen saturation is the golden reference to the tested pulse oximeter. The United States Food and Drug Administration and the International Organization for Standardization (ISO) 80601-2-61 (2026 and earlier) describe the guidelines for clinical studies with healthy volunteers for calibration and accuracy calculation of newly developed pulse oximeters based on photoplethysmography. Both poikilocapnic and isocapnic hypoxia are allowed and applied during open, non-randomised interventional studies to look for the accuracy of the test device.

During ISO 80601-2-61-based studies using the isocapnic approach, measured end-tidal CO_2 values guide the concentration of CO_2 that is added to inspiratory hypoxic gas mixtures via a face mask. This allows the end-tidal CO_2 level to be kept constant by changing the inspiratory CO_2. In contrast, during the poikilocapnic hypoxia approach, subjects breathe a hypoxic gas mixture without added CO_2, via face mask or in a normobaric hypoxia room. Consequently, subjects hyperventilate for hypoxic compensation resulting in hypocapnia. Both hypoxia protocols present advantages and disadvantages regarding arterial oxygen saturation reflection by pulse oximeters placed on skin during ISO 80601-2-61-guided studies.

This short review highlights assumed and proven differences between isocapnic or poikilocapnic human hypoxia experiments used for ISO 80601-2-61-guided hypoxia studies to determine final accuracy of a pulse oximeter test device.

Keywords: Poikilocapnic; Isocapnic Hypoxia; SpO_2; Oxygen; Hypocapnia

Introduction

For more than 50 years, pulse oxygen saturation (SpO_2) devices placed on the skin have been used to extend cardiopulmonary monitoring for patients. Later, thanks to decreased prices, miniaturisation, increased capacity to compute, or incorporation into consumer smartwatches, SpO_2 measurements are frequently used by the lay public. Pulse oximeters need to be closely linked to arterial O_2 pressure (PaO_2). Some pulse oximeters sold to the public do not accurately reflect arterial oxygen saturation (SaO_2), mainly in the lower ranges of viable SpO_2 [1,2], whereas in practice (para)medical workers depend on these inaccurate SpO_2 values.

Most pulse oximeters placed on the skin use light emitting diodes (LEDs) with wavelengths in the red (+/- 660 nm) or near-infrared spectrum (+/- 940 nm) for skin illumination. Sometimes daylight, lamp light or flash light by a smartphone are used as light sources. Green LED (+/- 560 nm) light can be used, but green light has a very low penetration into the skin and undergoes significant absorption by skin tissue [3]. Reflected or transmitted light is captured by light diodes (or a

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camera), resulting in captured photoplethysmographic signals. Reflected or absorbed light is highly, but not exclusively, dependent on the oxygenation status of hemoglobin in the red blood cells [4]. The amount of absorbed or reflected light is influenced by the tissue's blood volume, which changes during the cardiac cycle, the so-called alternating current. In addition, acute differences in the microcirculation of the skin capillaries and arterioles can influence absorption or scattering of the LED light illuminating the skin. SpO_2 devices have at least two LEDs that are alternatingly active, sometimes with a pause between. The captured light is electronically separated referring to the respective illumination of a particular LED. As such, cardiac cycle dependent waveforms are reflected and SpO_2 is calculated by an in-device algorithm. This algorithm is manufacturer-dependent and, in most cases, kept secret. Settings of LEDs in terms of duration and magnitude of emitted light are strongly manufacturer-dependent and are determined during pre-clinical observations.

According to the ISO and FDA recommendations, human subjects undergo hypoxia with SaO_2 or SpO_2 down to 70 %. There is a required evaluation of SpO_2 test devices (TD) in pre-clinical studies. These are crucial and are performed by the manufacturer in in-house or external laboratories, frequently using breath holding leading to rather limited oxygen desaturations or using phantom devices. These preclinical calibration and accuracy evaluations are followed by studies in healthy volunteers undergoing hypoxia, first non-invasively comparing TD results with an approved reference SpO_2 device, whereafter TD is compared to SaO_2 measured in arterial blood samples by a reference CO-oximeter to calculate the definite accuracy of the TD's SpO_2. Including healthy subjects, TD is tested during a feasibility and pivotal Investigational Device Exemption study for medical devices (here called: ISO-study). ISO-studies are interventional, open and non-randomized designed experiments for accuracy calculation of these Class IIa devices. Melanin, present in varying amounts in the skin, heavily absorbs light and determines skin tone. Effects of skin tone on the accuracy of TD is beyond the scope of this review.

In human life, hypoxia occurs in healthy subjects in altered environmental conditions (e.g. at high altitude, in a fire) or in diseased subjects under normal ambient conditions (e.g., respiratory diseases, heart failure, sleep apnea) or both. Hypoxia in experimental conditions might essentially differ in terms of progression of the induced inspiratory partial pressure of O_2 (PiO_2), positioning of the volunteer, exposed exercise, concomitant medication, gender, obesity, age, sleep, among other subject-independent factors such as changed death space. Hypoxia can be acute or chronic, continuous or intermittent, generalized or localized, hypo- or normobaric. Because both poikilocapnic (PH) and isocapnic hypoxia (IH) are allowed to be used for the ISO-studies, based on our experience with PH, we looked into the literature to discriminate both techniques in terms of cardiovascular and pulmonary physiology, bias-inducing conditions, influencing factors on SpO_2 measurements, accuracy, among others.

Throughout this overview, abbreviations used for (partial) pressures include gas pressure (P) followed by the name of the considered gas: inspiratory P (Pi), partial pressure of end-tidal CO_2 ($PetCO_2$), ambient or atmospheric P surrounding the volunteer (Pamb), and alveolar P (Palv). Air contains approximately 20,9 % of oxygen, whatever the altitude. Therefore, partial pressure of a gas compared to atmospheric P in gases is denoted in % avoiding more scientific terms as kPa or mmHg (Torr). PH stands for poikilocapnic hypoxia, and pH is used for the proton concentration in the blood that reflects its acidity or alkalinity.

Description of isocapnic hypoxia and poikilocapnic hypoxia techniques

Most hypoxia facilities for ISO-studies are clinical laboratories staffed by trained employees. ISO-studies recruit healthy volunteers, normally between 18 and 50 years old. Diseased volunteers, heavy smokers, subjects who are anemic or have abnormal hemoglobin or red blood cells, and subjects with low basal SpO_2 are excluded from these ISO-studies. All volunteers breathe spontaneously without mechanical support. Five stable $PambO_2$ plateaus are defined based on the reference SpO_2 device worn by the volunteer during both IH and PH: normal SpO_2 >97%, SpO_2 between 97-92; between 92-85, between 84-77 and between 77-70 %. Interindividual SpO_2 is known to vary during a particular oxygen concentration level, but also intra-individual SpO_2 variability is noted (see further). This implies that the PiO_2 is not pre-set in the ISO-study, but is adapted to the volunteer's SpO_2 measured by the reference SpO_2.

During IH, subjects wear a well-fitting face mask, connected to tubes, mostly with unidirectional valves. Gas mixtures contain nitrogen and oxygen. $PetCO_2$ is followed by mainstream or sidestream CO_2 monitors. $PiCO_2$ is increased to maintain or slightly exceed the pre-hypoxia $PetCO_2$ level, a technique called $PetCO_2$ clamping. Around 2% $PiCO_2$ is administered but the level is adapted during the ISO-studies using IH to maintain $PetCO_2$. Gas flows in the used system may significantly influence gas pressures, thus control of Pi in the mask seems necessary, but is ignored to report. Advantages of IH include shorter periods of hypoxemia for the subject, lower investment costs compared to a hypoxia room, coworkers not undergoing hypoxia, but theoretically more skilled coworkers ($N \geq 1$) near the subject are warranted. In general, due to the activity in the laboratory room surrounding the volunteers, subjects experience more external stimuli compared to PH. $PetCO_2$ needs to be measured which is not the case during PH in hypoxia rooms. During IH, the duration of plateaus of a particular hypoxia level takes about 15 minutes, immediately followed by a new level of hypoxia. Death space ventilation

is slightly higher in humans using a face mask, compared to non-masked ventilation by volunteers in a hypoxia room. Increased death space can result in increased $PaCO_2$-PetC02 gradients.

During PH, volunteers can receive a face mask with inspired gas mixtures only containing tracing amounts of CO_2, ranging between 0 and 0,04%. However, most PH studies use a hypoxia room with steadily decreasing oxygen levels to approximately 9,5 %. When using face masks, subjects undergoing PH feel discomfort due to sudden oxygen decrease with accompanying pronounced hypocapnia. In hypoxia rooms, several subjects can be measured simultaneously, in our center limited to 3 for a non-invasive ISO-study, and 2 for the invasive ISO-study. The room is inflated with 3% of oxygen created by a Vacuum Pressure Swing Absorption system. Continuous output of sensors for O_2, CO_2, Patm and humidity near the ceiling of the hypoxia room are recorded. The sensor for $PambO_2$ guides the generation of hypoxia in the room. As hypoxia rooms are almost hermetically closed, O_2 levels do not vary during the plateaus without 3 % O_2 injections. Variation of $PambO_2$ is thus avoided during these ISO-studies with PH.

Subjects breathe spontaneously in the room, with a slightly increased $PambCO_2$ level due to expired CO_2 by volunteers and coworkers in the room without immediate wash-out of CO_2 out of the room. A skilled nurse or an anesthesiologist has to accompany the volunteers during hypoxia. These coworkers can receive oxygen up to 1 L/min by a nasal tube, when needed, to keep their SpO_2 above 85%. Oxygen of 1L/min inflated into the room does not change the speed of decrease of $PambO_2$ of the room, the latter decreases exponentially from 21 % to 9,5 in about 82 minutes during the non-invasive part of the study. As inflated air contains 3 % of oxygen, the decrease of $PambO_2$ down to 9,5 % is grosso modo linear. PH seems a more physiological approach, as normal $PaCO_2$ with low PaO_2 is rare in non-ventilated subjects. It creates a more tranquil environment for volunteers because of less external stimulation. During PH in hypoxia rooms, volunteers can adapt progressively to decreasing PiO_2. Disadvantages of PH include fatigue and sometimes dizziness observed in some volunteers at lower SpO_2 with hypocapnia, longer duration of hypoxia, and exposure of one coworker to limited hypoxia. Observers can detect sleep in volunteers, however this was always denied by the subjects.

Variability of SpO_2 during hypoxia

Intra-individual variability of SpO_2, also called entropy, and inter-individual variability of SpO_2 to a particular $PambO_2$ correlates to the depth of hypoxia [5,6]. Entropy was also detected during our PH ISO-study in volunteers submitted to hypoxia in sitting or supine position [7]. In these PH studies, also a variability in SaO_2 was noted during the plateaus with stable ambient oxygen concentrations (non-published data). Interestingly, during several studies SpO_2 progressively decreased during a stable Pamb plateau (non-published data, [8]).

During ISO-studies using PH or IH, volunteers are breathing spontaneously and small changes in breathing pattern can be caused by, for instance, an external stimulus including coughing or periods of periodic breathing. Consequently, these small changes in respiration, referred to as respiratory variability, influence $PalvO_2$, and cardiopulmonary physiology with a concomitant rapid change in the lung's blood oxygen saturation. Oxygen saturation during lowered $PambO_2$ is located on the steep part of the oxygen-hemoglobin dissociation curve [9], so small changes in nominal PaO_2 may result in higher changes of SpO_2. Whatever the physiological explanation, SpO_2 variability has huge practical impacts during ISO-studies, making rigorous timing of capturing of SpO_2 and SaO_2 values used for pairing in statistical analysis. Due to entropy, SaO_2 needs to be registered at the time of sampling of non-diluted blood into an anticoagulating syringe. The average SpO_2 reflection during a time period specified by the manufacturer will be used for pairing. Timing needs to be clearly defined in the clinical investigation protocol before starting the ISO-study. It is, however, noted that reference devices, including the CO-oximeter, have an accuracy of about 2%.

Respiratory responses of subjects undergoing IH or PH.

Ventilatory responses to hypoxia are determined by multiple factors such as alveolar gas concentrations, alveolar-capillary gas exchange, systemic capillary-tissue gas exchange, lung tissue circulation delay, and feedback responses. Indeed, hypoxia determines the signals of peripheral chemoreceptors to the respiratory center [10]. Hypocapnia influences mainly the central chemoreceptor output [11]. High interindividual variability of ventilatory responses during hypoxia is described, including gender-dependent differences [12].

Both IH and PH elicit a biphasic ventilatory response called the hypoxic ventilatory response (HVR), characterized by an initial rapid increase in ventilatory minute volume followed by a progressive decline over the following minutes called the hypoxic ventilatory decline (HVD), which is affirmed by mathematical modelling [13]. It has been shown that breathing frequency and tidal volume are under different neural control. The growth phase of HVR is linked to the decline in arterial PO_2 and stimulation of the peripheral chemoreflexes, but under poikilocapnic conditions arterial PCO_2 plays a role. Indeed, the growth phase is higher during IH compared to PH [14]. Mechanisms underlying the decay phase are more obscure, perhaps related to decreased peripheral chemoreflex sensitivity to O_2. Arguments can be found that CO_2 is also involved [12,14,15]. During face mask

use, in contrast to hypoxic room use, theoretically a small increase in positive end-expiratory airway pressures can influence oxygen transport, but these changes are too small to take in consideration if gas fluxes in the ventilatory system are well controlled.

In a cross-over clinical study comparing ventilatory changes during IH or face mask PH, healthy volunteers were exposed for 20 minutes to hypoxia with end tidal oxygen of 10% [14]. Human ventilatory response to PH resulted in a hypocapnia (approximately - 5 mmHg), with a slight non-significant increase of minute ventilation without change in the breathing frequency, but a temporal increase in tidal volume. As expected, during IH higher tidal volumes, and increased breathing frequency were noted. During IH a decreased duration of the inspiration and expiration without significant difference compared with PH was noted in other studies [16]. Results of studies show different and contradictory information. Indeed, a higher variability of the respiratory rate was dependent on SpO_2, while tidal volume is not during PH [8], although others did not confirm all of these results [17,18].

Effects of IH and PH on $PaCO_2$ and pH.

The $PaCO_2$-$PalvCO_2$ gradient seems not to differ if comparing normoxia compared to hypoxia [19]. This is not confirmed by others, as in healthy subjects under normal environmental circumstances $PaCO_2$-$PetCO_2$ gradients exist, and are measured to be about 2 to 3 mmHg in healthy subjects. But the gradient was dependent on $PambO_2$ [20]. The amount of binding of CO_2 to hemoglobin is described by a non-S shaped CO_2 dissociation curve and is thus $PaCO_2$ dependent. Respiratory alkalosis during progressive PH is too short to be compensated by metabolic acidosis, resulting in an increased blood and cerebral pH. This increased pH during lowered $PaCO_2$ is not without consequences for an individual undergoing hypoxia. In our hypoxia room, PH with progressive decreasing $PambO_2$ down to 9.5%, $PaCO_2$ never decreased lower than 30 mmHg in eligible blood samples of volunteers who gave informed consent for using their results in addition to the captured SpO_2 and SaO_2 values ($N > 100$ volunteers, $N > 2000$ blood gases) but $PaCO_2$ varied substantially during plateaus of ambient oxygen (non-published results). The highest pH was found to be 7,533 in these arterial blood samples. Adverse events during PH with PambO2 < 12 %, fatigue, dizziness or small cognitive declines were observed, but disappeared immediately after normalisation of $PambO_2$.

Haldane effect on the oxy-hemoglobin dissociation curve

Hemoglobin is the most important oxygen carrier in the blood of humans. Oxygen binds to hemoglobin in the red blood cells at varying degrees of affinity, depending on the biochemical environment. The relation between PaO_2 and oxygen saturation of hemoglobin is reflected by a S-wave oxygen dissociation curve. Binding of O_2 to hemoglobin is subject-dependent, and is referred to as the Haldane-effect, as this binding is influenced by temperature, pH and CO_2 among other factors. In the lungs, during physiological circumstances, PCO_2 decreases as CO2 is diffused to the alveoli. This decrease in CO_2 implies that oxygen is better bound to hemoglobin. On the other hand, in the peripheral circulation PCO_2 is increased and binding of oxygen to hemoglobin is weaker, resulting in a better transfer of O_2 out of the red blood cells. During PH, however, $PaCO_2$ and alveolar CO_2 are decreased, which results in more tightly binding of O_2 to hemoglobin compared to IH protocols.

In the periphery, the lower the PCO_2 the lower the transport of O_2 to cells as O_2 is better bound to hemoglobin during hypocapnia. Compared to the hypocarbia during PH, during normocarbia in IH protocols O_2 binds at a lower degree to hemoglobin but in the periphery O_2 is more rapidly transferred to tissues. In conjunction with the effects of hypoxia and hypocapnia on microcirculation in the skin, one can hypothesize that the SpO_2-SaO_2 gradient is different between both techniques used for ISO-studies. The use of PH or IH might result in different calibration or accuracy results of the TD. As medical pulse oximeters are produced and distributed for all medical indications, it is possible that SpO_2 reflection differs between IH and PH tested devices during different medical situations.

Periodic breathing and PH

During PH, hypoxic responses result in hypocapnia. Hypocapnia affects mainly central chemoreceptors to decrease the ventilation in order to maintain the subject's pH. Peripheral chemoreceptors detecting hypoxia act faster compared to the slow reacting central chemoreceptors detecting hypocapnia [21]. The depressed ventilation can induce apnea in some subjects, most frequently encountered in males during sleep [22]. This phenomenon of temporal decrease or absence of ventilation is referred to as periodic breathing. Periodic breathing is frequently accompanied by increased SpO_2 variability. In our ISO-studies with 18 awake and freely breathing volunteers undergoing PH, periodic breathing was observed only in male subjects [23], and periodic breathing was dependent on the body mass index and age of the volunteer. It is noted that also healthy females can develop periodic breathing during experimental PH [24]. To the best of our knowledge, periodic breathing is not induced by IH.

Cardiopulmonary effects of hypoxia

By complex neuronal pathways built-up during evolution of mammals, $PaCO_2$ or pH and PaO_2 trigger the central or peripheral respiratory centers. In addition, ventilatory

responses to acute hypoxia or hypocapnia may alter the activity of both the sympathetic or parasympathetic autonomic nervous systems. The integrated cardiac and respiratory system display complicated dynamics that are affected by intrinsic feedback mechanisms controlling their interaction.

Clinically, acute effects of exposure to hypoxia lead to an increased cardiac output, mainly induced by an increase in heart rate with a modest increase of the mean arterial pressure. Heart rate variability, a value reflecting the autonomic nervous system, is changed during hypoxia [25]. Hypoxic exposure is shown to directly change blood flows, which is tissue-dependent (see microcirculatory changes). At the pulmonary level hypoxia elicits vasoconstriction. On the other hand, systemic blood pressure is kept relatively constant by the activity of arterial baroreceptors during hypoxia studies.

During alveolar hypoxia a hypoxic pulmonary vasoconstriction (HPV) becomes prominent which is reciprocally PalvO$_2$-dependent [26]. Acetazolamide is a carbonic anhydrase inhibitor that induces acidosis, mild diuresis and can inhibit hypoxic pulmonary vasoconstriction. This indicates that CO_2 can interfere with pulmonary vasoconstriction during hypoxia [27]. During normal environmental circumstances and in healthy subjects, vasculature of the lungs responds to local hypoxia in order to change ventilation/perfusion mismatch to optimize PaO_2. This results in altered lung blood flows to avoid lung regions with changed ventilation/perfusion quotients to be perfused. During systemic hypoxia, pulmonary arterial pressure increases significantly due to vasoconstriction [28]. The early phase of vasoconstriction starts within 100 msec, peaking at 5-20 min as a result of transient elevations of intracellular calcium concentrations. The decay is peaking at 60-120 min as a result of myofibrillar calcium-sensitization coupled with enhanced endothelial release of vasoconstrictive compounds and nitric oxide changes [28]. In vivo, animal or human studies show that hypercapnia induced vasoconstriction of the pulmonary vessels, but hypocapnia blunted this response to hypoxia. Clinically, in free breathing healthy humans undergoing hypoxia with different $PetCO_2$ levels, it was shown that hypercapnia accentuated hypoxic pulmonary vessel resistance directly with increased tricuspid regurgitation, whereas other regulatory mechanisms seem of less importance [29]. The contribution of dysregulation of the pulmonary vasculature to result in differences in SpO_2-SaO_2 gradients during IH compared to PH and the consequences on the accuracy of pulse oximeters is not studied in detail.

Effects on peripheral circulation

Several mechanisms exist to regulate blood flow in the skin [30]. Hypoxia influences the microcirculation [31] although the cutaneous blood flow seems to react differently to hypoxia compared to other tissues [32]. Mechanisms involved during changes of the microcirculation are not completely understood during healthy or disease circumstances [33]. Vascular autoregulation can be elicited by local hypoxia but is probably not influenced by changes in sympathetic or parasympathetic output. Local vascular regulatory mechanisms can thus influence the local blood flow in, and the density of, open small vessels < 100 micrometers and venules.

Skin blood flow is important during photoplethysmography and fast acting vascular mechanisms are seen. During one heart beat microvascular responses are noted. The regulatory mechanisms can influence photoplethysmographic SpO_2 signals as they are dependent on the amount of oxy-hemoglobin or deoxy-hemoglobin under the TD. This can probably influence a SaO_2-SpO_2 gradient depending on the type of measurements.

To the best of our knowledge, neither central temperature nor peripheral temperature at the area of Sp02 monitors are followed during ISO-studies. Setting of ambient temperature is important during these studies. It is clear that skin and core temperatures are of utmost importance in validation of SpO_2 test devices.

Effects on cerebral blood flow and cognitive function

The cerebral circulation uses CO_2 and O_2 as strong signals to adjust blood flow, primarily to maintain adequate oxygen delivery and match blood supply to the brain's metabolic needs. PH presents the brain with a difficult interaction between two opposing blood gas stimuli, hypercapnia causes vasodilation and increases cerebral blood flow (CBF), while hypocapnia decreases CBF by vasoconstriction.

During 48 hours of hypoxia, CBF followed the decline in PCO_2 during PH, whereas during IH CBF remained unchanged [34]. Steinback et al [13] reported an increase in CBF during IH whereas this response was biphasic during PH. Initially an increase in cerebral vascular resistance with decreased cerebral blood flow was observed. After a while, cerebral vascular resistance normalized and cerebral blood flow rose again. The near equivalency of middle cerebral artery blood flow velocity during IH and PH for about 20 min indicates that the hypoxic stimulus dominates late in the PH exposure during these human studies.

On the other hand, during IH and PH, it was demonstrated that cerebral autoregulation impairment in isocapnic hypoxia can be prevented with hypocapnia, highlighting the integrated nature of hypoxic cerebrovascular control, which is under strong CO_2 influence [35].

Hypoxia is associated with a decrease in cognitive function [36]. Bloomfield et al. demonstrated a neuroprotective effect of CO_2 in complex psychomotor task performance. Psychomotor performance decrease is seen during PH, and not during IH [37].

Interpretation

After acute exposure to hypoxia, most physiological responses show a growth phase followed by a decay phase. Pulse oximeters claim to reflect SaO_2. SaO_2-SpO_2 gradients of 2 to 3% are allowed in newly developed SpO_2 devices during ISO-studies, before application in patients. The type of hypoxia given during ISO protocols, IH or PH, may present differences in terms of the subject's ventilation, cardiovascular responses, $PalvO_2$, oxygen uptake and delivery in lungs and microcirculation in the skin.

Further comparative research is necessary to decide whether IH or PH tested pulse oximeters differ in reflecting SaO_2 during pathological conditions, an ultimate desire of clinicians. These conditions may include low perfusion cardiovascular diseases, altitude sejourns, sepsis, and ventilated or anesthetized patients. Probably the ideal pulse oximeter will never exist, as reference devices also have deviations in reflecting the true SaO_2 values. Considering rapid intra-individual variabilities of SpO_2, including variabilities of ventilation, cardiovasculatory and microcirculatory tones, timing of blood withdrawal to pair SaO_2 with SpO_2 averages reflected by a TD is absolutely necessary to define the accuracy of a pulse oximeter TD. Hopefully, the rapid increase of computing capacity can help us to unravel SaO_2-SpO_2 differences for optimal clinical reflection of SaO_2 by SpO_2.

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