Carbon Monoxide Toxicology: Overview of Altitude Effects on the Uptake and Dissociation of COHb and Oxygen in Human Blood

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FOREWORD

NFPA's requirements f or insta lling carbon monoxide equi pment relie s on Carbo xyhemoglobin (COHb) curve calculations for a ssumptions of equipment insta llation. However, at high er elevations (10,000+ ft), the committee has learned that listed equipment performs differently than at sea level. This raises the question of whether the COHb curve in humans is the same at high elevations than at lower altitudes. If it is different, installation instructions may need to be adjusted for higher elevations.

In addition, OSHA states that people at high altitudes (10,000+ ft) are more susceptible to carbon monoxide poisoning. In Carbon Monoxide and Human Lethality: Fire and Non-Fire Studies, edited by M.M. Hirschler, states "When pe rsons at hig h altitude ar e exposed to low conce ntrations of CO, sympto ms are exp erienced at much lower blood concentrations a nd the effects are more severe."

To provide the committee with add itional in formation on this topic, th e Research Foundatio n undertook a project with the goal of reviewing literature and data relating to the impact of altitude on COHb curve to serve as the technica l bas is for CO warnin g equipment installation requirements.

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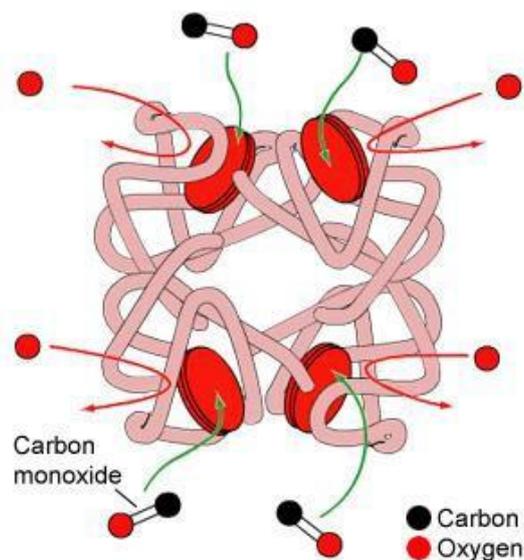
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1. Executive Summary

Carbon Monoxide (CO) inhalation is second only to opioid overdose as the leading cause of death via unintentional poisoning in the United Sates; with an average of 438 fatalities per annum. CO is both colorless and odorless; the early symptoms of exposure are often non-specific and easily mistaken for general fatigue or viral illness, making detection by the victim virtually impossible until they become too impaired for self-rescue or alerting others and may ultimately die.

Altitude has an exacerbating effect on CO uptake into the human bloodstream, and on the bonding of CO with the body's primary oxygen carrier (hemoglobin) to form carboxyhemoglobin (COHb). Therefore existing building standards for acceptable environmental CO levels may not be safe at significant altitudes above sea level. This claim is strongly supported by the fact that for any given concentration of CO exposure, the rate of uptake as well as steady state COHb production is increased under the effects of elevation. Furthermore the degree of impairment observed in both man and rodent is higher under such conditions

A review of existing literature has found gaps in terms of definitive quantitative data with regards to COHb production at altitude. Nevertheless there is a general consensus that altitude and CO exposure have an additive relationship. In addition to this it has become evident that the widely held belief- replicated even in the NFPA 720 official standard- that a simple correlation between COHb levels and the presentation of clinical symptoms exists is in fact false.

Early detection of CO in the atmosphere is of paramount importance in preventing severe accidents. The latter inherently requires determining a threshold value at which CO detectors should sound the alarm, since they are perhaps the single most important preventive safety measure. Although it is currently ambiguous what exactly this threshold value should be, it is abundantly clear that guidelines for sea level conditions are not well suited to environments at altitude. Therefore a review of mapping techniques between COHb levels and clinical symptoms, as well as new guidelines for safe levels of CO tailored specifically for residents at altitude are both urgently required.

2. Carbon Monoxide Poisoning

Carbon monoxide (CO) is a colorless, odorless and highly toxic gas. Virtually undetectable by an individual during exposure, it can cause a variety of non-specific symptoms such as headache or nausea, but can also be asymptomatic in leading the victim into unconsciousness and eventually death (1). Although overtaken by opioid overdose in recent years, CO was the leading cause of death via poisoning in the United States (US) from 1979 to 1988 (2). And continues to claim an average of 438 lives per annum even lately (1999-2012)(3) in the US alone while also being responsible for about half of the total number of fatal poisonings worldwide as of 2011(4).

 CO has been declared a hazardous air pollutant under the Clean Air Act, with the World Health Organization (WHO) and Environmental Protection Agency (EPA) providing extensive guidelines with regards to levels of exposure that must not be exceeded. The Occupation Safety and Health Administration (OSHA) has mandated that employers of workers with the risk of occupational exposure must incorporate engineering controls to ensure CO levels remain acceptably low at all times. However there is no law requiring contractors to install such controls in private homes. (5)

Produced during combustion of carbon containing substances, common sources include malfunctioning furnaces and water heaters, gas-powered tools and electrical generators, open fire places, stoves, charcoal, propane, and natural gas grills, automotive exhausts, household heaters, and accidental fires as well as natural sources such as forest fires. Although the use of tobacco is the most common cause of elevated CO levels in the body, tobacco abuse does not cause acute CO poisoning (6).

This review considers four main topics of interest in the field of CO toxicology: the mechanism through which exposure to CO affects the body; an analysis of hemoglobin and myoglobin dissociation curves with respect to oxygen; modeling levels of CO in the blood with the accompanying symptoms; and then the effect of altitude on the poisoning process. This choice of topics was made on the basis that it is by understanding the actions of CO at a physiological level, combined with the behavior of its primary movers in the blood stream (hemoglobin and myoglobin), that we can begin to appreciate the macroscopic effect on an organism.

The main objective of this review is evaluating the effect of altitude, as recent information suggests that at high elevations the onset of symptoms occurs at much lower concentrations of CO than expected. This is primarily due to oxygen starvation as a result of altitude (generalized hypoxia) initiating compensatory mechanism by the body in an attempt to increase oxygen uptake. However these same mechanisms cause an increase in CO uptake as well(7). Quantification of this relationship is essential in providing safe guidelines for CO detectors.

3. Biological Mechanisms of Carbon Monoxide Poisoning

Carbon monoxide (CO) has an affinity for hemoglobin about 210 times that of oxygen under standard physiologic conditions of pH and serum concentrations of 2,3-Bisphosphoglyceric acid (2,3 BPG) . Note that 2,3 BPG regulates the oxygen affinity of hemoglobin; the effect of deviations from normal serum concentrations is discussed in Section 6. Carbon monoxide enters the body through the lungs and is subsequently taken up by the blood by bonding with hemoglobin found in red blood cells. The rate of uptake of CO is so fast that its partial pressure in the capillaries remains low, thus it is a diffusion-limited reaction (i.e. it is taken up as quickly as it can diffuse across the membranes). (1)

CO acts as a competitive inhibitor to oxygen as both gases compete for the same binding site on the hemoglobin molecule. The resultant structure following attachment of CO is called carboxyhemoglobin (COHB). Occupancy by either oxygen or CO at one out of the four, binding sites on the hemoglobin tetramer increases the affinity of the other three sites for oxygen- this is termed allosteric binding. By this mechanism, CO poisoning can impair the ability of hemoglobin to offload oxygen at tissue delivery sites. Oxygen starvation due to inhibition of hemoglobin in this way serves as one major mechanism leading to death during an exposure event. Moreover not only does CO reduce the total amount of oxygen being transported, but the nature of allosteric binding hinders delivery as well. While high concentrations of CO can even disrupt cellular activity directly.(8)

Despite hemoglobin being the primary carrier of oxygen in that it facilitates uptake from the lungs and transports it around the body, muscle tissue (cardiac muscle in particular) require significantly larger supplies of oxygen, hence contain myoglobin. Myoglobin is similar to hemoglobin in function but differs in structure and location. The former is found within muscle tissue as opposed to the latter being present in red blood cells. Myoglobin acts as a store of oxygen and promotes facilitated diffusion of oxygen from the blood to the mitochondria, which is the site of energy release via respiration, essentially acting as an intermediary for oxygen from the blood to the intracellular regions of aerobic activity within the cells themselves. In summation, myoglobin is a store site and a carrier that takes oxygen from hemoglobin at the edge of cells, and delivers it to the small structures inside cells that need it, this is possible due to its higher affinity for oxygen(9). CO can inactivate myoglobin, but these effects only become prominent in the later stages of CO poisoning(8).

Although the general cause of death in CO poisoning is a result of cellular respiration being interrupted due to oxygen deprivation, the gas also has the potential to interrupt cellular activities directly, provided sufficiently elevated levels are present in the body(8). These effects include increased oxidative stress, which is essentially an imbalance between the production of free radicals and the ability of the body to nullify their harmful effects via antioxidants(10). A particular example is the increase in concentrations of the free radical nitric oxide, which can lead to leaking of macromolecules into organs as well as impair lymphocytes (a type of white blood cell)(11).

CO can also affect the central nervous system (CNS), by bringing about the degradation of essential fatty acids in the myelin sheaths of nerve cells. For example one study yielded 73 consecutive patients presenting some form of brain injury following CO exposure. It has been suggested that this is a result of oxidative stress producing reactive oxygen species(12)(13) . In addition there exists the possibility of CO directly impairing the activity of oxidoreductases (an enzyme), although as of yet little data exists on the relative significance of this during an exposure(14) .

The physiological response to CO poisoning is largely neurological and cardiovascular, with a great deal of variation between individuals. Blood flow rate is increased in an attempt to compensate for the decreased oxygen delivery. This is usually effective at first but begins to decline as the exposure

continues due to the progressive inactivation of myoglobin. The problem in later stages is not necessarily sufficient oxygenated blood reaching the heart and other tissues, but rather the inability of that oxygen to go from the blood to the mitochondria fast enough without active myoglobin. Clearly certain underlying cardiovascular diseases or defects can have an aggravating effect, in particular conditions that compromise blood flow to the heart or brain. (8)

Additional response mechanism include: redirecting blood flow to more critical organs and increasing the amount of oxygen extracted from the blood. The latter is possible as during normal conditions only about 25% of the available oxygen in human blood is taken up by respiring tissue, however this is not always true for certain organs such as the brain which require a larger supply .

Recent work has suggested that the aforementioned compensatory mechanisms are far more effective than previously thought, placing doubt on the effect of CO on hemoglobin being the primary cause of symptoms, while placing greater importance on mechanism such as free radical generation and direct inhibition. For example several studies(15) monitoring cerebral oxygenation, have failed to find the global deficit in oxygen content one would come to expect based on the CO-hemoglobin relation, finding instead that much higher levels of COHb than predicted are needed before the onset of measurable falls in oxygenation. The extent to which mechanisms other than the inactivation of hemoglobin play a part is a topic of much current debate and research.

Factors influencing an individual response to CO exposure include age, with the elderly and infants being most susceptible. In addition to this a blood alcohol level up to 0.3% has been found to exert some form of partial protection as shown by lower blood COHb levels manifesting in fire victims. Although the reasons for this are not entirely clear it has been suggested that it may be due to the calming effect of alcohol(16). This claim is supported by studies(8) comparing the response between restrained and unrestrained mice finding that stress has a degenerative effect. However the benefit does not carry forwards for higher blood alcohols levels and the hypothesis for the perceived calming effect of alcohol has not yet been thoroughly tested.
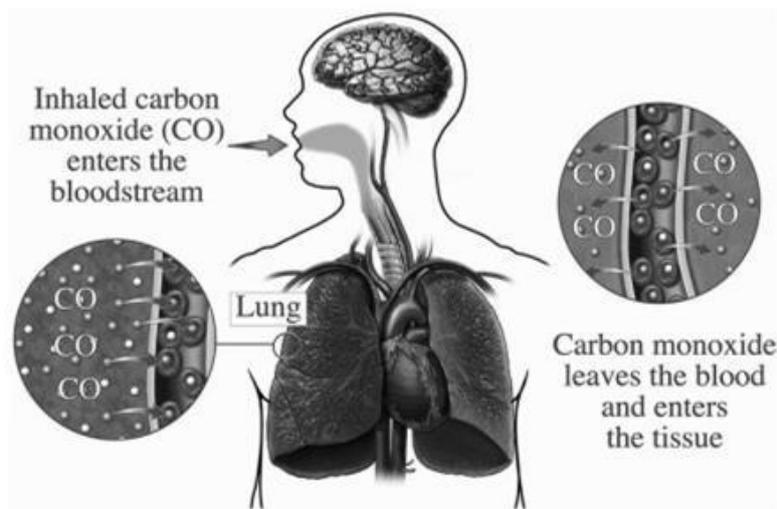

Figure 1 . Sketch showing carbon monoxide crossing the walls of the alveoli in the lungs to make its way into the blood where it bonds with hemoglobin found in red blood cells. Eventually after having been carried away by the circulatory system, it leaves the red blood cells and crosses the walls of the capillaries into the surrounding tissues. After (17).

4. Hemoglobin and Myoglobin Dissociation Curves

Hemoglobin molecules consist of 4 protein chains, each of which is wound around an iron core in a complex 3D structure. Each chain can carry one molecule of oxygen at a time. The affinity of an oxygen molecule to a binding site on hemoglobin varies considerably depending on the status of the other 3 sites. Such a dependence on pre-existing saturation levels is termed ligand co-operativity. In the case of hemoglobin it is a positive relationship, meaning after one molecule of oxygen is taken up, it is easier to pick up the next due to changes in the complex structure. Note that the bond formed is reversible, therefore following the same principle; once one molecule is released, it is easier to release the next. It is due to the latter that the hemoglobin-oxygen saturation curve has a sigmoidal shape as shown in Figure 2. Positive co-operativity is an essential quality for hemoglobin to be an effective oxygen carrier, as it means in the lungs where the partial pressure of oxygen in the surrounding tissue is higher than the blood supply it quickly saturates. While as the oxygenated hemoglobin is moved further and further away into regions with less and less oxygen it can release more of it progressively easily, so as to meet local demands. The partial pressure difference between surroundings and the blood is of particular interest as it can facilitate the release or uptake of oxygen by hemoglobin as well as provide favorable diffusion gradients(18) .
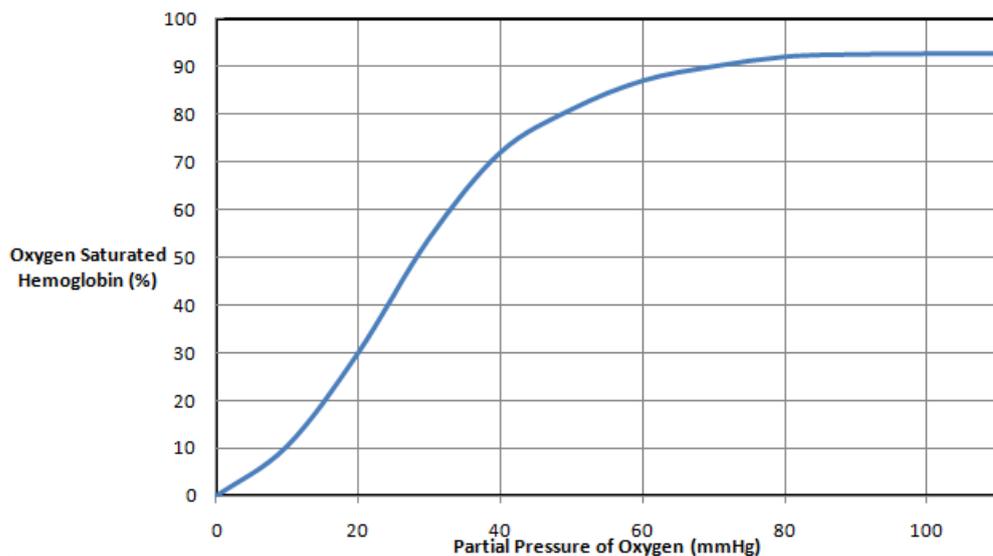

Figure 2. Diagram showing a generic hemoglobin dissociation curve of percent oxygen saturated hemoglobin vs. the partial pressure of oxygen in surrounding tissues. Note that under ideal gas assumptions and at a fixed temperature, partial pressures are directly proportional to concentrations. After (19).

Two important safeguards in the nature of oxygen transport are evident in Figure 2. Firstly the asymptotic nature close to high saturation levels giving rise to a plateau, along which a substantial drop in surrounding partial pressures of oxygen can occur without a significant drop in saturation. This protects against adverse effects due to compromised air in the lungs, meaning that hemoglobin leaving the lungs is generally always close to saturated even if the partial pressure of oxygen in inspired air is less than optimal. Secondly the steep region of the curve is useful in the unloading of oxygen to respiring tissues, as the gradient of the curve represents a relatively small drop in the

partial pressure of oxygen in the blood compared with the amount of oxygen being released from a hemoglobin molecule. In other words as the tissues take up oxygen from the blood, the partial pressure of oxygen remains sufficiently high to maintain a suitable supply somewhere else(19).

A right shift of hemoglobin's dissociation curve indicates decreased affinity for oxygen, as for a particular partial pressure of oxygen the hemoglobin molecule is now less saturated. Endogenous production of carbon dioxide (CO_2) acidifies the surrounding tissue as the gas dissolves to form carbonic acid. The accompanying fall in pH induces a localized right shift in order to promote greater dissociation of hemoglobin and hence greater delivery of oxygen to the respiring cells. This manipulation of hemoglobin's affinity for oxygen by controlling pH is termed the Bohr Effect.(20)

In contrast, when CO occupies a ligand binding site on hemoglobin, a left shift as shown in Figure 3 occurs, representing the increased affinity for oxygen(19) . Now not only is the relative saturation of hemoglobin higher, but the total amount of oxygen being carried is also lower. Essentially the surroundings must experience a greater degree of oxygen starvation before the oxygenated hemoglobin dissociates.
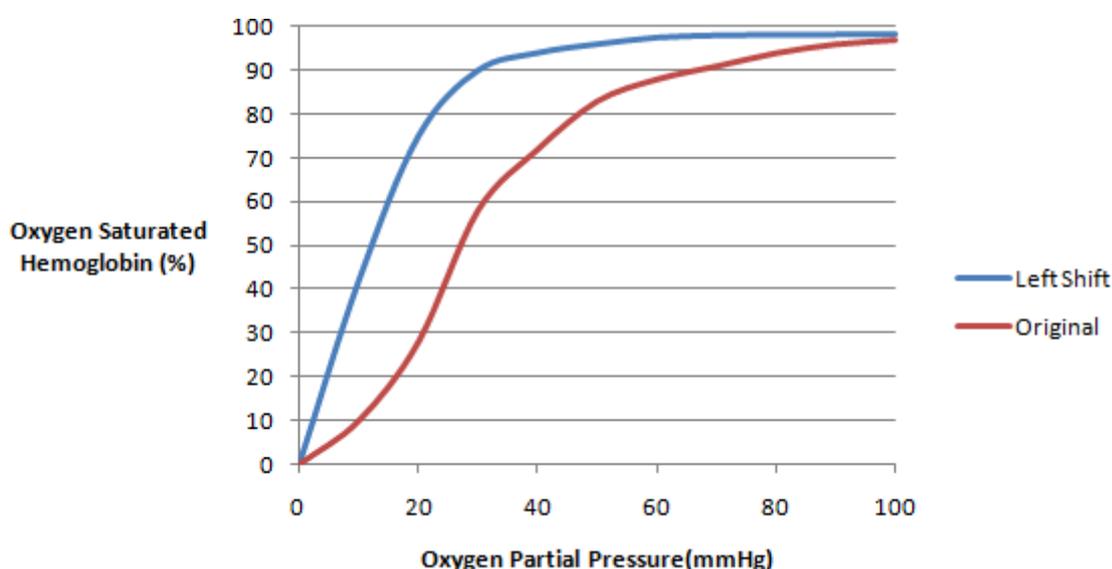

Figure 3. Diagram showing shift induced by COHb. The sharper gradient for shifted curve represents a larger change in oxygen partial pressure needed for the same change in saturation. After (21).

A useful quantity representative of a particular dissociation curve is termed P50, and is the partial pressure of oxygen at which hemoglobin is 50% saturated. A low P50 is representative of easier loading of oxygen in the lungs, while a high value shows a prioritization of offloading oxygen into the tissues. Studies (22) have found that a lower P50 is a common adaption for living at high altitude, in both animals and humans (22). While Figure 3 displays a lower P50 in the presence of CO, the effect is so pronounced that combined with decreased oxygen carrying capacity of hemoglobin, the resultant effect is detrimental rather than advantageous.

Altitude alone has the opposite effect to CO on the dissociation curve; inducing a right shift. Almost 40% of the total shift is brought about by previously mentioned Bohr Effect with about 50% of the increase in P50 occurring over the first 15 hours of acclimatization to a new altitude(23). Representative of decreased oxygen affinity, it was originally thought to be a favorable adaptive mechanism in response to the reduced oxygen partial pressure in inspired air by allowing greater

extraction of oxygen from the blood by surrounding tissue(24). However several more recent studies have found this hypothesis not to be true, claiming the adaptive benefit to be insignificant(23).

Other natural responses to altitude include production of 2,3 BPG and increased serum pH levels during initial acclimatization. The physiological basis for this will be discussed in Section 6. Consider here instead that 2,3 BPG has the effect of decreasing oxygen affinity (i.e. inducing a right shift) while increased pH effectively counteracts the Bohr Effect by resulting in a left shit, thus promoting oxygen starvation of tissue.(25)

Myoglobin on the other hand has one polypeptide chain (i.e. is a monomer) and can only carry one molecule of oxygen at a time therefore is incapable of allosteric binding. From the much higher concentrations present in marine mammals who spend longs period of time underwater as one piece of evidence, it was deduced that it serves an essential role as an oxygen store. Since the affinity for oxygen is much greater, it only really dissociates in conditions of oxygen deprivation. Also it provides a parallel path for diffusion of oxygen to the mitochondria, acting as a buffer of sorts to maintain adequate oxygen levels during periods of aerobic stress(26). The affinity of myoglobin for CO is even greater than that of hemoglobin, however as previously discussed myoglobin inactivation only takes place in the later stages of exposure, most likely due to the distance of myoglobin stores from the lungs(21).

Figure 4 shows the myoglobin-oxygen curve and that of hemoglobin for a direct comparison. As can be seen myoglobin has a much lower P50 as it must have the ability to pick up any oxygen released by hemoglobin. Its P50 is also lower so as to allow it to load and unload oxygen appropriately in the conditions of muscle tissue, which has a partial oxygen pressure that is much lower than that to which hemoglobin is exposed(19). The hyperbolic shape of the myoglobin dissociation curve-as opposed to the sigmoidal one for hemoglobin-is a direct result of there being only one monomer chain in myoglobin, making positive co-operativity impossible.
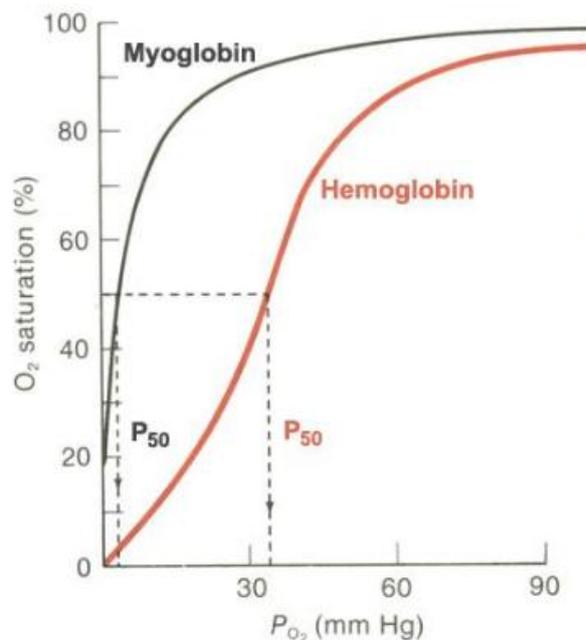

Figure 4(27). Diagram showing myoglobin and Hemoglobin dissociation curves. Note steepness of curve leading to saturation of myoglobin, indicative of how easily it picks up oxygen.

5. Blood COHb Levels and Symptoms

When defining an exposure to CO, both the concentration and length of time are key distinguishing factors. It is vital to note however that individuals exposed to the same source simultaneously can exhibit differing levels of COHb(28) and that environmental CO levels are not the same as blood COHb levels. Two distinct strategies exist in developing a model to predict the COHb levels that would form for a given exposure; early work in particular consisted almost entirely of regression models based on empirical evidence. Although much simpler, such models suffer the restriction of only being accurate for the precise exposure conditions that they were based on. The second approach is mechanistic in nature and attempts to incorporate an understanding of biological mechanisms and responses. Of these the most widely used and extensively validated is a differential equation attributed to Coburn, Foster and Kane (CFK)(7).

The CFK equation incorporates the main physiological parameters involved in CO uptake and can be used not only to predict uptake but elimination as well. Although both a linear and non-linear version exists, the linear CFK equation is considered a better estimate during CO uptake as opposed to during elimination (29). Furthermore although the non- linear CFK equation has been shown to be accurate across a wide range of conditions and even at high levels of CO, relatively little work has been done on determining exactly when the transition from linear to non-linear relationships should be made, with the former being currently used by many even at high concentrations- something for which the non-linear CFK is better suited (30) .There is however an intrinsic difficulty in determining the individual parameters involved, many of which require models of their own, with individual parameters fluctuating in importance during different stages of exposure(29).

Symptoms of CO poisoning are numerous and varying as well as non-specific, often leading to a misdiagnosis. They include headache, dizziness, confusion, visual disturbances and eventual collapse (31). It is common to relate blood COHb levels directly with the presentation of clinical symptoms as shown in Figure 5. However as will be discussed shortly this is not a reliable means of classification.
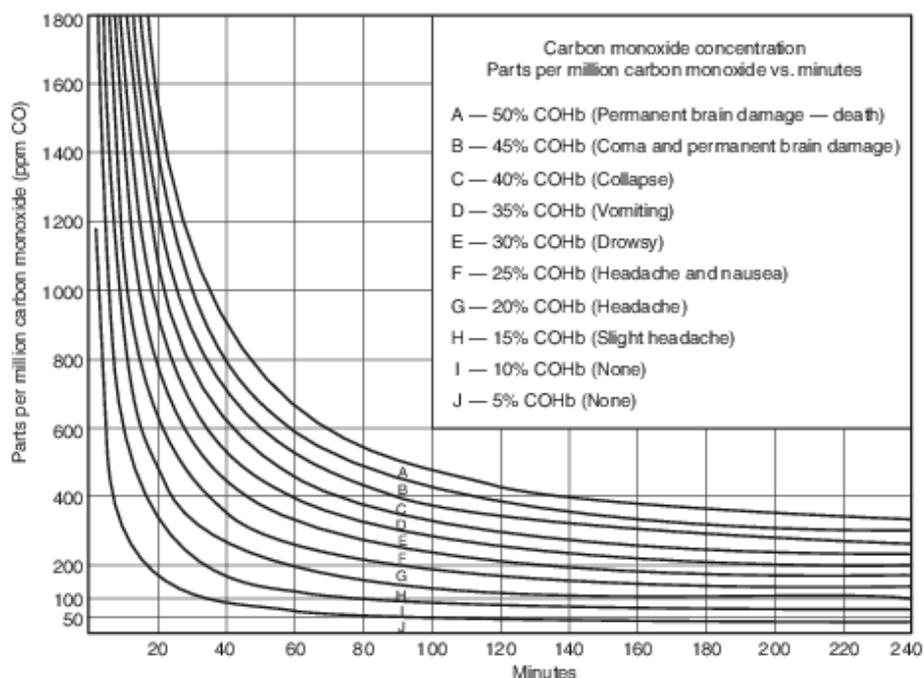

Figure 5. Extract from current NFPA 720 (32), illustrating the relationship between environmental CO and blood COHb as well as indicating estimated symptom onset thresholds.

The correlation shown in Figure 5 between COHb levels presented in the blood and clinical symptoms has been widely refuted as inaccurate and highly unreliable. One study (33) looked into the records of 1407 patients brought in for medical attention due to CO poisoning, but failed to find any utility of initial blood COHb as markers of clinical status. Although the delay from time of exposure to blood testing at the hospital admittedly could have skewed the results somewhat, it is very unlikely that this single source of error managed to account for the entirety of the significantly large spread in symptoms across a wide range of COHb levels that was seen.

The notion of being unable to directly relate the COHb concentration with a patient's physiological state across a general population is also further supported by subsequent studies, some claiming that perhaps part of the reason that that this misconception has propagated so thoroughly into the scientific community is due to unverified replications. This is to say that a review (34) of 25 publications using a similar 'symptoms table' had references that lead simply to other papers using the same figure with no actual traceable source material. One such table that is found frequently in modern literature originates from a 1923 US government investigation which only used three men in a grand total of 10 experiments(35). Clearly the latter is not an accurate representation for the general population.

Broadly speaking health effects of CO can be split into either cardiovascular or neurological. Various studies have shown decreases in work capacity at COHb levels below 5%, with patients of pre-existing heart conditions in particular displaying onset of chest discomfort much earlier than usual after exposures leading to COHb levels as low as 2-5%. For example, a study by Aronow showed a 2% blood COHb level to have an effect on time to onset of angina. This was rejected by the US EPA however on two grounds, firstly on the basis that in order to obtain the desired COHb levels, the patients were exposed to much higher concentrations of CO than that experienced by the general population, and secondly the marker for angina onset was thought to be rather subjective(36). However based on the review of more modern literature, the validity of the first claim is questionable, as the other option would have been to use a much lower concentration of CO for a longer period of time. However it is estimated that almost a third of the body's CO stores are found outside of the blood, in a state not bonded to hemoglobin(8). With a shorter and higher exposure leading to higher levels of blood COHb, as a longer and lower exposure allows more time for CO to penetrate more deeply into tissues(8). With this in mind the approach adopted by Aronow seems if anything an underestimate, as the route suggested by the EPA would allow a greater impact due to direct mechanisms of toxicity described earlier.

In terms of neurological effects, such as impairment of skills requiring sustained attention, once again several studies have found symptoms being exhibited at levels of COHb as low as 5%, however the EPA considers 20% to be a more modest estimate as a threshold for acute neurological symptoms(36). Figure 6 depicts the most common symptoms that occur across the spectrum of exposure as already discussed above.
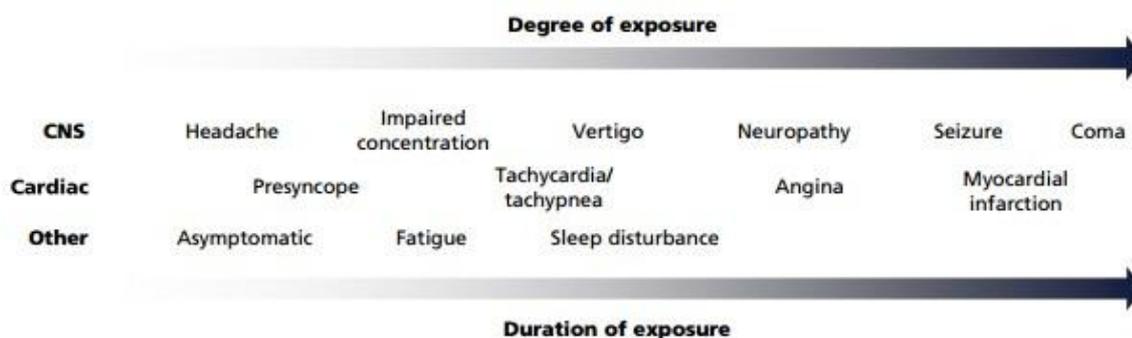

Figure 6. Diagram showing spectrum of acute symptoms as a result of CO poisoning. After (30).

Acute CO poisoning can cause neuronal cell death (necrosis), leading to persistent neurological sequelae (PNS), either due to CO-induced injury alone or in combination with hypotension and/or hypoxia. There is also growing evidence that CO exposure can trigger programmed cell death (apoptosis), causing delayed neuropsychological sequela (DNS). In DNS, patients experience apparent recovery from the signs and symptoms of CO poisoning, only to develop signs of neurologic injury days to weeks later. Typical symptoms of DNS include depression, anxiety, amnesia, cognitive dysfunction and symptoms akin to those of Parkinson's disease. There are currently no reliable models to predict which patients will develop PNS or DNS following a given CO exposure.(37)

To place all of the above in context, one should keep in mind that even healthy individuals do contain a small amount of COHb at any given moment as it is produced endogenously and has several vital roles in cell metabolism. This can range from around 0.4-0.7% with higher values found in residents of highly populated urban areas(38). Generally a COHb value in the range of 3-4% is considered out of normal limits in nonsmokers. Carboxyhemoglobin levels in smokers vary widely, as do measurements of population norms n smokers; generally, a COHb level of greater than 10% in a smoker is considered unexpected(39).

6. Effect of Altitude

An increase in elevation naturally brings about numerous physiological responses to the reduced atmospheric pressure such as amplified ventilation rates and cardiac rhythm in order to compensate for the oxygen deficit. The former also inadvertently promotes increased removal of carbon dioxide, which essentially counteracts the Bohr Effect by increasing serum pH; giving rise to the condition of blood alkalosis. This is counterproductive as it discourages oxygen release to tissues but fortunately is eventually compensated for by the body over the next few days by excretion through the kidneys of excess bicarbonate. Furthermore the chemical 2,3 BPG is released which promptly binds with hemoglobin and increasing the likelihood of its dissociation in the process. In addition to this, larger amounts of the hormone erythropoietin (EPO) are secreted which results in increased RBC production. The latter response is sustained for the duration of stay at altitude and is beneficial in delivering greater amounts of oxygen to cells however can develop into the medical disorder called polycythemia which is a condition involving an elevated ratio of RBC in the blood.(25)

Additional environmental factors also need to be considered, such as how combustion tends to produce more CO at altitude (due to lower oxygen availability leading to more incomplete burning)(40). For example automobiles tuned for operation at sea level produce around 4 times the amount of CO when being driven at 2440m (8000 ft), while even a vehicle tuned for 1610m (5280 ft) produces around 1.8 times more at such conditions. The driving of vehicles up steep slopes and low speeds as is common in mountainous areas also adds to the production of CO, with the reduced air volume high above sea level hindering the effective dispersal of such pollutants(41) .

Haldane's First Principle predicts an increase in COHb levels for a given partial pressure of CO in the blood purely due to the fall in partial pressure of oxygen associated with ascending higher into the atmosphere. Note that a higher COHb has been predicted even in the absence of ambient CO, which has been attributed to increased endogenous production (as will be discussed later)(41).

In addition to this the half-life of COHb, is dependent on the partial pressure of oxygen. Meaning the more oxygen present, the faster a COHb molecule eventually dissociates back into its constituent hemoglobin molecule and CO. Therefore there is a concern that increased half-life of COHb at high altitude due to decreased ambient oxygen can result in accumulation over time(42). At particular risk are groups such as mountaineers who are exposed to subsequent camp or cooking fires. In summation although a single camp fire might not be enough to reach toxic levels of COHb, because it persists longer at higher altitudes there is a longer window of build-up before the body starts to recover . Increased accumulation over time is one out of many possible explanations for why mountaineers tend to have higher COHb levels when descending as opposed to ascending(43). The effect of multiple exposures at high altitudes is a topic requiring further study, especially since other factors such as increased ventilator rate due to altitude hypoxia may also be responsible for the higher levels of COHb found in campers.

Another threat of exposure at altitude is a possible shift in storage mechanisms. Studies on dogs as well as rebreather apparatus (a system that allows the inhaling of exhaled air) have shown that during hypoxia CO moves out of the blood and penetrates deeper into the tissues significantly instead. The physiological implications of this have already been discussed in an earlier section of this review and are severe. In particular models have been developed attempting to explain these observations, and suggest that at particular conditions CO moves out of the blood and into cardiac or skeletal muscle, increasing the proportion of inactivated myoglobin to inactivated hemoglobin(41) . Factors contributing to the latter include how at high altitudes redirection of blood away from the skin

and more towards vital organs could favor translocation of CO out of the blood, while a decreased plasma volume results in a higher relative concentration for a given amount of toxicant, as such facilitating greater peripheral tissue pick up(44).

The combination of altitude and CO results in several unique physiological effects and symptoms. Of these it has been suggested that the most susceptible is an impairment in visual sensitivity(45). One study by Mcfarland et al.(46) dating back to the 1940s found an impairment in this visual sensitivity at COHb levels as low as 5%, and claimed the effect to be equivalent to that which would have been brought about by an altitude of about 2440-3050m (8000-10000 ft). Based on the premise that a given concentration of CO at simulated altitudes, produces an identical effect to an elevation that would result in a decrease in oxygen capacity of the same magnitude, the study yielded the figure replicated below. Where the physiological altitude is defined as the equivalent altitude that would have the same effect on the body as any given combination of true altitude and %COHb. Note that it was found that this detrimental effect on vision lags behind removal of CO from the blood and even at the time of the study it was hypothesized this was due to interactions at a cellular level in the central nervous system (47).
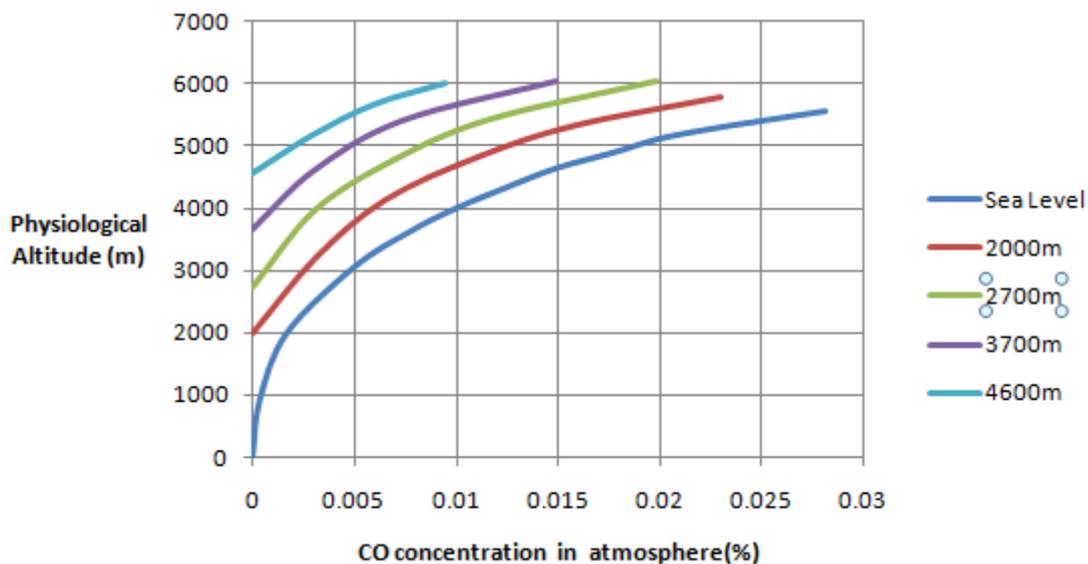

Figure 7. Showing how combinations of altitude and CO exposure culminate. For example a pilot flying at 3700m (12140ft) in an environment with 0.005% CO, is experiencing the same conditions as someone at 5000m (16404ft). After (46).

A common testing parameter for visual sensitivity is the Flicker Fusion Frequency (FFF), defined as the critical frequency at which a flickering light appears to be steady. The latter was the protocol the works of McFarland et al mentioned earlier were largely based on, he even claimed the test was sensitive enough to measure the effects produced from smoking a single cigarette. In other words the design of the test was such so as to measure even sub-clinical levels of CO poisoning. A slightly later study(48) largely validated his findings and went on to find that hypoxia as a result of altitude alone brought about an impairment at 2743-3657m (9000-12000 ft), while although COHb levels of 5-10% and altitudes of 1524-1828m (5000-6000 ft) individually do not produce a measurable detriment, in combination they have an additive effective and result in impairment at a much smaller elevation threshold.

The effects of hypoxia due to CO and due to altitude are very similar, and generally the literature agrees they are additive at the very least, particularly at low levels of exposure. However the physiological responses to each of the two are very different. COHb lowers the saturation of hemoglobin, but does not have a pronounced enough effect on the partial pressure of oxygen in the blood so as to induce hyperventilation, while altitude hypoxia does. As such this physiological response to altitude can have an additive effect on CO symptoms as the increased ventilation rate means more CO is taken into the lungs. The latter is most pronounced during the early acclimatization process, after which ventilation rates reach a maximum at about 100 hours and then decline. However even natives residing at high altitude have been found to exhibit higher base breathing rates to some degree(44).

In summation the compensatory mechanisms in response to increased elevation include: progressively increasing ventilation until a new quasi-steady-state is achieved, increased cardiac output, a decrease in plasma volume resulting in a higher Hb concentration than at sea level, as well as 2,3 BPD and EPO release. The dissociation of oxyhemoglobin into oxygen and hemoglobin is also considerably affected by the blood's pH, a phenomenon known as the Bohr Effect; the acid base equilibrium will readjust at altitude to facilitate greater transport of oxygen. As such all of the above compensatory changes will inadvertently favor greater CO uptake as well(29) .

One study(49) into the effect of COHb on hypoxia tolerance measured various parameters during and after exercise for certain combinations of both CO and altitude. Based on changes in pulse rates the author arrived at a quantitative conclusion that a 1% increase in blood COHb was equivalent to a 102m (335ft) increase in elevation. The latter was only determined for an altitude lying between 2133m (7000ft) and 3048m (10000ft), with a COHb of at least 13%. Note however that during this study the author took no measures to control smoking habits , with more recent findings suggesting that smokers adapt to short term altitude hypoxia much better than non-smokers who suffer much more severe symptoms, possibly due to chronically elevated COHb levels resulting in some partial tolerance(29) .

Despite all the factors discussed above promoting higher COHb levels at altitude, it has been found that under vigorous exercise the blood COHb concentration can be lower than that for similar conditions at sea level. Recall that this does not however necessarily imply less severe clinical symptoms as explained earlier. Regardless possible causes for the aforementioned phenomena are the suppression of COHb formation or the compartmental shift discussed earlier or perhaps even both(29) . Since the latter observation contradicts mechanisms discussed earlier, greater research is needed.

Chronic studies regarding CO exposure at high altitude are limited in number, although several in have been carried out in the past on animals such as rats. For example McGrath carried out work on rats kept in altitude chambers, with an interest in changes in organ weights in particular, yet he concluded that although there did seem to be a tendency for increased spleen and heart weights in response to combinations of altitude and CO, the results were not significant. Of particular note is that he found the effect of CO to be very limited at extremely high altitudes. A different study however found that the increase in capillary networks around the heart as an adaption to altitude might be inhibited by CO, resulting in lower cardiac efficiency(41) .

Figure 8 has been generated based on data from an experiment(50) investigating the combined effect of chronic CO and altitude on rats. Each data point was based off of 6 specimens, and fall into 2 categories; the tests were carried out across 3 altitudes-1005m, 3048m and 4572m (3300 ft, 10000 ft and 15000 ft)- with 1005m being considered ambient and environments either absent of

CO or with an exposure concentration of 9ppm. Keep in mind that as discussed in an earlier section 9ppm within the Clean Air Act for outdoor air quality. The length of exposure was chosen at 6 weeks so as to allow considerable time for long term physiological adaptions. As expected the data support the conclusion that for the same concentration of CO increasing altitude results in higher COHb levels. However the evidence also quantifies substantial relative increases in COHb levels even in the absence of environmental CO. The author suggested this was primarily due to a decreased partial pressure of oxygen in the blood as a result of altitude hypoxia. In other words since CO and oxygen compete for the same hemoglobin molecules, even if endogenous CO production stays constant the decrease in oxygen tilts the balance to allow for easier formation of COHb. The author also suggested the possibility of increased absolute amounts of CO produced as an additional cause. Nevertheless it is unlikely that interactions at such a physiological level play a significant role in acute poisoning.
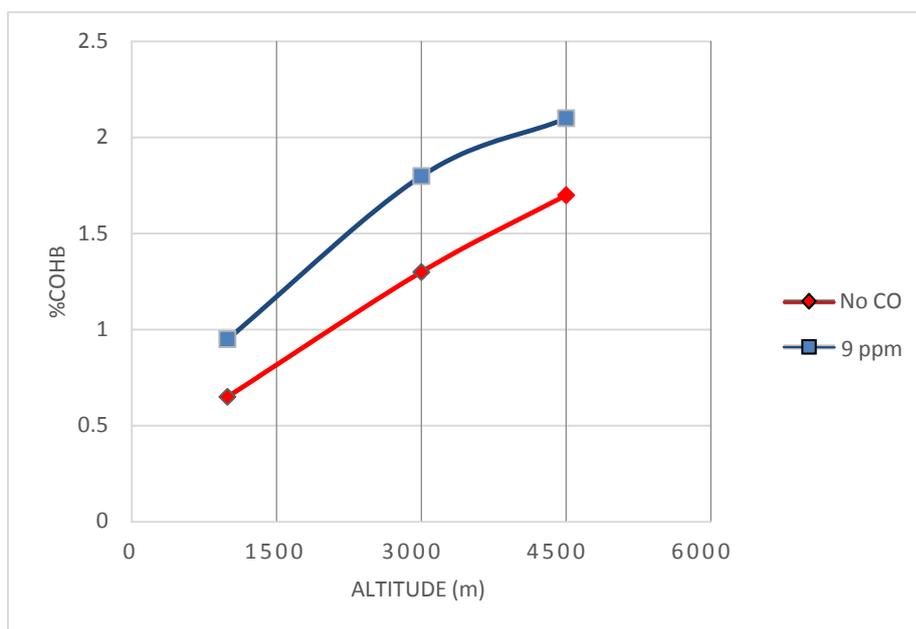

Figure 8. Showing %COHb in the blood after being exposed to either no CO or a concentration of 9ppm across 3 altitudes. Exposure lasted 6 weeks. After (50).

Decreased learning capacity in regards to complex tasks has been documented due to altitude hypoxia alone, at 1524m (5000ft), the majority of subjects displayed slower reaction times during the early stages of learning a new task. Once the task was learned however elevations up to 2438m (8000 ft) seemed to have no effect. Whether a combination of CO exposure and altitude can produce a more aggravated effect is yet to be determined(44) .

It has already been demonstrated that the relationship between CO exposure and altitude is additive in nature rather than synergistic. However it is important to note that during prolonged stays at significant elevation, long term physiological adoptions take place in lieu of the short term compensatory mechanisms already discussed. This means that it is possible a simple additive model is only valid during the early stages of acclimatization. In other words the new visitor will be at greater relative risk than native residents at high altitude. The window of vulnerability would be greater in particular for the elderly as the speed of the acclimatization process decreases with increasing age. (29)

7. Conclusion

For a given exposure to the same partial pressure of CO, persons at altitude will exhibit a greater rise as well as steady state value of COHb levels than similar persons at sea level. Acute symptoms for a particular level of blood COHb also seem to be magnified at altitude, whether this translates to a greater risk of death is unknown. It is therefore clear that guidelines for CO exposure at sea level are not well suited to elevated environments.

Several gaps in knowledge requiring further research or validation remain, for example there is growing evidence suggesting direct interruption of cellular activity by CO plays a greater role than previously thought. The effect of altitude on such secondary means of toxicity needs to be explored further. As already mentioned the possibility for greater accumulation across multiple consecutive exposures at elevation also needs validation.

This review has also brought to light several studies suggesting that the 10% threshold for onset of symptoms due to COHb at sea level needs revaluation as this is at best an upper bound only and does not effectively mitigate risk of exposure at altitude. Although a conclusive carboxyhemoglobin curve with quantitative data at altitudes is yet to be determined, a very useful figure has been included in this report which combines the effects of altitude and CO exposure into an equivalent 'physiological altitude'. However whether this data can be extrapolated to beyond the experimental conditions is unknown.

Studies into chronic exposure at altitude are limited in number and mostly based on animals rather than humans; there is some evidence to suggest however that long term sojourners or natives high above sea level are relatively less at risk due to long term morphological changes having taken place. Therefore new investigations into effects of CO should perhaps focus on the more susceptible groups such as tourists and the elderly.

Perhaps one of the most important highlights of this project was shedding light on the misconception currently present even in the latest NFPA 720 standard, with regards to correlating COHb levels to clinical symptoms. Since the primary purpose of CO detection is to initiate a warning before symptom onset, this issue *must* be resolved prior to furthering the discussion into the realm of altitude effects. As a first approach a more comprehensive study where COHb levels are measured directly after exposure for a large sample population is recommended. The latter is likely to be become feasible shortly as recently a hand help pulse CO oximeter capable of easily and non-invasively recording COHb values (among other parameters) was marketed. If at some point this technology becomes available to firefighters or first responders, we could see the influx of much more accurate data.

The highest continuously occupied human habitation in North America is 11,680 feet (3,560 meters), at which atmospheric pressure is approximately 66% of sea level pressure. Safety system designed to prevent CO poisoning must incorporate thresholds that are safe at altitudes where people reside. There is clearly a profound difference in CO toxicity at elevation, in terms of uptake, half-life as well the physiological response. On this basis we recommend that further research be carried out to produce a quantitative carboxyhemoglobin curve to complement the existing one for sea level. Once this first hurdle is cleared the relationship between COHb and symptoms can be reinvestigated under the influence of altitude.

8. Acknowledgements

9. References

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