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A relationship between temperature, oxygen dissolved in blood and viral infections

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Abstract

An investigation is made on the environmental factors that may determine the seasonal cycle of respiratory affections. The driving role of temperature is examined, for its inverse synergism with the dissolution of oxygen in human plasma. Two best-fit equations are discussed to interpolate the experimental data about the oxygen solubility and the saturation levels reached at various temperatures, referring to the value of the basic alveolar temperature. A vulnerable condition is when the airways temperature is lowered, e.g. breathing cold air, or increasing the breathing frequency. In winter, the upper airways reach lower temperatures and greater oxygen concentrations; the opposite occurs in summer. As low temperatures increase the dissolution of oxygen in plasma, and blood oxidation favours viral activity, an explanation is given to the seasonality of infections affecting the respiratory system.

Keywords: Temperature; Oxygen solubility; Body temperature; Respiratory disease; Viral infection; COVID-19.

1. Introduction

Since the period of the earliest meteorological observations, attention was paid to investigate the relationships between climate, agricultural production and human diseases. Among the most famous scientists who gave the most significant contributions to this field, specific mention should be made to Bernardino Ramazzini for his yearly reports about agricultural and human epidemics related to the seasonal climate variability [Ramazzini, 1718] and his book on occupational illnesses and injuries [Ramazzini, 1700] in which he considered the impact of the environmental conditions on health. James Jurin coordinated an international Network of the Royal Society, London, concerning indoor observations useful for climate and health studies [Jurin, 1723], especially useful considering the conditions of the sick buildings in the 18th century. This Network was followed by a similar one organized by Felix Vicq d'Azyr and Father Louis Cotte. They set up a series of national and international records on behalf of the newly founded *Societé Royale de Médecine* (Royal Society of Medicine), Paris, [Cotte 1774; 1788]. Giuseppe Toaldo took and analyzed meteorological records studying the relevance of seasonal and astronomical cycles. He published a famous meteorological essay to relate the influence of the Moon and other celestial bodies, the seasonal cycles, the dry or rainy weather, the extreme weather events and the frequency in human mortality [Toaldo, 1770]. This book was translated in French, English and German and was reprinted several times.

Today it is known that certain viral forms, but not all, have a seasonal character. The relationship with temperature is clear for SARS-CoV-2 [Chin et al., 2020]. As far as COVID-19 is concerned, Briz-Redón and Serrano-Aroca [2020] found no evidence. On the other hand, Roy [2020] found that global temperature played an important role and a moderately cool environment was the most favourable state for virus transmission. The risk from the virus was reduced significantly for warm places and countries. The seasonal risk has been confirmed by the European Centre for Disease Prevention and Control [ECD, 2020]: the number of COVID-19 deaths in Europe, as of 29 December 2020, shows a marked peak in April, a flat minimum over summer and then a sharp rise starting from October.

However, even in cases where seasonality is evident, the complete mechanism has not been clarified, especially for diseases transmissible person-to-person [Shek and Lee, 2003; Lofgren et al., 2007; Chan et al., 2011; Fisman, 2012; Alvarez-Ramirez and Meraz, 2020; Chen et al., 2020; Gutierrez-Hernandez and Garcia, 2020; Moriyama et al., 2020]. Explanations have been based on a series of environmental, physical, chemical, biological, medical, social and other factors, that may be grouped into three categories:

- environment and climate-related factors, e.g. temperature, humidity, solar radiation and in particular UV radiation acting as a disinfectant for contaminated nonporous materials or because it favours the synthesis of vitamin D in the body and the body defence [Sloan et al., 2011; Azziz Baumgartner et al., 2012; Beck et al., 2016; Isaia and Medico, 2020; Isaia et al., 2020; Sagripanti and Lytle, 2020; Schuit et al., 2020; Ratnesar-Shumate et al., 2020]; air pollution [Lebowitz, 1996; Cui et al., 2003] and transport of viruses (e.g. arrival of migratory birds) [FAO, 2007].
- social activities and human behaviour that may increase transmission (e.g. longer residence time inside poorly ventilated rooms, crowding, contagion opportunities, droplet transmission) [Willem et al., 2011; Zayas et al., 2012; Han et al., 2013; van Doremalen et al., 2020; Liu et al.; 2020]. Besides, low relative humidity levels, either caused by heating or air conditioning, enhance indoor dustiness and the suspension time of airborne particulate matter [Chan et al., 2011; Camuffo, 2019] thus increasing the probability of inhaling viruses.
- human body defence (e.g. response of the mucosal surface of the respiratory tract), physiological risk factors (e.g. age, obesity) and other medical items [Fokkens and Scheeren, 2000; Iwasaki et al., 2017; Li et al., 2011; Moriyama et al., 2020].

The above factors, alone or in synergism, are supported by reasonable explanations, correlations and statistical calculations. Some researchers [Fisman, 2012; Gutierrez-Hernandez and Garcia, 2020] agree that cool and dry environments are most frequently related to the virus diffusion, but their feeling is that there are only indications, rather than scientific evidence, i.e. atmospheric conditions may explain a limited part of the dynamics of viral affections.

This paper is not intended to analyse the virus life, viral concentration in air, diffusion in indoor and outdoor environments, transmission from person to person etc. that are widely studied in scientific literature. This paper investigates other possible linkages to relate viruses to environmental conditions, in particular the potential effect of some small changes in temperature of certain organs inside the body. The inhaled air, with its physical characteristics, constitutes the starting point, regardless of where it is breathed, either indoors or outdoors. A three-step mechanism is considered, i.e. the relationship between specific physical characteristics of the inhaled air (e.g. temperature, relative humidity, ventilation rate) and the oxygen dissolved in blood; how the temperature of the various parts of the body is subject to change; why the consequences of this fact may be relevant for viral infections. The work is organized in three sections. The first section calculates the amount of oxygen dissolved in blood as a function of the ambient temperature. The second deals with the temperature of the respiratory system, that is neither constant nor homogeneous, because the temperature of the upper airways is driven by the temperature of the inhaled air. The third considers that different temperatures will cause different saturation levels of the oxygen in the blood and that some viral affections may take advantage from higher oxygen concentrations.

2. Air temperature and the oxygen dissolved in blood

The oxygenation of blood is a mechanism that may explain a significant synergism between environmental and physiological factors. Oxygenation is highly relevant because oxygen acts as terminal electron acceptor at the end of the electron transport chain whereby oxidative phosphorylation results in the synthesis of adenosine triphosphate (ATP). This coenzyme supplies energy to all active metabolic processes [Dunn et al., 2016], including viral activity. In addition, it has been demonstrated that antioxidants display relevant antiviral activity [Silva et al., 2011; Wangkheirakpam, 2018]. Therefore, an elevated oxygen concentration in blood constitutes a vulnerable situation because it favours viral activity.

Gaseous oxygen is first dissolved in plasma and then most of it is chemically combined with the haemoglobin.

Oxygen dissolution constitutes the input of the complex system that distributes oxygen to all parts of the body. Oxygen delivery in the human respiratory system depends on several factors including the partial pressure of oxygen, the efficiency of gas exchange, the concentration and affinity of haemoglobin to oxygen and cardiac output [Law and Bukwirwa, 1999]. The highest oxygen concentration is typically found in the respiratory tract, from where it is distributed throughout the body.

The oxygen content of arterial blood is the sum of the oxygen bound to haemoglobin and oxygen dissolved in plasma [Dunn et al., 2016]. The solubility of oxygen in an aqueous solution is regulated by the Henry's Law [Pauling, 1947] that states that, at a constant temperature, the concentration of oxygen in the aqueous phase is proportional to the partial pressure of oxygen in the gaseous phase in equilibrium with the liquid. However, the coefficient of proportionality is an inverse function of temperature, i.e. decreasing when temperature increases and may be represented with a single or a combination of exponential functions. This has been established for pure water, ponds, aquacultures, marine environments [Millero et al., 2002; Geng and Duan, 2010; Karbowiak et al., 2010; Valderrama et al., 2016; Eze and Ajmal, 2020], but also for physiological aqueous solutions of NaCl and human plasma [Christoforides et al., 1969; Christmas and Bassingthwaighte, 2017].

Christoforides et al. [1969] measured the concentration of oxygen X_{O2} [mL(gas)/L(fluid)] dissolved in human plasma at different temperatures T (°C) in the interval from 10 to 60° C, at standard atmospheric pressure. The observed data may be interpolated with two best-fit equations (Figure 1).

The logarithmic best-fit is

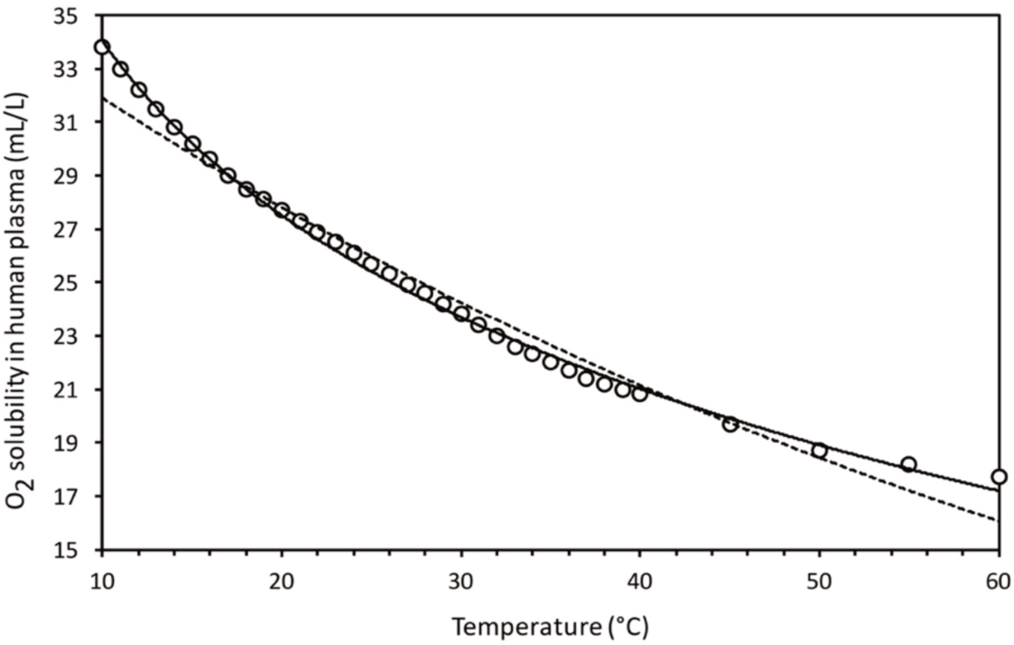

Figure 1. Solubility of oxygen in human plasma X_{O2} [mL(gas)/L(fluid)] at standard atmospheric pressure. Circles: experimental data by Christoforides et al. [1969]; continuous line: logarithmic interpolation; dashed line: exponential interpolation.

$$X_{O2} = -9.401\ \ln(T) + 55.684 \tag{1a}$$

with excellent determination coefficient $R^2 = 0.997$ and, over the whole range, the observed values depart less than 1 [mL(gas)/L(fluid)] from the logarithmic best-fit. The exponential best-fit is

$$X_{O2} = 36.616\ \exp(-0.014\ T) \tag{1b}$$

with slightly smaller R^2, i.e. $R^2 = 0.971$. The exponential approximation is equally good within the 20-40°C interval but, externally to it, the observed values depart from the best-fit, reaching 2 [mL(gas)/L(fluid)] at the lower extreme (i.e. 10° C), and a similarly at the upper one (i.e. 60° C). However, in the 20-40° C interval, that is the most relevant for the human body, both approximations are satisfactory.

3. Uneven distribution of temperature in the respiratory system

The temperature of the body of a healthy person has an uneven distribution. Under normal conditions, the internal organs benefit of thermoregulation and keep a fairly constant temperature, i.e. 37°C that is the basic situation for the blood oxygenation in the lung alveoli [D'Amato et al., 2018]. As opposed, the temperature of the peripheral areas of the body, the skin and the upper airways may be variable. This temperature is determined by complex exchanges of heat and moisture (i.e. sensible heat and latent heat) between the body and the environment. The environmental factors that should be considered for this complex heat balance are: air temperature, infrared radiation and, secondarily, relative humidity and ventilation [Fanger, 1982; ISO-7730, 2005]. The airways represent an internal interface between the body and the environment. The epidermis is the external interface and constitutes a very small secondary respiratory system, i.e. 5% of the total. Over the year, the various parts of the body undergo a temperature cycle whose relevance is determined by their position and function.

The exhaled breath temperature can be easily measured [Popov et al., 2012]. However, with the use of catheters with thermistors, fiberoptic bronchoscopes and other devices, also the temperature inside the respiratory ways has been monitored. It has been found to be determined by ambient temperature and ventilation, i.e. exchanged air volume [Afonso et al., 1962; McFadden et al., 1985]. In winter, when cold air is inhaled, the upper airways from nose to trachea are severely affected by cooling and the cooling decreases progressing in the lower airway inside lungs. The expiration too is affected: the greater the cooling during inspiration, the lower the temperature during expiration. For instance, experiments made with very cold air (i.e. -18.6° C) at various ventilations (VE) per minute shown that during inspiration the glottis temperature falls from 28° C at VE = 15 min^{-1} to 20.5° C at VE =100 min^{-1} and during expiration from 29.5° C at VE 15 min^{-1} to 22.5° C at VE=100 min^{-1} [McFadden et al., 1985]. Each cold inhalation is followed by a milder, humid exhalation, determining a sinusoidal trend in which the solubility of oxygen is favoured during the colder inhalation phase.

In winter, under normal conditions, each breath brings in cold, dry air, that exchanges sensible and latent heat at a frequency of 12 to 20 inhalations per minute [Flenady et al., 2017]. When cold air is inhaled, the airway tissues are cooled and dried, with negative effects on the lungs for people with respiratory diseases and in particular asthma [D'Amato et al., 2018].

4. Consequences of the different saturation levels reached by oxygen in blood

The studies concerning the gas solubility in plasma and the temperature changes of the respiratory airways may be combined to explain some respiratory morbidity related to the seasonal climate cycle. This means to calculate how the dissolved concentration of oxygen in blood changes in relations to the reference value X_{O2} = 21.4 [mL(gas)/L(fluid)] found by Christoforides et al. [1969] at normal lung temperature, i.e. 37° C, and at standard atmospheric pressure.

In this paper, the amount of oxygen dissolved in the human plasma has been calculated for temperatures from 20 to 45° C and the result has been expressed in percent (%) of the typical saturation value at 37° C, assumed to be 100%. (Figure 2). The result is a comparison between the various oxygen saturation levels (SL_{O2}); the percent representation is similar to the output of a saturimeter, also called oximeter, i.e. the medical instrument to monitor the blood oxygenation level. The selected range is representative of the upper airways [McFadden et al., 1985].

This variable has been calculated with the equation

$$SL_{O2}\,(T) = 100\,\frac{X_{O2}\,(T)\text{-}X_{O2}(37°\,C)}{X_{O2}(37°\,C)} + 100 \tag{2}$$

In the 20 to 45°C range, the logarithmic and the exponential interpolations

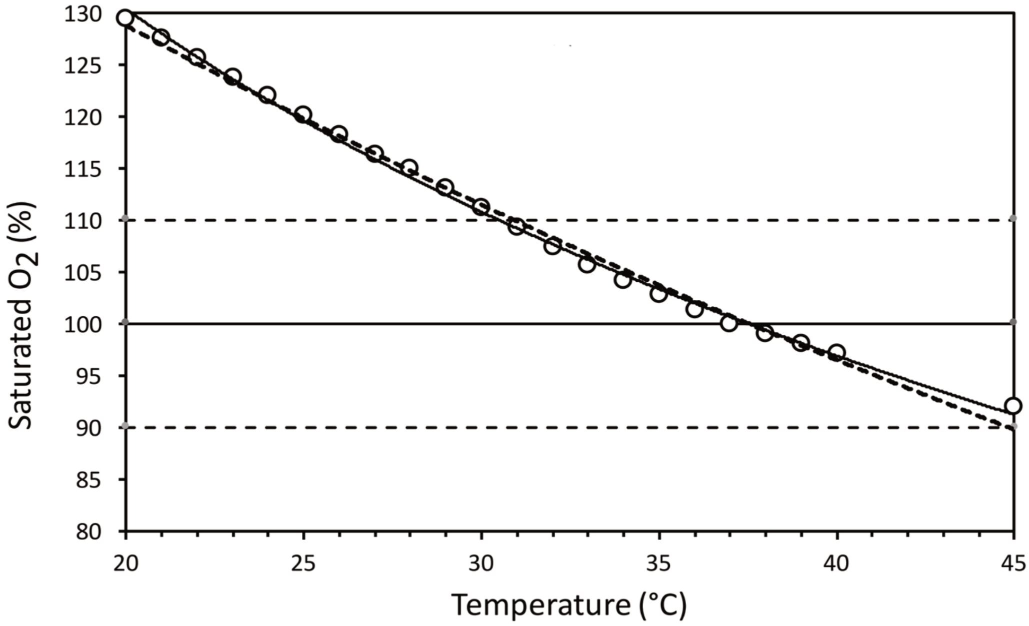

Figure 2. Saturation level of the oxygen dissolved in human plasma at various temperatures, referring to the value at 37° C, assumed to be 100%. Circles: saturation of experimental data; continuous line: logarithmic interpolation; dashed line: exponential interpolation. Horizontal lines pinpoint the 90, 100 and 110% levels.

$$SL_{O2} = -48.28 \ln(T) + 275 \quad (3a)$$

$$SL_{O2} = 171.8 \exp(-0.014\, T) \quad (3b)$$

are characterized by similar determination coefficients, i.e. $R^2 = 0.998$ for the logarithmic interpolation and $R^2 = 0.994$ the exponential one. Both equations can be used to evaluate how much the oxygen solubility and the reached saturation level are increased when the blood cools, or depressed when the blood warms.

To illustrate the mechanism, some hypothetical examples of oxygen dissolved in blood at selected temperatures are reported in Table 1. The first row includes the headings with selected temperatures. The next two rows report the percentage difference compared to the normal alveoli temperature assumed to be 100%.

Temperature	20° C	25° C	30° C	35° C	40° C	45° C
Saturation value	129 %	120 %	111 %	103 %	97 %	92 %
Difference from 37° C	+29 %	+20 %	+11 %	+3 %	-3 %	-8 %

Table 1. Comparison between the levels of oxygen dissolved at saturation in human plasma at selected temperatures, making reference to the basic value at normal alveoli temperature, i.e. 37° C.

The table shows the example that, if the temperature drops to 30° C or 20° C, the oxygen saturation level will increase by +11% or +29% respectively, compared to the reference value at 37° C. Conversely, it decreases if the temperature rises. In particular, in the interval around the normal alveolar temperature, the change rate is 1.4 %/° C.

In winter, the respiratory system lowers its temperature, oxygenation increases efficiency and tends to hyperoxemia, like the effect of higher ventilation. Airborne viruses find more oxygenated cells that constitute the very first hosting site and determine the prerequisite for their development and harmfulness. Generally, viruses that naturally infect well-oxygenated organs (i.e. in the cold season) are less able to infect cells under hypoxic conditions (i.e. in the warm season) and vice-versa [Gan and Ooi, 2020]. Some viral affections, typical of the cold season, take advantage from the higher oxygen concentration in blood. This suggests that the greatest vulnerability is in winter, when one enters a crowded building, because the temperature of the upper airways is lower, the oxygenation level higher, and the virus transmission easier.

As opposed, any temperature increase, such as the febrile response, would decrease the oxygen dissolution and increase the resistance to viruses [Ogoina, 2011]. Fever generates a temporary increase in body temperature to fight infections, reducing the availability of oxygen and reproduces the mechanism determined by the warm season.

In this respect, besides to filter air, protective face masks provide, although to the minimum extent, another unexpected advantage. They reduce the free exchange of air and the CO_2 dissipation, which implies fewer airways cooling and lower oxygenation rate and both these factors contribute to reduce viral infections.

The inhalation of hot summer air raises the airway temperature and oxygenation will decrease tending to hypoxemia, with an effect similar to lower ventilation. It is known that summer heat waves may lead to hypoxia, as it has been observed in human communities, animals and marine environments [Frölicher and Laufkötter, 2018; Stillman, 2019; McArley et al., 2020]. It is also known that cardiovascular affections dramatically increase in hot days [Petralli et al., 2012; Grasso et al., 2017] and in urban heat islands [Paravantis et al., 2017] for the effort of combining thermoregulation with intense heart activity needed to compensate for the lower oxygen concentration.

Last but not least, if high summer temperatures represent an adverse situation for viruses living in cold environments, rooms overcooled with air conditioning systems may break the physiological protective cycle that the warm season offers to the upper airways, altering the degree of oxygenation with not easily predictable implications for respiratory morbidity.

The saturation level of peripheral oxygen, as well as the respiratory frequency, are considered the first and second most sensitive vital signs, used as predictors of in-hospital mortality [Barfod et al., 2012].

4. Conclusions

This paper has considered that the ambient air temperature, its influence on the upper airways, the dissolution of oxygen in blood and the viral activity generate a sequential mechanism and each step of it is in accordance with findings reported in the literature.

This mechanism may offer the key to understanding some relationships between environmental and physiological factors, including the seasonality of viral infections. Of course, this study does not include the contribution of human factors and transmission opportunities. The applications to human health are of potential interest but need a thorough multidisciplinary analysis and verification before being applied.

The upper airways are exposed to direct contact with inhaled air, airborne aerosols and viruses and follow a dynamic equilibrium with the external temperature and, secondarily, relative humidity. The seasonal cycle of environmental variables (i.e. the temperature and, secondarily, relative humidity) affects the temperature and the moisture balance of the upper tract of the respiratory system.

It has been found that the best-fit of the oxygen solubility may be represented either by a logarithmic or an exponential function, but the logarithmic one is supported by a slightly higher determination coefficient. This investigation has shown that the seasonal cycle of temperature determines a cycle of the oxygen concentration in blood and the saturation level changes at a rate of 1.4 %/° C.

The temperature-oxygenation relationship and related hypothermia and hyperthermia, are physical mechanisms and the human body can take advantage of them (e.g. the fever as a form of defence of the organism against viral infections) or disadvantage (e.g. heat waves and hypoxia; weak immune defence).

Global warming, heatwaves, urban heat islands and bad climatisation are new challenges affecting the oxygen dissolution and the potential increase of morbidity for respiratory and cardiovascular diseases.

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