Chapter 2
Absorption and Release of Hydrogen Gas in Body

Dong Cao, Zhouheng Ye and Wenwu Liu

Abstract The definition of inert gases is different in the fields of chemistry and physiology. Physiologically, inert gases mainly include hydrogen, helium, and nitrogen and refer to those that cannot react with other substances in human body although hydrogen is a highly active gas in chemistry. Under normal condition, the human body is saturated by nitrogen. When we inhale another inert gas at a high pressure or normal pressure, the new inert gas may enter the human body in the drive of pressure gradient force. The law of saturation and desaturation of inert gases has been summarized by Haldane, a Scottish physiologist. In this chapter, we discuss the saturation and desaturation of inert gases, with nitrogen as an example. Drinking hydrogen water or injection with hydrogen saline has similar pattern in the absorption and washout of hydrogen in human body to the inhalation of hydrogen except for the high velocity for hydrogen. Also, since hydrogen diffuse rapidly, it could release through skin when the concentration of hydrogen is out of capacity.

Keywords Diffusion · Blood · Saturation · Desaturation · Concentration

2.1 Hydrogen Gas Is Physiologically Inert Gas

Inert gases that are often mentioned in diving medicine have different concepts and meanings from the chemically inert gases. The chemically inert gases refer to those molecules with the outermost shell of their atom filled with electrons, and mainly consist of helium family gases, namely helium, neon, argon, krypton, xenon,

W. Liu (✉)
Department of Diving Medicine, Second Military Medical University, Shanghai, China
e-mail: liuwenwu1980@hotmail.com

D. Cao
Department of Osteology, The sixth people's hospital, Shanghai, China

Z. Ye
Department of Navy Aeromedicine, Second Military Medical University, Shanghai, China

X. Sun et al. (eds.), *Hydrogen Molecular Biology and Medicine*,
DOI 10.1007/978-94-017-9691-0_2

Table 2.1 Commonly used physical parameters of various inert gases

Gas	MW	Density (g/L, STP)	Ratio (with air as 1)	Viscosity (μPa·s, STP)	Diffusion coefficient (cm^2/s, STP)	
					In water	In air
H_2	2	0.09	0.0695	8.4	[a]5.2×10^{-5}	0.63
He	4	0.18	0.138	18.6	7.9×10^{-5}	0.503
Ne	21	0.90	0.695	29.8	3.48×10^{-5}	0.222
N_2	28	1.25	0.967	16.6	3.01×10^{-5}	0.190
Ar	40	1.79	1.379	21.0	2.52×10^{-5}	0.159
Kr	83.8	3.70	2.868	23.3	1.75×10^{-5}	0.110
Xe	131.5	5.58	4.525	21.0	1.39×10^{-5}	0.088

STP standard conditions (temperature, pressure), *MW* molecular weight
[a] Measured at 21°C

and radon. These gases have very good chemical stability and are difficult to participate in chemical reaction under general condition; therefore, they are termed as inert gases. However, inert gases in diving medicine and physiology, which are also known as "neutral gases," refer to those gases only present within the body in a physically dissolved state, and maintain their original nature. They do not react with other substances in the body, do not participate in the body's metabolism, and freely diffuse according to the partial pressure gradient of the gases in vitro and in vivo. By definition, helium, nitrogen, and hydrogen are used as inert gases in diving medicine (Table 2.1). However, according to the results in hydrogen molecular biology, hydrogen may have some reactions with other substances in vivo. Then whether gases that can react with other substances are still considered inert gases? The only effective means to solve this problem is to modify the definition of inert gas in diving medicine. From this perspective, the research on the biological effects of hydrogen can at least lead to a reconsideration about the gases in diving medicine, and also have a very important role in promoting studies in diving medicine.

The inert gas that is most commonly used in medicine and physiology is nitrogen. But its outermost shell is not filled with electrons, so it does not belong to chemically inert gases; hydrogen has an active chemical property, but it has been demonstrated as an inert gas used in diving. Helium is an inert gas often used in deep diving. Thus, it is obvious that inert gases in diving medicine-physiology not only include some chemically inert gases but also include some nonchemically inert gases, or even chemically active gases. Therefore, these gases should be interpreted as "physiologically inert gases."

Inert gases are not useless or dispensable for human survival; instead, they are indispensable component of the gas medium to maintain life. To maintain the oxidation–phosphorylation energy metabolism which is essential to life, the inhaled gas must contain a certain proportion of oxygen. But if the partial pressure of oxygen is too high or even pure oxygen, then it will cause damage to the body or even death since the presence of excessive oxygen is toxic to the body. Typically, the air we breathe contains 21 % of oxygen. Oxygen of this concentration and pressure, which is termed as normoxia, is optimal for human survival. It is the 78% of nitrogen contained in the air that helps maintain the state of normoxia. Nitrogen plays a role of "oxygen diluent" in this condition. When doing diving/high-pressure operations, pure oxygen is only used in some certain forms of shallow depth or short duration, while inert gases shall be used in other forms of operation with specific conditions, i.e., using a mixture of inert gas and oxygen as breathing medium under high pressure. Although the air is a mixture of nitrogen and oxygen, the mixed gases, we generally refer, are gases artificially mixed with oxygen and inert gases in a specific ratio. The commonly used mixed gases include the mixtures of nitrogen and oxygen, helium and oxygen, hydrogen and oxygen, and other types of mixture gases.

After the inhaled oxygen dissolves into blood, it forms chemical compounds and is continuously consumed. When a body inhale a gas mixture that is different from the composition of air, the inert gas in the mixture will dissolve into blood and accumulate gradually, and reach a state called "saturated" in which the tension of the dissolved gas achieve an equilibrium with the partial pressure of the gas in the environment. At this time, if the air pressure of the environment falls (reduce pressure) or if the total air pressure of the environment does not fall but the concentration of the inert gas is reduced (replaced by other kinds of gases), then the tension of the previously mentioned dissolved inert gas is higher than the partial pressure of the gas in the environment, forming a state called "supersaturated." At this time, the dissolved gas in the tissue will diffuse into the environment and become free gas, which is known as "desaturation," until it reaches an equilibrium state again.

When the body breathes a new gas mixture of different components, it must go through three phases—a phase of start breathing, a stable phase, and a phase of stop breathing. To facilitate understanding, we refer to the case of breathing high-pressure air to explain how the inert gas enter into the body in the beginning, what is the distribution characteristics in the body, and how inert gases are released from the body during the phase of stop breathing or during the decompression process. These laws are put forward by Haldane in early twentieth century. Through summarizing the practical experience of air diving and carrying out animal experiments, they elaborated the movement rule of nitrogen, one of the inert gases, in the body when diving, and established a corresponding doctrine, forming a classical theory on the movement rule of the inert gases in vivo in the modern diving medicine. The subsequent development and improvements of the movement rule are based on this theory. This chapter focuses on the basic theory of Haldane doctrine and takes nitrogen as an example to clarify the movement rule of an inert gas during the pressurization and decompression processes.

Although breathing a small amount of hydrogen is somewhat different from breathing high-pressure hydrogen or nitrogen, but their basic rules are similar. The rules of breathing different inert gases are similar. Furthermore, if hydrogen enters into the body through gas routes such as intraperitoneal injection or drinking water containing hydrogen, then hydrogen will be rapidly absorbed by the body according to concentration gradient. Although the speed of absorption and the way of breathing in this case differ from normal breathing of hydrogen, there is still similarity in their way of releasing hydrogen.

2.2 Absorption of Hydrogen Gas

2.2.1 Saturation and the Degree of Saturation

In chemistry, the term “saturation” refers to a condition that the concentration of solute in the solvent reaches the maximum solubility limit.

In this book, the concept of “saturation” is different from its chemical concept. Moreover, it is not only used as a noun, adjective, but also used as a verb, which are listed below [1]:

1. If a gas is dissolved in the body fluid or tissue and its tension is equal to the partial pressure of the gas in vitro, i.e., the amount diffusing back out is equal to the amount diffusing in per unit time, then this state of dynamic equilibrium will be called “saturation.”
2. If dissolved gases in a certain tissue reach saturation, then the tissue is called “saturated tissue.”
3. When the partial pressure of a gas in the environment is higher than the tension of the gas in tissue, the in vitro gas will diffuse into the body by the pressure gradient. Over time, the tension of the gas in body will increase gradually until the pressure gradient disappears. This process is known as “saturation.”

“Saturation” is a term used to indicate the saturation level in hyperbaric medicine. For the convenience of quantitatively expressing the different degrees of saturation and accurately calculate and compare them, a state of saturation is called complete saturation; a state that does not reach complete saturation is called a partial saturation state. If a partial saturation state reaches half of the expected full saturation, then it is called to be in a half-saturation state.

The saturation of inert gas in vivo is commonly expressed as a percentage. For example, 100 % saturation means complete saturation, 50 % means half-saturation, and so on. Correspondingly, the shortfall of saturation is also expressed as a percentage which means the unsaturated level. There is a reciprocal relationship between saturation and saturation shortfall. Their sum equals to 1.

2.2.2 Half-Saturation Time and Half-Saturation Time Unit

Half-saturation time is first proposed by Haldane. It refers to the time needed for “filling” half of the inert gas saturation shortfall that exists in certain types of tissue, and it is usually expressed as a symbol $t_{1/2}$. For example, “filling” half of the nitrogen saturation shortfall in blood or lymph needs 5 min, while “filling” half of the nitrogen saturation shortfall in the gray matter of the central nervous system needs 10 min; this 5 min is considered the half-saturation time of nitrogen in the blood, lymph, and some other tissues; and this 10 min is considered the half-saturation time of nitrogen in the gray matter of the central nervous system.

Half-saturation time is used as a timing unit to represent the saturation time for the inert gases, and it is called “half-saturation time unit.” The half-saturation time unit (n) is equal to the quotient of the actual time (T) divided by the half-saturation time:

$$n = T / t_{1/2}.$$

For example, if the human body is exposed to the compressed air for 40 min, then for the blood and lymph ($t_{1/2}=5$), $n=40/5=8$ half-saturation time units; while for the gray matter of the central nervous system ($t_{1/2}=10$), $n=40/10=4$ half-saturation time units.

2.2.3 Process of Saturation

1. Completing saturation process through respiratory and circulatory system

After the body entering into a high-pressure environment, breathing gases of different compositions is similar to this case. If the partial pressure of nitrogen in the gas mixture is higher than the tension of dissolved nitrogen in the blood, then the gaseous nitrogen will spread rapidly through the alveoli into the blood and be taken by arterial blood to body tissues. The areas of the alveolar wall and the systemic blood capillary are very large and their walls are very thin; therefore, gas exchange between the lungs and body tissues can be said to be done in an instant. The main time of the saturation process is spent on the transport of gas through blood. It takes about 18 s for blood to circlulate inside the whole body. After the gas is delivered by blood to the tissues, the regurgitant venous blood will reengage with the alveoli. By this time, the pressure gradient of nitrogen between the mixed gases and the blood has been reduced compared to that in the previous circulation, and the diffusion of the inert gas from the alveoli into the blood and from the blood to the tissues is also decreased compared to that in the previous circulation. Repeatedly, over time, the tension of an inert gas within the tissues will reach equilibrium with the partial pressure of the gas in the environment, and the pressure gradient of the inert gas among alveolar air, blood, tissues, and venous blood will all disappear.

2. The growth rate of saturation reduces exponentially when the number of circulation or time units increases

Under atmospheric pressure, the tension of nitrogen in the body has been in a state of equilibrium with the partial pressure of nitrogen in the air. For a general adult male, the dissolved nitrogen in his body is approximately 1000 ml. Among this amount, the dissolved nitrogen in the blood is about 39 ml, which accounts to approximately 4% of the total dissolved nitrogen in the body. When the body has just entered the high-pressure, the saturation shortfall is 1. After a cycle of the systemic blood circulation (18 s), the body will increase the nitrogen saturation by 4%

Table 2.2 Nitrogen saturation calculated with blood circulations as timing unit

Order of time unit (n)	Cumulative time (s) ($n \times 18$)	Saturation completed ($4\% \times (1-4\%)^{n-1}$)	Saturation shortfall ($(1-4\%)^n$)	Cumulative saturation ($1-(1-4\%)^n$) (%)
1	$1 \times 18 = 18$	$4\% \times (1-4\%)^0 = 4\%$	$(1-4\%)^1$	4.000
2	$2 \times 18 = 36$	$4\% \times (1-4\%)^1 = 3.84\%$	$(1-4\%)^2$	7.840
3	$3 \times 18 = 54$	$4\% \times (1-4\%)^2 = 3.68\%$	$(1-4\%)^3$	11.526
4	$4 \times 18 = 72$	$4\% \times (1-4\%)^3 = 3.54\%$	$(1-4\%)^4$	15.064
5	$5 \times 18 = 90$	$4\% \times (1-4\%)^4 = 3.40\%$	$(1-4\%)^5$	18.461
6	$6 \times 18 = 108$	$4\% \times (1-4\%)^5 = 3.26\%$	$(1-4\%)^6$	21.722
7	$7 \times 18 = 126$	$4\% \times (1-4\%)^6 = 3.13\%$	$(1-4\%)^7$	24.853
8	$8 \times 18 = 144$	$4\% \times (1-4\%)^7 = 2.88\%$	$(1-4\%)^8$	27.858
9	$9 \times 18 = 162$	$4\% \times (1-4\%)^8 = 2.77\%$	$(1-4\%)^9$	30.744
10	$10 \times 18 = 180$	$4\% \times (1-4\%)^9 = 2.66\%$	$(1-4\%)^{10}$	33.514
11	$11 \times 18 = 198$	$4\% \times (1-4\%)^{10} = 2.55\%$	$(1-4\%)^{11}$	36.173
12	$12 \times 18 = 216$	$4\% \times (1-4\%)^{11} = 2.45\%$	$(1-4\%)^{12}$	38.726
13	$13 \times 18 = 234$	$4\% \times (1-4\%)1^2 = 2.35\%$	$(1-4\%)^{13}$	41.527
14	$14 \times 18 = 252$	$4\% \times (1-4\%)^{13} = 2.26\%$	$(1-4\%)^{14}$	43.527
15	$15 \times 18 = 270$	$4\% \times (1-4\%)^{14} = 2.17\%$	$(1-4\%)^{15}$	45.786
16	$16 \times 18 = 288$	$4\% \times (1-4\%)^{15} = 2.08\%$	$(1-4\%)^{16}$	47.955
17	$17 \times 18 = 306$	$4\% \times (1-4\%)^{16} = 2.08\%$	$(1-4\%)^{17}$	50.000
⋮	⋮	⋮	⋮	⋮
34	$34 \times 18 = 600$		$(1-4\%)^{34}$	75.000
⋮	⋮	⋮	⋮	⋮
51	$51 \times 18 = 900$		$(1-4\%)^{51}$	87.500
⋮	⋮	⋮	⋮	⋮
102	$102 \times 18 = 1800$		$(1-4\%)^{102}$	98.437

and the remaining saturation shortfall is "$1-4\%$;" the second cycle of circulation will complete 4% of the remaining shortfall, i.e., 4% $(1-4\%)$, and the remaining shortfall is $(1-4\%)^2$, and so on. Thus, we can see that the saturation that the latter circulation gained is diminishing exponentially compared to the previous one (Table 2.2). This is repeated until it is completely saturated.

If we use the half-saturation time as the timing unit, then the saturation of the inert gas gained in the first time unit is 50% and the saturation shortfall is 50%. In the second time unit, 50% of the saturation shortfall left in the first time unit is "filled," i.e., $50\% \times 50\% = 25\%$. The cumulative saturation that these two time units gained is 75%, and at this time, the saturation shortfall is 25%. In the third time unit, 50% of the saturation shortfall left in the second time unit is "filled," i.e., $25\% \times 50\% = 12.5\%$. The cumulative saturation reaches 87.5%, and by now the saturation shortfall is 12.5%, and so on. With the increase of the number of time units, the cumulative value of the saturation increases and the saturation shortfall left decreases (Fig. 2.1).

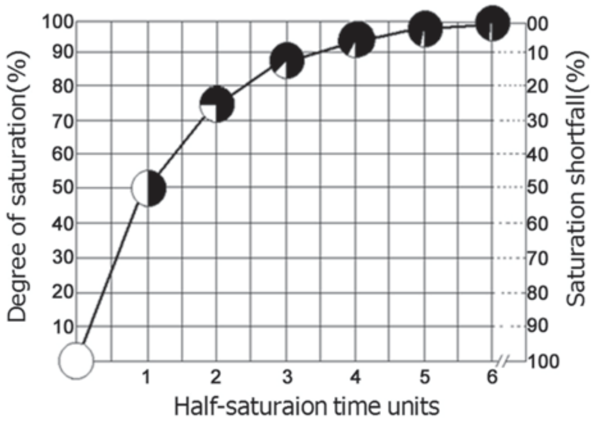

Fig. 2.1 The saturation growth diagram of inert gas (within the *circle* on the curve, the *blank* indicates the proportion of saturation shortfall, and the *blackened* indicates the proportion of the saturated)

In theory, to approach complete saturation needs numerous time units. But in general, when the saturation reaches 98 % after six time units, we will deem this saturation as 100 % saturation. The specific time of $t_{1/2}$ in different tissues is different. However, different tissues gained the same proportion of saturation within these six time units for the shortfall that inert gas left in the tissues.

The total saturation(s) cumulated after a certain number of time units (n) can be calculated using the following formula:

$$S = 1 - (1 - 50\%)^n.$$

Typically, this formula is simplified as $S = (1 - 0.5^n) \times 100\,\%$.

According to this formula, the cumulative value of nitrogen saturation after different time units of exposure can be calculated in detail (Table 2.3).

3. Inert gas in different tissues have different saturation velocity

If parameters of nitrogen dissolution in every tissue and in the blood are the same and the blood perfusion of every tissue is very abundant and smooth, then it will cost only 5 min to accumulate 50 % of nitrogen saturation in the whole body (see Table 4.2). However, components of body's various tissues vary from the blood, the solubility coefficients of nitrogen in different tissues differ greatly, and the blood perfusion statuses among different tissues also have a great difference. Thus, the half-saturation time cannot be the same in different tissues; that is, saturation velocities are different in different tissues.

If a tissue is high in lipid, then because the solubility of inert gas in lipid is higher than in water and the tension of gas in tissue rises slowly, so its half-saturation time is long (slow); if a tissue has a rich blood supply, then because it can dissolve more inert gas per unit of time, the tension of gas in tissue rises more quickly, so its half-saturation time is short (fast). For tissues high in lipid and rich in blood supply, their half-saturation time may not be long; while for tissues low in lipid but less in blood supply, their half-saturation time may not be short. Of course, for tissues with more lipid and less blood supply, their half-saturation time will be very long ("slow tissue");

Table 2.3 Nitrogen saturation calculated with half-saturation time units as timing unit

Half-saturation time units (n)	Growth rate of saturation ($50\% \times (1-50\%)^{n-1}$)	Saturation shortfall $(1-50\%)^n$	Cumulative saturation[a] $(1-(1-50\%)^n)$
1	$50\% \times (1-50\%)^0 = 50\%$	$(1-50\%)^1 = 50\%$	$1-(1-50\%)^1 = 50\%$
2	$50\% \times (1-50\%)^1 = 25\%$	$(1-50\%)^2 = 25\%$	$1-(1-50\%)^2 = 75\%$
3	$50\% \times (1-50\%)^2 = 12.5\%$	$(1-50\%)^3 = 12.5\%$	$1-(1-50\%)^3 = 87.5\%$
4	$50\% \times (1-50\%)^3 = 6.25\%$	$(1-50\%)^4 = 6.25\%$	$1-(1-50\%)^4 = 93.75\%$
5	$50\% \times (1-50\%)^4 = 3.12\%$	$(1-50\%)^5 = 3.12\%$	$1-(1-50\%)^5 = 96.8\%$
6	$50\% \times (1-50\%)^5 = 1.56\%$	$(1-50\%)^6 = 1.56\%$	$1-(1-50\%)^6 = 98.437\%$
...	...	...	...

[a] Commonly used formula: $S = (1-0.5^n) \times 100\%$

for tissues with less lipid and more blood supply, their half-saturation time will be very short ("fast tissue").

2.2.4 Theoretical Tissue Compartments

The body tissues were classified into five categories by Haldane depending on the nitrogen half-saturation time in the tissues, and such tissues are termed as the theoretical tissue compartment.

According to the length of half-saturation time, Haldane classified the body tissues into the following five categories (I–V) of theoretical tissue compartments:

Type I tissue compartments: $t_{1/2} = 5$ min, and also known as 5 -min tissues, including blood, lymph, etc.

Type II tissue compartments: $t_{1/2} = 10$ min, and also known as 10 -min tissues, including the gland, the gray matter of the central nervous system, etc.

Type III tissue compartments: $t_{1/2} = 20$ min, and also known as 20 -min tissues, including muscle, etc.

Type IV tissue compartments: $t_{1/2} = 40$ min, and also known as 40 -min tissues, including lipid, the white matter of the nervous system, etc.

Type V tissue compartments: $t_{1/2} = 75$ min, and also known as 75 -min tissues, including tendons, ligaments, etc.

The five theoretical tissue compartments have different half-saturation time, but as long as they were giving the same number of time units, they will achieve the same saturation. After six units of the respective half-saturation time unit, the saturation of all the five theoretical tissue compartments can reach 98%. We can also calculate the time required for each theoretical tissue compartment to achieve "complete saturation" according to their half-saturation time (t_s). The formula is $t_s = t_{1/2} \times 6$.

According to this calculation formula, the time required for the five theoretical tissue compartments to achieve "complete saturation" were, in order, $5 \times 6 = 30$ min, $10 \times 6 = 60$ min, $20 \times 6 = 120$ min, $40 \times 6 = 240$ min, and $75 \times 6 = 450$ min. Thus, it is visible that the longer the half-saturation time of a tissue is, the longer time is needed to achieve "complete saturation." But if the body is exposed to air for 450 min, then nitrogen in all kinds of theoretical tissue compartments will achieve "complete saturation."

From the above discussion, we can grasp two important messages. First, when human body breathes a concentration of hydrogen (e.g., 2 %), the hydrogen concentration in the human body increases gradually; second, different tissues differ in the increase rate of hydrogen concentration. According to the law of theoretical tissue compartment, the concentration in the blood increases first and then brain tissue while the increasing speed in some slow tissues is very slow. The maximum saturation concentration in the blood can be reached in 30 min, and continue to breathe hydrogen will not increase the hydrogen concentration in the blood. However, the brain requires 60 min to achieve the same maximum saturation concentration and other tissues require more time.

2.3 Release of Hydrogen Gas

With regard to the whole body, when a body exposed to the high pressure returns back to atmospheric pressure and within a period of time, the tension of inert gas that have been dissolved in the body in the high pressure is higher than the external partial pressure of the gas. As a result, the inert gas will diffuse into the outside according to the pressure gradient until the tension of inert gas reaches an equilibrium with the partial pressure of the gas. This process is termed as desaturation of inert gas. The hydrogen partial pressure in vivo will exceed that in the external respiratory gas after the end of hydrogen breath or other means of hydrogen supply, the in vivo hydrogen will be released to the outside in a manner similar to circulation and respiration. Because hydrogen has a very large diffusion capacity, the proportion of hydrogen released through the skin cannot be ignored.

Haldane believed that the inert gas desaturation and saturation only differ in the opposite direction of diffusion; that is, the direction of dissolved gases carried by the blood when desaturation is not from the lungs to the tissues, but from the tissues to the lungs. But, in fact, in addition to the opposite direction, the time needed for desaturation is much longer than that for saturation. There are two main reasons: (1) When desaturation happens, gas will diffuse from the liquid phase to the vapor phase and thus the gas molecules will be bound by the liquid. If the liquid contains substances like colloidal protein, then the binding effect will be more obvious. (2) In order to ensure safety, the desaturation process also needs to be controlled by the safety factor of supersaturation. As to the law that inert gas takes advantage of the pressure gradient to diffuse, it is the same to that of saturation, that is:

1. The completion desaturation process is also through the functional activities of the respiratory and circulatory systems. Other ways of desaturation can also

be ignored. Many factors affect desaturation rate through directly or indirectly affecting the activities of the respiratory and circulatory systems.

2. Tissues that are faster to be saturated are also faster to be desaturated; tissues that are slower to be saturated are also slower to be desaturated. Customarily, the former is called fast tissues and the latter the slow tissues.
3. Completion of 50 % desaturation needs a half-saturation time unit; completion of 98 % desaturation ("complete desaturation") needs six time units. In short, the longer the residence time at a lower pressure, the more complete the desaturation is (Fig. 4.2).
4. The degree of desaturation is also according to the order of time units. The desaturation degree of the latter time unit diminishes exponentially compared to the former.

The saturation and desaturation law of inert gas can be used to interpret the change rules and characteristics of hydrogen in vivo. For example, due to a slower blood circulation in human than in small animals, the increase in rate of hydrogen concentration in human blood is lower than that in small animals at the same dose of hydrogen. If hydrogen breathing or hydrogen injection of same amount is stopped when its concentration in the blood and tissues reaches the maximum, the decline rate of its concentration in human body is also relatively slower than that in smaller animals. Both the increasing and reducing processes of the hydrogen concentration are in line with the exponential change law of the inert gas saturation and desaturation.

Reference

1. Tao HY. Diving medicine. Shanghai: Shanghai Science and Technology Press; 2010. pp. 79–90.

http://www.springer.com/978-94-017-9690-3

Hydrogen Molecular Biology and Medicine
Sun, X.; Ohta, S.; Nakao, A. (Eds.)
2015, IX, 117 p. 15 illus., 9 illus. in color., Hardcover
ISBN: 978-94-017-9690-3